Socio-Affective Processing and Cognitive Control in Adolescence

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Cognitive Neuroscience.

I, Emma Jayne Kilford, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: 

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ABSTRACT

Research has shown that the brain undergoes substantial development during human adolescence, particularly in regions associated with cognitive control and social cognition. Successful transition to adulthood requires the refinement and integration of these processes. The studies in this thesis aimed to investigate how interactions between social cognition, motivational-affective processing, and cognitive control change over adolescent development, and how this is influenced by individual differences in affective reactivity and genetics.

The studies described in the first two experimental chapters examined the development of several aspects of cognition and how this is affected by a common genetic polymorphism associated with dopaminergic variation (*COMT*). **Chapter 2** investigated the development of social, relative to non-social, working memory, and how this is moderated by *COMT*. **Chapter 3** explored developmental changes in the association of *COMT* with the processing of self-generated information, and self-reported trait anxiety. Together, these studies demonstrate the importance of considering genetic variation from a developmental perspective.

Adolescence is characterised by changes in learning and decision-making, processes that require the coordination of motivational-affective processing and cognitive control, and this is the subject of **Chapters 4** and **5**. **Chapter 4** used a computational reinforcement learning paradigm to investigate how adolescents, as compared to adults, learn from reward versus punishment, and from counterfactual feedback about their decisions. In **Chapter 5**, developmental changes in social reward sensitivity, and whether this is related to variation in social anxiety, were investigated.

This thesis also investigated how variation in cognitive control and socio-affective processing relates to the development of affective disorders. While **Chapters 3** and **5** used self-report measures to explore the relationship between affective reactivity and development of cognitive control and socio-affective processing, **Chapter 6** examined how interactions between these processes relate to the onset of adolescent depression in a one-year longitudinal sample of high-risk adolescents.

IMPACT STATEMENT

Adolescence is a period during which social cognition, motivational-affective processing, cognitive control, and the neural systems supporting these processes, become increasingly refined and integrated. This thesis uses a combination of genetic, cognitive and computational research techniques, in both healthy and clinical populations to investigate how interactions between these cognitive processes change over development, and how this is influenced by individual differences in affective reactivity and genetics. The studies in this thesis demonstrate that effects of genetic variation on social cognition, motivational-affective processing, executive functions and their integration are best understood from a developmental perspective. Furthermore, taking the effects of genetic dopaminergic variation on cognition into account can increase our understanding of developmental changes occurring to these processes, and the neural systems that support them. From a methodological perspective, the genetic studies detailed in this thesis also demonstrate the utility of genetic association studies as a non-invasive tool to indirectly study dopaminergic variation, and its influence on cognition, during healthy human development.

The work presented in this thesis also provides evidence of developmental changes in the processing of both monetary and social rewards, at the level of hedonic reward value,

motivational salience, reward and punishment learning, and the use of counterfactual information to guide decision-making. These findings underline the complexity of motivational processing and the neurocognitive systems that facilitate it, and highlight the advantages of taking a computational approach to modeling the heterogeneous components involved in learning and decision-making. Recommendations for future application of these methods to study of motivational processing in both typical and atypical development are outlined, such as how individual differences in these processes and their integration may contribute to the development of affective disorders.

Successful transition into an independent adult role requires the refinement and integration of broad a range of higher-level cognitive processes, which the studies in this thesis indicate show continued development throughout adolescence. Taken together, the studies described in this thesis demonstrate the importance of taking individual differences in affective reactivity and genetic variation into account when investigating the development of social cognitive, motivational-affective, and cognitive control systems during in adolescence. Variation in these processes and their integration, as a result of developmental changes and individual difference factors, likely impacts upon an individual's behavior, decision-making and mental health outcomes. The majority of mental illnesses have their onset during adolescence, and many of the processes, and their associated neural systems, that undergo pronounced development during adolescence are also implicated in poor mental health. Even brief and relatively mild mental illness can have significant disruptions to a young person's development, and is often associated with impairments in social functioning, educational attainment, and substance misuse later in life. Therefore, increasing our understanding of developmental changes in these systems, and how they vary both between individuals and over time may provide insight into why adolescence is a period of elevated vulnerability to mental illness, who may be most at risk, and how best to design interventions.

CONTENTS

INDEX OF FIGURES

INDEX OF TABLES

ABBREVIATIONS

ACC	anterior cingulate cortex
AGN	Affective Go/No-Go task
ANOVA	analysis of variance
ATC	anterior temporal cortex
ADHD	attention deficit hyperactivity disorder
BART	Balloon Analogue Risk task
BIC	Bayesian Information Criterion
CAPA	Child and Adolescent Psychiatric Assessment
CBT	Cognitive Behavioural Therapy
COMT	catechol-O-methyltransferase
CPB	Child Psychiatry Branch
CPT	cumulative prospect theory
dlPFC	dorsolateral prefrontal cortex
dmPFC	dorsomedial prefrontal cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
DTI	diffusion tensor imaging
EPAD	Early Prediction of Adolescent Depression
fMRI	functional magnetic resonance imaging
FA	fractional anisotropy
IFG	inferior frontal gyrus
IQ	Intelligence quotient
IGT	Iowa Gambling Task
LPP	Laplace approximation to the model evidence
LSAS	Liebowitz Social Anxiety Scale
M	mean
MAO	monoamine oxidase
MFLD	myelinated fibre length density
MRI	magnetic resonance imaging
Met	methionine
NCD	Neurocognitive Development
PFC	prefrontal cortex
PIT	Pavlovian-Instrumental Transfer

PP	posterior probability of the model
pSTS	posterior superior temporal sulcus
RL	reinforcement learning
RMET	Reading the Mind in the Eyes Test
RT	reaction time
SAD	social anxiety disorder
SD	standard deviation
SE	standard error
SI	stimulus-independent
SNP	single nucleotide polymorphism
SO	stimulus-oriented
SRQ	Social Reward Questionnaire
SRQ-A	Social Reward Questionnaire for Adolescents
STAI	State-Trait Anxiety Inventory for Adults
STAI-C	State-Trait Anxiety Inventory for Children
TPJ	temporoparietal junction
UCL	University College London
VS	ventral striatum
Val	valine
WASI	Wechsler's Abbreviated Scale of Intelligence
WM	working memory
XP	exceedance probability
vlPFC	ventrolateral prefrontal cortex
vmPFC	ventromedial prefrontal cortex

CHAPTER 1: INTRODUCTION

1.1 Adolescence

Adolescence can be defined as the period of life between the biological changes of puberty and the achievement of self-sufficiency and the individual attainment of a stable, independent role in society (Blakemore & Mills, 2014). While the concept of adolescence is recognised across cultures and throughout history, the nature of its biopsychosocial definition can make it challenging to define chronologically, as the timings of both pubertal onset and adult role transition vary both between and within cultures (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). This transitional period of development has long been associated with physical, social, behavioural and cognitive changes. More recently, advances in brain imaging technology have enabled increased understanding of structural and functional changes in the human brain during this developmental period (Blakemore & Mills, 2014; Casey, Jones, & Hare, 2008; Ernst & Fudge, 2009; Lenroot & Giedd, 2006), and how they relate to social, motivational, affective and cognitive development. Successful transition to adulthood requires the rapid refinement and integration of these processes and many adolescent-typical behaviours, such as risky decision-making, peer influence and sensitivity to social exclusion, involve dynamic interactions between these processes, and the neural systems that support them. Investigating the development of these processes, and the way in which they interact with each other, forms a key part of increasing our understanding of adolescent cognitive development. Many of the behavioural and cognitive changes associated with adolescence assist the transition to an independent adult role, however they can also confer vulnerability. The rate of accidents, unsafe sexual behaviour and substance abuse show a marked increase during this transitional period (Patton & Viner, 2007; Viner et al., 2011; Willoughby, Good, Adachi, Hamza, & Tavernier, 2013), and the majority of mental illnesses have their onset in adolescence (Kessler et al., 2005, 2007). Studying the way in which these systems and their

interactions vary between individuals and across development, could increase our understanding of adolescent brain and behavioural development in both typical and atypical populations.

1.2 Structural development of the brain in adolescence

1.2.1 Histological and post-mortem studies

Anatomical studies of post-mortem human brain tissue provided some of the first evidence that the brain undergoes profound changes in anatomy across the first decades of life (Petanjek et al., 2011; Webb, Monk, & Nelson, 2001; Yakovlev & Lecours, 1967). Despite the limited sample size and age ranges of these studies, they provided evidence of protracted cellular changes, likely reflecting important developmental processes such as myelination and synaptic reorganisation, and thus challenged the notion that the human brain ceased to develop after early childhood.

1.2.1.1 Myelination

Humans are born with relatively low levels of cortical myelin (Miller et al., 2012), an insulating membrane that ensheaths axons, and therefore the majority of myelination occurs postnatally, as a result of reciprocal communication between neurons and oligodendrocytes. Myelination results in enhanced neuronal transmission speed, thus facilitating increased efficiency and synchronisation of information transfer within and between brain networks (Fields & Stevens-Graham, 2002), a crucial hallmark of mature neural connectivity. Human post-mortem studies showing that myelination continues throughout the first two decades of life were the first to provide evidence of protracted developmental increases in white matter during adolescence (Benes, Turtle, Khan, & Farol, 1994; Yakovlev & Lecours, 1967; discussed further in **Section 1.2.2.2**). These studies found that different areas of the brain showed different developmental trajectories of myelination. While primary sensory regions showed significant early increases in

myelination, plateauing later in childhood, the association cortices, areas involved in the integration and co-ordination of different sensory inputs, continued to gain myelin into the second and third decades of life (Benes, 1989; Yakovlev & Lecours, 1967). A more recent study by (Miller et al., 2012) assessed myelinated fibre length density (MFLD) in post-mortem samples to quantify developmental changes in myelination. Consistent with earlier post-mortem findings, they found evidence that myelination shows regional differences across the brain, and continues to develop across the first three decades of life. Despite the rate of myelination slowing after infancy, by adolescence and early adulthood (11-23 years) it had only reached 60% of adult levels (≥ 28 years), with adults showing significantly greater mean MFLD by comparison (Miller et al., 2012).

1.2.1.2 Synaptic development

The adult brain is characterised by the existence of many diffuse, yet synchronised, neural networks, facilitated by complex patterns of synaptic connections between neurons (Power, Fair, Schlaggar, & Petersen, 2010). It has been proposed that a key mechanism underlying diversity in patterns of neural connectivity is an initial period of synaptic overproduction, followed by a period of activity-dependent selective synaptic elimination (Changeux & Danchin, 1976). Early histological studies are consistent with this notion, indicating that in humans synapse formation begins prenatally in the third trimester, and by birth synaptic density is already within the range of that observed in adults, despite the existence of morphological differences (Huttenlocher, 1979). Unlike non-human primates (Bourgeois, Goldman-Rakic, & Rakic, 1994; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986), the time-course of cortical synaptic development shows pronounced regional differences. Synaptogenesis continues postnatally, resulting in a substantially greater synaptic density than that observed in adulthood. However, while primary visual and auditory cortical areas show a fast postnatal increase in synaptic density, peaking at approximately 3-4 months, synaptogenesis in the prefrontal cortex (PFC) is slower, continuing until approximately 3.5

years of age (Huttenlocher & Dabholkar, 1997). After this initial period of synaptogenesis, during which synaptic density substantially exceeds adult levels, synaptic density shows a subsequent period of decline, the time course of which is also heterochronous, reaching adult levels and stabilising earlier in the primary sensory cortices than in the PFC, where it extends to approximately 16 years of age (Huttenlocher, 1979, 1990; Huttenlocher & Dabholkar, 1997).

While this period of decline has been hypothesised as reflecting a period of synaptic elimination, it should be noted that, without brain volume data, it is not possible to be certain that synapses are actually lost during development of the frontal cortex, although the fact that synaptic density continued to decline beyond declines in neuronal density was consistent with this hypothesis. A more recent study examined synaptic dendritic development in the PFC of 32 human post-mortem brains (aged 1 week to 91 years; Petanjek et al., 2011), with a greater number of samples from individuals between the ages of 16 and 30 compared with Huttenlocher's earlier work (6 vs. 1; Huttenlocher & Dabholkar, 1997). Petanjek et al.'s (2011) results indicated that prefrontal dendritic spine density increased during infancy and childhood, peaking in late childhood to around 2-3 times greater than adult levels, before declining in adolescence, during which it still remained significantly higher than in adulthood. These findings extend earlier post-mortem findings by Huttenlocher (Huttenlocher, 1979, 1990; Huttenlocher & Dabholkar, 1997), suggesting a protracted period of synaptic spine elimination occurs throughout adolescence, extending into the third decade of life before stabilising (Petanjek et al., 2011).

1.2.2 Structural MRI studies

Histological studies have been hugely important in characterising human brain development at the cellular level, however they tend to be limited in sample size, and therefore generalizability, and by definition are cross-sectional so cannot characterise structural developmental trajectories within the same individual over the lifespan. Over the past 20 years

the development of new neuroimaging technologies, particularly structural magnetic resonance imaging (MRI), has enabled the investigation of anatomical changes in the living human brain across development. In structural MRI, data from MRI scans is used to quantify the volume of brain tissue, which can be subdivided into grey and white matter, three-dimensionally throughout the brain. While MRI does not possess the resolution to examine brain structure at the cellular level, these technological advances have enabled us to build on evidence provided by histological studies, providing an increased understanding of adolescent human brain development at both the microscopic and macroscopic level.

1.2.2.1 White matter

Data from structural MRI scans can be classified into white and grey matter, with white matter largely consisting of axons and associated myelin sheaths and glia. In a collaborative, multi-site project, Mills et al. (2016) examined the developmental trajectories of cortical white and grey matter tissue at the whole brain level in four separate longitudinal datasets from three different countries (Norway, the Netherlands and the United States). The authors used a team science approach, in which identical analytical techniques were used across sites, in an attempt to minimise between sample variation arising from differences in the quality control measures or analysis procedures used. Collectively, the four samples included 391 participants, ranging from 8 to 30 years of age, with a total of 852 structural scans. Their findings provide converging evidence that global cortical white matter volume increases from late childhood until mid-to-late adolescence, before stabilising in adulthood (Mills et al., 2016; see **Figure 1.1A**).

Longitudinal structural MRI studies indicate that despite some variability in the precise magnitudes of change observed at different ages, the developmental trajectories of white matter volumes for individual cortical lobes are relatively similar to that observed at the whole brain level, showing steady monotonic increases during the first two decades of life (Aubert-

Broche et al., 2013; Lebel & Beaulieu, 2011; Lenroot et al., 2007). While there have been mixed findings as to whether these increases continue into the third decade of life (Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011) or stabilise during mid-late adolescence (Mills et al., 2016), an adolescent increase in cortical white matter has been consistently observed across longitudinal studies from a range of samples (Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011; Lenroot et al., 2007; Mills et al., 2016).

Although MRI lacks the resolution to examine the cellular mechanisms underlying these changes, a protracted developmental increase in white matter volume is consistent with findings from histological studies of an extended period of myelination and axonal growth in adolescence (Yakovlev & Lecours, 1967; see **Section 1.2.1.1**), thought to facilitate developmental increases in connectivity within and between brain regions. Networks enabling the integration of information from distinct brain regions continue to mature during adolescence, including connections between cortical and subcortical areas. The connectivity of brain regions can be visualised using diffusion tensor imaging (DTI), a technique which uses MRI to determine the direction of water flow in the brain to produce a map of interconnecting bundles of white matter. DTI also enables the assessment of axonal integrity using fractional anisotropy (FA), which measures the strength of white matter connections in the developing brain, with higher FA indicating greater integrity and more efficient neural signalling. As would be predicted on the basis of increased myelination and axonal calibre during adolescence, FA shows increases during childhood and adolescence (Lebel & Beaulieu, 2011; Peters et al., 2012; Tamnes et al., 2010), which continue into the third (Tamnes et al., 2010) and even fourth decade of life (Lebel & Beaulieu, 2011).

1.2.2.2 Grey matter

Grey matter consists mainly of neuronal cell bodies, dendrites and synapses, as well as associated glial cells and vasculature. Early longitudinal MRI studies of cortical grey matter

volume (Giedd et al., 1999; Lenroot et al., 2007) reported inverted U-shaped developmental trajectories, whereby grey matter volume increased during childhood, peaked during late childhood/early adolescence, and then decreased. More recent longitudinal studies have indicated that cortical grey matter is at its highest in late childhood (around 8 years), and then decreases steadily throughout late childhood and adolescence, before eventual stabilisation in the twenties (Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011; Mills et al., 2016; Tamnes et al., 2017; see **Figure 1.1B**).

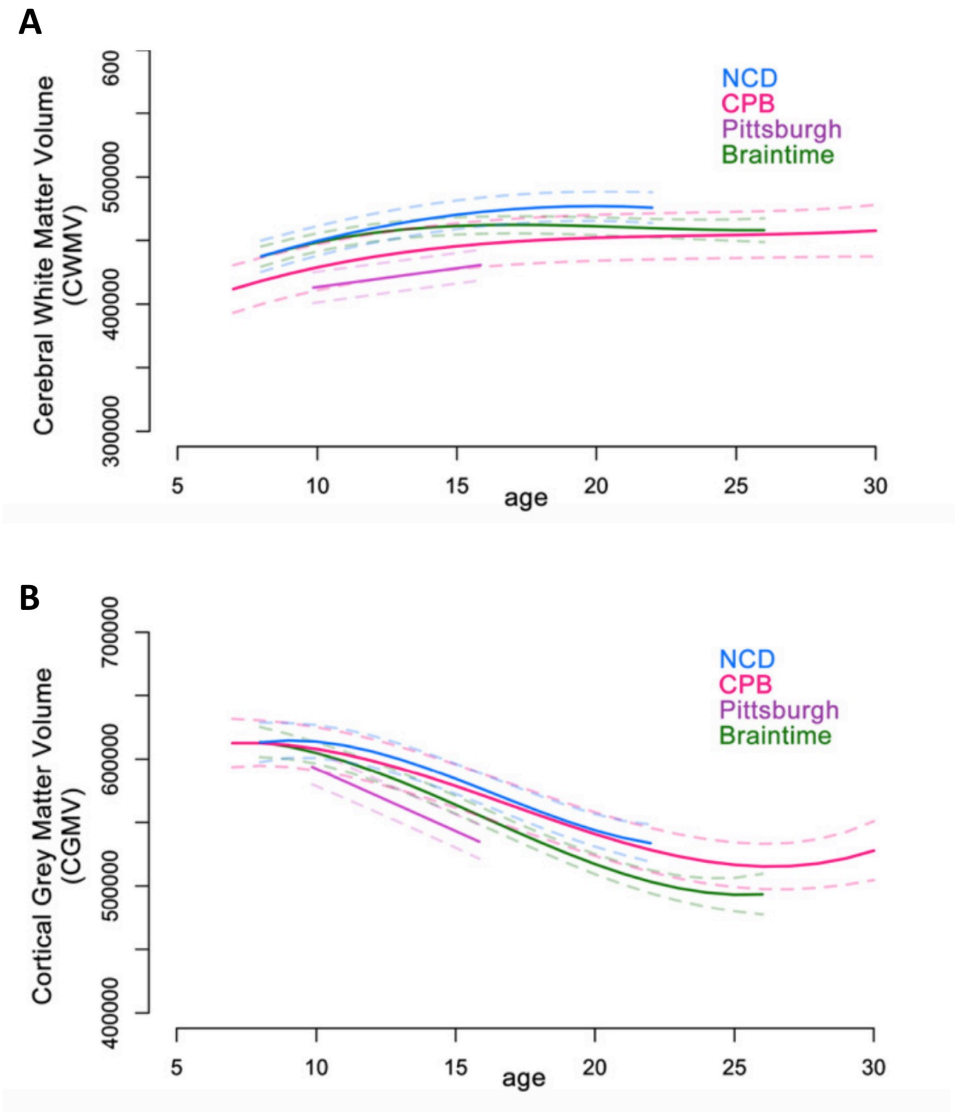

Figure 1.1. Developmental changes in cortical white and grey matter volumes. Changes in white **(A)** and grey **(B)** matter volume are shown for four separate longitudinal samples. Age in years is shown on the X-axis, and raw volumes (mm^3) is shown along the Y-axis. CPB: Child Psychiatry Branch; NCD: Neurocognitive Development. Reproduced from Mills et al. (2016).

Changes in brain volume arise through several important and interactive developmental changes in structural measures, including cortical thickness, surface area and gyrification (Hogstrom, Westlye, Walhovd, & Fjell, 2013; Mills, Lalonde, Clasen, Giedd, & Blakemore, 2014; Tamnes et al., 2017; White, Su, Schmidt, Kao, & Sapiro, 2010). Cortical thickness, one index of the time-course of changes in grey matter, shows diverse developmental patterns and is not uniform across the brain. During late childhood, cortical thickness increases in medial prefrontal and anterior temporal cortices (Sowell et al., 2004), decreases in the frontal pole (van Soelen et al., 2012) and decreases in lateral parietal lobes (Sowell et al., 2004; van Soelen et al., 2012). Investigations of cortical thickness during adolescence and early adulthood have shown increases in the temporal lobe until mid-adolescence (Shaw et al., 2008) and decreases in medial frontal and lateral parietal lobes (Shaw et al., 2008; Tamnes et al., 2010, 2013; see **Figure 1.2**). These findings support a posterior-anterior theory of cortical maturation (Jernigan, Baaré, Stiles, & Madsen, 2011), whereby posterior regions, such as primary sensory cortices, show the greatest rates of decrease in cortical thickness during childhood, and more anterior regions, such as the association cortices, show greater rates of decrease later in adolescence (Gogtay et al., 2004; Shaw et al., 2008; Tamnes et al., 2013, 2017). It has been suggested that this systematic pattern of maturation, with later maturation of the frontal and temporal lobes, may be because these regions require a greater degree of functional co-ordination across regions, due to the complex and integrative nature of the neural processes they facilitate (Raznahan et al., 2011).

Inconsistencies between the results of previous studies of cortical volume have resulted in some disagreement regarding the precise developmental trajectories of cortical grey matter volume and its structural components, particularly that of cortical thickness (Mills & Tamnes, 2014; Tamnes et al., 2017; Walhovd, Fjell, Giedd, Dale, & Brown, 2016). One way of addressing these inconsistencies is through multi-site, multi-sample studies, such as that of Mills et al. (2016; described in **Section 1.2.2.1**). In another study, the same multi-sample longitudinal MRI

datasets were used to examine developmental changes in cortical thickness and surface area, and how interactions between these two structural measures influence changes in cortical volume during adolescence (Tamnes et al., 2017). The results were generally consistent across the samples analysed, and indicated widespread, non-linear decreases in cortical volume and thickness, which varied across cortical lobes. For all samples, the parietal lobe showed the greatest rate of cortical thickness decrease, followed by the frontal, then temporal and lastly occipital lobes. The authors also found evidence of steady decreases in surface area, however these were comparatively smaller, with cortical thickness being the dominant influence on decreases in cortical volume (Tamnes et al., 2017).

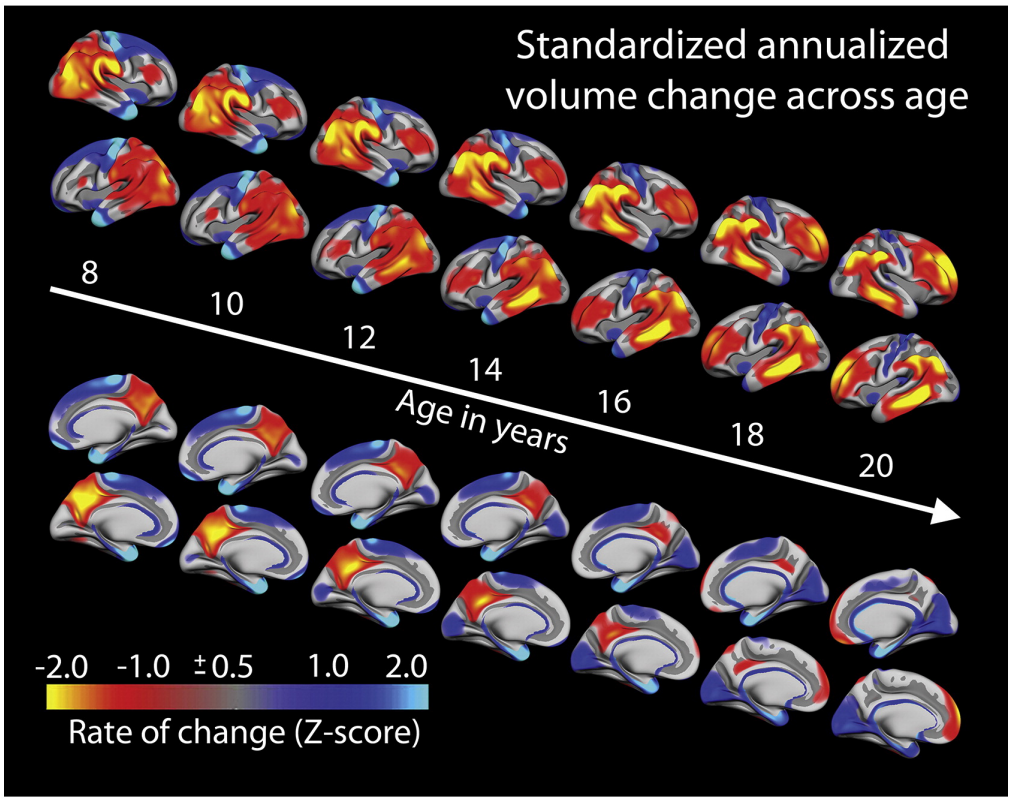

Figure 1.2. Developmental changes in cortical volume. Standardised annual cortical volume change across age in children and adolescents. Red-yellow areas indicate regions with the largest rates of cortical volume reduction, while blue-cyan areas indicate regions with relatively smaller rates of reduction. Reproduced from Tamnes et al. (2013), with permission from Elsevier.

The relationship between reductions in cortical grey matter volume and underlying cellular changes are still debated (Paus, Keshavan, & Giedd, 2008; Poldrack, 2010). Animal and post-mortem human brain tissue studies provide support for periods of synaptic reorganisation and elimination (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011; see **Section 1.2.1.1**) and increases in myelination and axonal diameter in the PFC during adolescence (Benes, 1989; Benes et al., 1994; Miller et al., 2012; Yakovlev & Lecours, 1967; see **Section 1.2.1.1**). Both of these neurodevelopmental processes would result in decreases in grey matter volume. While the pruning of synapses would result in a direct decrease in cortical grey matter volume, increases in white matter volume due to increased myelination and axonal diameter, with no increase in overall brain volume after late childhood (Mills et al., 2016), would necessarily also result in decreased grey matter volume (Paus et al., 2008).

In a cross-sectional study, Whitaker et al (2016) used MRI to measure both cortical thickness and intracortical myelination in 297 participants, aged 14 to 24 years, to examine the relationship between cortical thinning during adolescence and increases in intracortical myelination, and whether this was greater regions of the brain with particularly high anatomical levels of interconnections, such as the association cortices. They found that at age 14, association cortices showed the relatively greatest level of cortical thickness, and the lowest levels of myelination. Across the brain, the authors observed steady decreases in cortical thickness and increases in myelination across the age range studied, however there were regional differences in the rates of these changes, with the association cortices showing significantly greater rates of both cortical shrinkage and myelination, consistent with findings from histological and post-mortem studies; see **Section 1.2.1**). These change rates were negatively correlated, indicating that regions showing faster rates of cortical shrinkage also had faster myelination rates, however mediation analyses showed that adolescent cortical thinning was significantly but not fully accounted for by changes in intracortical myelination. -

These findings suggest that while myelination is a key factor contributing to changes in grey matter volume, it does not fully account for it.

While previous longitudinal studies have predominantly focused on structural changes in the cortex, some have investigated the development of subcortical structures. Those that have, have yielded less conclusive results than studies of cortical development, or have focused exclusively on only one subcortical structure (e.g. Gogtay et al., 2006; Lenroot et al., 2007; Mattai et al., 2011; Tiemeier et al., 2010). This may in part be due to the location, size and complexity of these small, heterogeneous midbrain structures, and the challenges posed in obtaining stable and high quality measures using traditional neuroimaging techniques as compared to cortical regions (Ernst & Luciana, 2015; Tamnes, Bos, van de Kamp, Peters, & Crone, 2018). In addition to analysing longitudinal changes in cortical volume, Tamnes et al. (2013) also examined developmental changes in the volumes of multiple subcortical structures. Although most subcortical structures showed decreases in volume during adolescence, these changes were heterogeneous across structures, and on average were at a lower rate than those observed cortically. Herting et al. (2018) conducted a multi-site study of subcortical development in three independent longitudinal samples. While the developmental trajectories of the amygdala, putamen and nucleus accumbens showed generalizability across all three samples, the thalamus, caudate, pallidum and hippocampus showed notable between-sample variability. These findings suggest either that current results are not yet conclusive, or that individual difference factors (discussed further in **Section 1.6**) , such as pubertal (reviewed in Herting & Sowell, 2017), genetic or environmental variation, may have a greater influence on sub-cortical than cortical development, resulting in greater variability both within and between samples.

In this section I have described research showing that the human brain continues to develop structurally throughout childhood, adolescence and into adulthood. Both histological and

structural neuroimaging studies have shown that one of the brain regions that undergoes the most striking and prolonged changes during adolescence is the PFC (Gogtay et al., 2004; Huttenlocher, 1990; Lenroot et al., 2007; Sowell et al., 2004; Tamnes et al., 2013), a brain region involved in a range of functions including cognitive control (see **1.3.1**). It has therefore been hypothesised that changes in behaviour and cognition during adolescence may be associated with protracted developmental changes in the brain occurring during this period of life, which is discussed in the following section.

1.3 Cognitive control and motivational-affective processing in adolescence

1.3.1 Cognitive control

Cognitive control can be defined as the ability to actively guide behaviour, and involves the coordination of a heterogeneous set of sub-processes ('executive functions') that focus attention on goal-relevant information, while inhibiting goal-irrelevant information (Casey, Durston, & Fossella, 2001; Miller & Cohen, 2001; Norman & Shallice, 1986). The PFC mediates these cognitive capacities, and efforts have been made to map these sub-processes onto distinct prefrontal neural networks (see Goldman-Rakic, Cools, & Srivastava, 1996 for a review). These sub-processes, such as inhibitory control, performance monitoring, and working memory (WM) continue to mature into late adolescence and early adulthood (Casey et al., 1997; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Durston, Thomas, Worden, Yang, & Casey, 2002; Luna et al., 2001; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015; Rubia et al., 2006), and during this period there is a steady increase in the ability to use cognitive control processes to guide thoughts and actions (Asato, Sweeney, & Luna, 2006; Huizinga, Dolan, & van der Molen, 2006; Luna, Padmanabhan, & O'Hearn, 2010). Developmental neuroimaging studies show correlations between the protracted development of the PFC and maturing cognitive abilities during adolescence (Casey, Giedd, & Thomas, 2000; Giedd et al., 1999; Gogtay et al., 2004;

Rubia et al., 2000; Tamm, Menon, & Reiss, 2002), and there is considerable evidence for developmental changes in PFC recruitment during cognitive control tasks over the course of adolescence (see Luna et al., 2010, for a review).

1.3.2 Theoretical models of adolescent neurocognitive development

Adolescents are often characterised as prone to engage in risky decision-making, which although probably adaptive in many circumstances (Blakemore & Mills, 2014; Sercombe, 2014; Willoughby et al., 2013), can sometimes result in negative real life outcomes, such as substance misuse, unsafe sexual behaviour, violent and non-violent crime and dangerous driving (Eaton et al., 2012; Patton & Viner, 2007; Viner et al., 2011, 2012; Willoughby et al., 2013). Adolescence is also associated with a marked increase in affective reactivity and mood and anxiety disorders (Kessler et al., 2005, 2007; Kim-Cohen et al., 2003; Lewinsohn, Rohde, & Seeley, 1998; Thapar, Collishaw, Pine, & Thapar, 2012; see **Section 1.6.2**).

Several influential models of neurocognitive development have been proposed to account for these nonlinear changes in motivational-affective behaviour observed between childhood and adolescence. While early theories attributed adolescent behavioural changes solely to the protracted development of the PFC, more recent models focus on the relationships between regulatory and affective-motivational processes and their associated neural circuits, and how these change during adolescence (Casey et al., 2008; Ernst & Fudge, 2009; Ernst, Pine, & Hardin, 2006; Steinberg, 2008).

Dual-systems models hypothesise that cognitive control mechanisms, mediated by the PFC, develop later and more slowly than subcortical mechanisms of emotional responsiveness and motivation, such as the amygdala and ventral striatum (VS; Casey et al., 2008; Somerville, Jones, & Casey, 2010; Steinberg, 2008, 2010). This maturational discrepancy is proposed to result in adolescents having a disproportionately developed 'hot' motivational system

compared with a relatively immature 'cold' cognitive control system that is not yet strong enough to consistently restrain potentially hazardous impulses (Albert & Steinberg, 2011; Casey & Jones, 2010; Casey, Jones, & Somerville, 2011; Somerville & Casey, 2010; Steinberg, 2008; **Figure 1.3**).

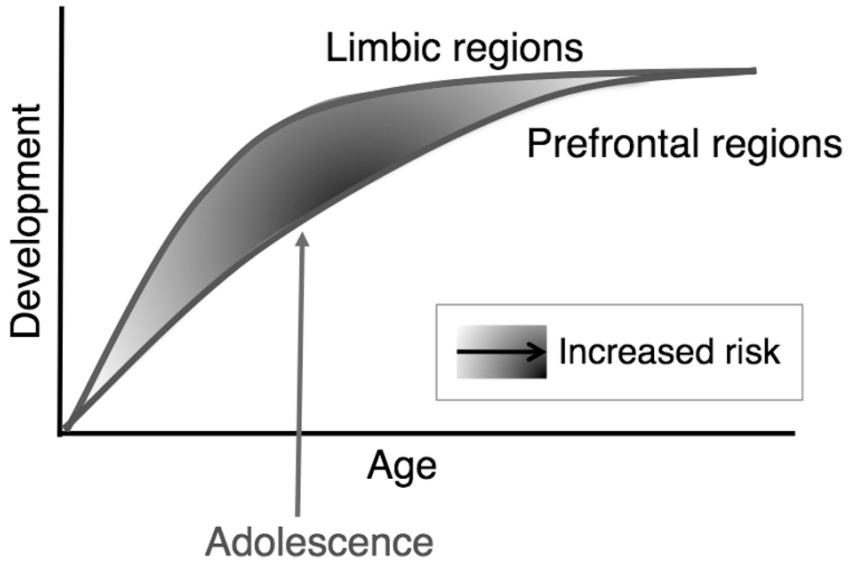

Figure 1.3. Dual-systems model of adolescence. This diagram illustrates the dual-systems hypothesis of adolescent neurocognitive development. The relatively earlier maturation of limbic regions such as the amygdala and VS/nucleus accumbens, combined with the later maturation of prefrontal regions is proposed to result in a maturational mismatch (shaded area), during which there is an elevated risk of engaging in affectively driven or risky behaviours. Reproduced from Somerville et al. (2010), with permission from Elsevier.

Extending the dual-systems models, Ernst et al.'s (Ernst & Fudge, 2009; Ernst et al., 2006) triadic model advocates three neural systems, and the interplay between them, as important in understanding adolescent development: 1) a reward/approach processing system; 2) an avoidance processing system; and 3) a regulatory system exerting top-down cognitive control over reward and avoidance systems. A key tenet of these models is that adolescent behaviour and cognition is associated with changes in the balance between the different circuits (Ernst & Fudge, 2009; Ernst et al., 2006; Somerville et al., 2010). Individual differences in the developmental trajectories of neural circuits and the cognitive processes they subserve are

proposed to interact with environmental factors, manifesting in a unique neurocognitive developmental profile. This variation may confer increased vulnerability to negative outcomes as a result of risky actions (e.g. accidents, injuries, unwanted pregnancies, addiction, criminal convictions) and/or heightened emotionality (e.g. mental health problems, self-harm, suicide) for some adolescents.

There is a growing body of work investigating the interplay between cognitive control and motivational-affective processing, in part arising from the theoretical framework provided by dual systems models. In the following section I summarise key findings from experimental studies investigating the development of these interacting neurocognitive systems.

1.3.3 Interactions between cognitive control and affective processing

1.3.3.1 Emotional regulation

Cognitive control and motivational-affective responding are mutually influential processes. When cognitive control processes interact with affective information, as is typical in everyday life, there are two key types of interplay, both of which can be termed types of emotional regulation. The first is the explicit top-down regulation of affective responses by cognitive control (reviewed in Ochsner and Gross, 2005), and the second is the bottom-up modification or disruption of cognitive control processes by affective information.

It is thought that cognitive control plays an important role in the developmental of emotional regulation (Fernandez-Duque, Baird, & Posner, 2000; Posner & Rothbart, 2000). The ability to exert top-down control over affective responses has received attention in developmental cognitive neuroscience research, in part because it fits with dual-systems models of adolescent development (Casey et al., 2008; Somerville, Jones, & Casey, 2010; Steinberg, 2008, 2010; see **Section 1.3.1**). These models hypothesise that the gap between the onset of motivational-affective changes in early adolescence and the protracted development of regions adults use

to modulate affective responses (e.g., the PFC and its connections with subcortical structures implicated in affective processing; Adolphs, 2002; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Somerville et al., 2010) results in a reduced capacity to exercise emotional regulation, which may contribute to a window of risk for emotional dysregulation (Cohen-Gilbert & Thomas, 2013).

1.3.3.2 Emotional regulation in adolescence

Experimental studies investigating emotional regulation in adolescence have largely focused on inhibitory control, the ability to suppress behaviour that is prepotent or goal-irrelevant, in the context of affectively valenced information. These studies have demonstrated improvements in the ability to resist interference from affective information between adolescence and adulthood (Cohen-Gilbert & Thomas, 2013; Cohen Kadosh, Heathcote, & Lau, 2014; Dreyfuss et al., 2014; Grose-Fifer, Rodrigues, Hoover, & Zottoli, 2013; Hare et al., 2008; Ladouceur et al., 2006; M. D. Lewis, Lamm, Segalowitz, Stieben, & Zelazo, 2006; Somerville et al., 2011; Tottenham, Hare, & Casey, 2011). In addition to evidence for developmental improvements in the ability to resist emotional distractors in pursuit of a goal during adolescence, there is also experimental evidence of improvements in the ability to explicitly regulate emotional responses. The ability to successfully engage in cognitive reappraisal, a strategy in which emotional scenarios are consciously re-evaluated in a more positive light, shows developmental improvements during adolescence, at least when participants receive explicit instruction to do so (Silvers, McRae, Gabrieli, & Gross, 2012).

Neuroimaging studies indicate that adolescents (13-17/18 years) exhibit greater amygdala and striatal reactivity to distracting emotional stimuli than children or adults (Hare et al., 2008; Somerville et al., 2011). Adolescents (11-17 years) also show decreased responses to emotional stimuli in the ventromedial PFC (vmPFC), relative to adults (Barbalat, Bazargani, & Blakemore, 2013; Etkin et al., 2006; Hare et al., 2008). The vmPFC plays an important role in

affect regulation and in the formation and pursuit of socio-affective goals (Davey, Yücel, & Allen, 2008), and its functional connectivity with the amygdala is associated with the habituation of emotional stimuli (Barbalat et al., 2013; Etkin et al., 2006; Hare et al., 2008). In another study, children and adolescents exhibited increased PFC activation to distracting negative emotional stimuli, relative to neutral stimuli, and this modulation was correlated with age (Perlman, Hein, & Stepp, 2014). This study also found that prefrontal activation was correlated with trait emotional ability, whereby adolescents with lower emotional reactivity showed greater activation, which may suggest that adaptive prefrontal modulation of affective responses is associated with both normative developmental changes and individual differences in emotional reactivity (Perlman et al., 2014).

Neural models of emotional regulation implicate a network of extensively interconnected brain regions, including the PFC, amygdala and VS (Ochsner & Gross, 2005). These connections demonstrate marked maturational changes during adolescence (Cunningham, Bhattacharyya, & Benes, 2002) and developmental studies of functional connectivity suggest age-related increases in connectivity between the vmPFC and both the amygdala and VS during the processing of affective information (Gee et al., 2013; Guyer et al., 2008; Pfeifer et al., 2011; Somerville et al., 2013; Spielberg et al., 2014, 2015; van den Bos, Cohen, Kahnt, & Crone, 2012).

To summarise, experimental studies of emotional regulation indicate continuing developmental improvements in both implicit and explicit regulation (see Ahmed, Bittencourt-Hewitt, & Sebastian, 2015 for a more in depth review). Neuroimaging findings are largely consistent with dual systems/triadic models (see **Section 1.3.1**), yielding evidence of increased limbic reactivity, reduced prefrontal control, and maturational changes in the connectivity of these regions.

1.3.4 Interactions between cognitive control and motivational processing

Dual systems models (Casey et al., 2008; Somerville, Jones, & Casey, 2010; Steinberg, 2008, 2010; see **Section 1.3.1**) also propose that differences in the developmental trajectories of the neural systems implicated in reward processing and cognitive control during adolescence can manifest in suboptimal decisions when faced with real-life gambles, like choosing to drink and drive or engage in risky sexual behaviour (Patton & Viner, 2007; Viner et al., 2011; Willoughby et al., 2013), either as a result of heightened reward sensitivity, delayed maturation of cognitive control regions, or a combination of the two.

Significant changes in value-based decision-making are observed during adolescence (Blakemore & Robbins, 2012). Experimental evidence supports the idea that in hot (i.e., affective) contexts, adolescents show less advantageous choice behaviour (van Duijvenvoorde, Jansen, Visser, & Huizenga, 2010) and are more likely than children and adults to make risky decisions (Burnett et al., 2010; Cauffman et al., 2010; Figner et al., 2009; reviewed in Blakemore and Robbins, 2012). In contrast, cold (i.e. non-affective) tasks tend to elicit either no change or decreases in risk-taking with age between childhood and adulthood (Crone, Bullens, van der Plas, Kijkuit, & Zelazo, 2008; Figner et al., 2009; Paulsen, Platt, Huettel, & Brannon, 2011; Rakow & Rahim, 2010).

Studies using risky decision making and probabilistic reward paradigms are mostly consistent with the hypothesis that adolescents are biased to taking risks due to heightened reward sensitivity (Ernst et al., 2006; Galvan, 2010; Luciana, Wahlstrom, Porter, & Collins, 2012; Van Leijenhorst, Zanolie, et al., 2010). As a type of reward, gains are linked to dopamine innervations, which lead to a robust signal in the VS (Haber & Knutson, 2010). Several cross-sectional studies have reported that VS response to receiving gains is elevated in adolescents compared with children and adults (Braams, Peters, Peper, Güroğlu, & Crone, 2014; Ernst et

al., 2005; Galvan, 2010; Galvan et al., 2006; Van Leijenhorst, Moor, et al., 2010; Van Leijenhorst, Zanolie, et al., 2010), and that this neural response correlates with self-reported risk-taking behaviour in the real world (Braams, Peper, van der Heide, Peters, & Crone, 2016; Galvan, Hare, Voss, Glover, & Casey, 2007; although see Pfeifer et al., 2011) and individual differences in risk-taking tendencies on experimental paradigms (Braams, van Duijvenvoorde, Peper, & Crone, 2015). However, some studies have found the reverse, i.e. a pattern of striatal hypo-sensitivity to rewards in adolescents (12-17 years) compared with adults (Bjork, 2004; Bjork, Smith, Chen, & Hommer, 2010), and behavioural risk-taking measures do not consistently show a peak in adolescence (for a meta-analysis, see Defoe, Dubas, Figner, & van Aken, 2015).

The fact that behavioural risk-taking tasks do not always show the same non-linear developmental trajectories observed in real-world risk-taking (Eaton et al., 2012; Patton & Viner, 2007; Viner et al., 2011, 2012; Willoughby et al., 2013) may be due to critical differences between the controlled experimental paradigms that tend to be used in the lab and more naturalistic risky decision-making situations, such as whether to have unprotected sex, use drugs, or drink and drive (Paulsen, Platt, Huettel, & Brannon, 2012). Firstly, individual preference for risk, differs across contexts, for example across financial vs. social risks and situations (Weber, Blais, & Betz, 2002). Secondly, real-world decisions tend to be characterised by the hot - heightened affective-motivational – contexts that are associated with increased risk-taking in adolescence, as well as hot outcomes: real-world decisions can lead to financial success or ruin, social rejection or acceptance. Finally, real-world decisions tend to be characterised by ambiguity, rather than the known outcome probabilities that characterise experimental risk paradigms (Paulsen et al., 2012).

Experimental paradigms in which, in addition to uncertain outcomes, risk is unpredictable have indicated that adolescents show a greater tendency to gamble when risk probabilities are not

known (Tymula et al., 2012). Another task in which risk probabilities are not known is the Balloon Analogue Risk task (BART; Lejuez et al., 2002), a well validated paradigm which shows associations with some real-life risk taking behaviours such as substance misuse (Lejuez et al., 2003). In the task, participants earn monetary rewards for inflating a balloon and choose when to stop and claim their reward. With each pump, the potential payoff increases, however if the balloon explodes no reward is given. A longitudinal study of 254 participants aged between 8 and 27 years indicated a quadratic effect of age that peaked in adolescence, on the tendency to take-risks on the BART task, a pattern which was also found for VS sensitivity to monetary reward (Braams et al., 2015).

Risky decision-making involves both reward sensitivity, loss sensitivity and risk sensitivity, which are often confounded in experimental paradigms. While reward sensitivity is often associated with the VS (although see Delgado, Li, Schiller, & Phelps, 2008), it has been argued that the amygdala plays an important role in loss aversion processes (De Martino, Camerer, & Adolphs, 2010), but is not related to risk preferences, which have been instead associated with the insula (Mohr, Biele, & Heekeren, 2010; Paulsen, Hallquist, Geier, & Luna, 2015). Developmental changes in risk sensitivity may be a factor in the development of mature risk aversion – risk aversion appears to increase slowly between childhood and adulthood (Levin & Hart, 2003; Levin, Hart, Weller, & Harshman, 2007; Rakow & Rahim, 2010; Weller, Levin, & Denburg, 2011), however motivational-affective and contextual factors can also moderate this pattern. While the prevailing view in psychology and economics has been that risk-aversion occurs for gains and risk-seeking occurs for losses (given medium to high probabilities for both gain and loss outcomes; Kahneman & Tversky, 1979), an alternative hypothesis is that valence (gains vs. losses) and risk exert independent influences on decisions (Wright et al., 2012). In a study separating the effects of risk and valence in adolescents (11-16 years), Wolf et al (2013) demonstrated that younger adolescents were more risk-averse, specifically for losses; fewer riskier decisions were made for losses than for gains. This effect of valence decreased across

adolescence: compared with mid-adolescents, younger adolescents were more biased away from the riskier option by losses relative to gains, an effect which was not driven by a change in responses to gains or losses alone (Wolf, Wright, Kilford, Dolan, & Blakemore, 2013).

In addition to evidence for heightened sensitivity to both rewards and losses, there is evidence supporting the idea that in such hot situations, adolescents do not engage regulatory prefrontal regions to the same extent as adults (Geier & Luna, 2009), For example, Eshel, et al. (2007) found that when making decisions in the context of rewards, adults activated regions associated with cognitive control processes more than adolescents (9-17 years) did. Furthermore, a functional MRI (fMRI) study of 14 to 16 year olds that examined the processes that occur immediately before making a decision in which taking a risk was associated with varied and unpredictable reward and punishment outcomes found that risky decisions were preceded by heightened activity in the VS, whereas safe decisions were preceded by activity in the right inferior frontal gyrus (IFG), a region associated with cognitive control (Kahn, Peake, & Dishion, 2014).

1.3.4.1 Computational studies of adolescent motivational processing and learning

The ability to learn from both positive (rewarding) and negative (punishing) feedback appear to develop into early adulthood, with behavioural studies suggesting that younger participants are more affected by irrelevant negative feedback, experience more arousal in response to anticipated loss and exhibit an increased learning rate from events that are worse than expected compared to adults (Crone & van der Molen, 2007; Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015; Hooper, Luciana, Conklin, & Yarger, 2004; van der Schaaf, Warmerdam, Crone, & Cools, 2011). Both the amygdala and striatum have been shown to support processes implicated in the ability to learn from rewards and punishments (Cohen et al., 2010; Delgado et al., 2008; Gallagher & Holland, 1994; Paulsen et al., 2015). Therefore, it has been hypothesised that developmental changes in the reactivity of these regions, and their

connectivity with prefrontal regions may result in developmental changes in decision-making and behaviour during adolescence, including the ability to learn from motivationally/affectively salient information (Luciana & Collins, 2012; Luciana et al., 2012).

However, motivational processing is complex, and involves several overlapping, yet distinct psychological components, including pleasure, learning and salience (Sescousse, Caldú, Segura, & Dreher, 2013). While reward (hedonic) value describes the degree of pleasure experienced by an individual from the receipt of a rewarding (or punishing) stimulus, motivational salience refers to the extent to which a stimulus captures an individual's attention and drives their goal-directed behaviour, for example, the amount of effort they will expend, and/or the degree of risk they will accept, in order to attain or avoid a given outcome (Puglisi-Allegra & Ventura, 2012). Although the intensity of received rewards, an indication of reward value, has been shown to correlate with VS activity (Blood & Zatorre, 2001; Izuma, Saito, & Sadato, 2008; Smith & Hayden, 2010), reward value is intrinsically correlated with prediction error (a learning signal indicating the difference between received and expected rewards; Schultz, 2016). Studies with adult samples that have attempted to explicitly disentangle the correlation of VS activity with reward value and prediction error suggest a stronger association with the latter (Hare et al., 2008; Rohe, Weber, & Fliessbach, 2012). Furthermore, the VS has also been shown to be involved in the computation of negative prediction errors (Delgado et al., 2008), and thus it has been proposed that the VS is implicated in the prediction error coding of salient stimuli, regardless of the stimulus type or valence (Metereau & Dreher, 2013). As a result, it can be challenging to draw definitive conclusions regarding precisely which aspects of reward processing develop during adolescence from traditional behavioural or neuroimaging studies, and how this relates to changes in learning and decision-making (see also **Section 1.5.4**).

The computational framework of reinforcement learning (RL; Daw, 2014; Rangel, Camerer, & Montague, 2008) can be used to investigate developmental changes in the different component processes involved in value-based decision-making during adolescence. Rather

than examining *where* changes are occurring in the brain, computational models allow the investigation of *how* the computations performed by the brain may change during development. RL refers to the ability to learn to improve one's future choices in order to maximise the expected value. The simplest RL algorithm (Q-learning) learns action-outcome associations on a trial and error basis, by directly tracking the prediction errors (Rescorla & Wagner, 1972; Watkins & Dayan, 1992). Differences in RL strategies may in turn contribute to an explanation of features of adolescent value-directed behaviour. In **Chapter 4**, I investigate the development of the computational strategies involved in the ability to learn from both rewards and punishment, and the ability to learn from counterfactual feedback, complex aspects of motivational processing requiring the integration of multiple neurocognitive systems.

Computational neuroimaging studies of adolescent value-based decision-making have provided some evidence that simultaneous developmental changes of both reduced sensitivity to negative feedback, and increased sensitivity to reward in adolescence may contribute to observed adolescent peaks in reward-approach behaviour (Humphreys et al., 2015). Cohen et al. (2010) found heightened VS activation in association with positive prediction errors in adolescence, which only emerged in the mid- to late-adolescent group (14-17 years), and while younger participants have shown stronger VS-medial PFC connectivity after negative feedback, with age this has been shown to shift toward stronger connectivity after positive feedback (van den Bos, Cohen, et al., 2012). There is also evidence for increased engagement of frontal-parietal areas to negative feedback with age (Crone, Zanolie, Van Leijenhorst, Westenberg, & Rombouts, 2008; van Duijvenvoorde, Zanolie, Rombouts, Raijmakers, & Crone, 2008), which have been interpreted as suggesting cognitive control regions may be involved in adolescent changes in response to both negative and positive feedback.

Another computational study showed that following positive outcomes on a probabilistic reward learning paradigm, there was increased connectivity between the striatum and the medial PFC with age during adolescence (8-22 years; van den Bos, Cohen, et al., 2012), suggesting that signals from the VS may recruit cognitive control systems, which drive subsequent behavioural adjustments. These results have been interpreted as suggesting that heightened reward sensitivity in adolescence may result in an enhanced ability to flexibly up-regulate cognitive control, possibly indicating a modulatory relationship between striatal regions and frontal regions supporting inhibitory control. This explanation is consistent with experimental studies comparing adolescents and adults, showing that when successful inhibitory control was rewarded (monetary incentive), relative to non-rewarded (neutral) trials, adolescents displayed faster inhibitory responses, made fewer inhibitory errors, and showed increased VS activation (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011), in addition to heightened frontal activity during response preparation (Geier et al., 2010). The fact that reward appears to enhance some aspects of cognitive control in adolescence to a greater extent than in adulthood (Geier & Luna, 2009, 2012; Geier et al., 2010; Jazbec et al., 2006; Padmanabhan et al., 2011) and childhood (Padmanabhan et al., 2011) is indicative of the complex relationship between motivational processing and cognitive control, and its development during adolescence.

1.3.5 Limitations of dual systems models

While dual systems models (Casey et al., 2008; Somerville, Jones, & Casey, 2010; Steinberg, 2008, 2010; see **Section 1.3.1**) have been instrumental in increasing our understanding of adolescent neurocognitive development, and have given rise to a large number of behavioural and neuroimaging studies of the development of affective-motivational and regulatory processes during adolescence (as reviewed above), they are not without limitations. Crone and Dahl (2012) argue that developmental neuroimaging studies do not support a simple model of

frontal cortical immaturity as an explanation of adolescent behaviour and cognition. Indeed, based on a results from a meta-analysis, they suggest that the degree of variability in fMRI studies of cognitive control is difficult to reconcile with such a model (Luna et al., 2010). One factor that almost certainly contributes to this degree of variability is the fact that much of the experimental support for dual systems models is derived from cross-sectional data, and is focused on characterising group averages, rather than investigating the relationship between brain development and behaviour at the individual level (discussed further in **Section 1.6**). A longitudinal study by Mills et al. (2014) attempted to address this by examining the relative structural development of the PFC, amygdala and nucleus accumbens (a region of the VS) at both the level of group averages and at an individual level. While the majority of individuals studied did show earlier maturation (defined as the stabilisation of grey matter volume) of the amygdala and/or nucleus accumbens than the PFC, in line with the dual systems hypothesis, at the individual level there was wide variation in the developmental trajectories of all three regions, with some participants showing great differences in the maturity rates between regions, and others showing no differences (see **Figure 1.4**). The authors also investigated whether the degree of difference in maturation rates between prefrontal and limbic regions for each individual was associated with their level of self-reported risk-taking during adolescence, but found no evidence for such a relationship (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014).

Several research groups have argued instead for a more nuanced understanding of the interactions between cognitive, motivational-affective and social processing in understanding how these systems develop, and how this relates to adolescent behaviour (Casey, Galván, & Somerville, 2016; Crone & Dahl, 2012; Nelson & Guyer, 2011; Nelson, Jarcho, & Guyer, 2016; Pfeifer & Allen, 2012, 2015; Schriber & Guyer, 2015; van den Bos & Eppinger, 2015). Crone and Dahl (2012) propose that adolescents show flexibility in PFC recruitment and cognitive control that is particularly sensitive to social and affective context. Cognitive control is hypothesised to

be less automatic during adolescence, giving rise to greater variation in performance, but also to more creative and adaptive responses. This flexibility is conceptualised as both advantageous in learning to navigate the complex and rapidly changing social challenges of adolescence, and as having the potential to confer risks and vulnerabilities in the face of individual risk factors and risky environments. A more nuanced approach is also consistent with the Social Information Processing model of adolescent development (Nelson, Leibenluft, McClure, & Pine, 2005), which proposes that hormonally induced changes to socio-affective systems result in increased salience of social contexts in adolescence.

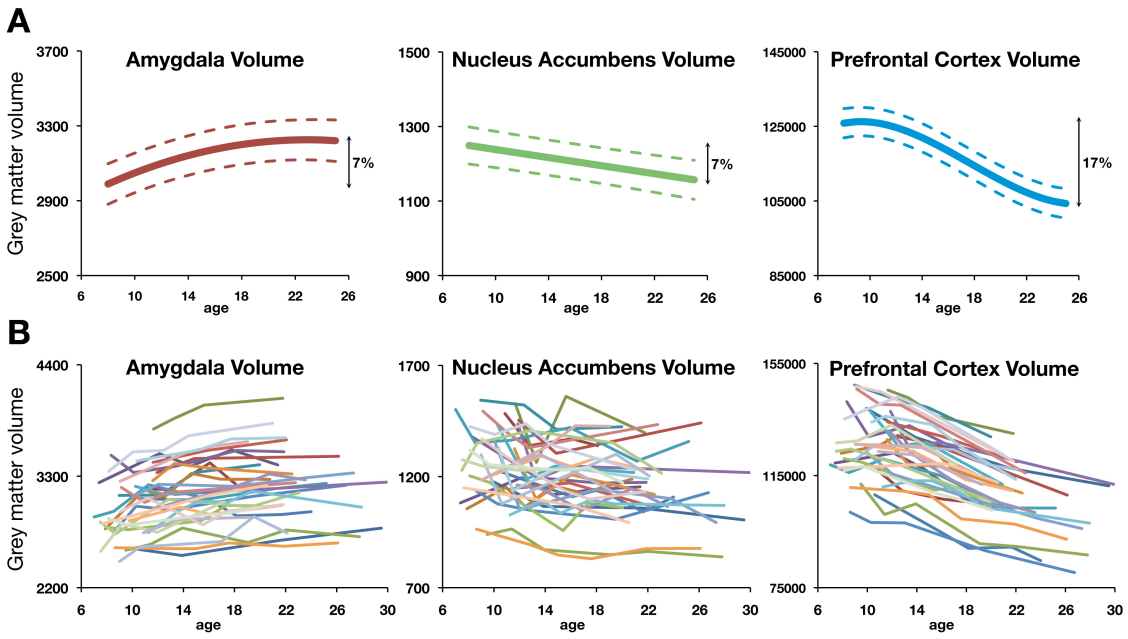

Figure 1.4. Average (A) and individual (B) developmental trajectories of amygdala, nucleus accumbens and PFC grey matter volumes. A. The best-fitting group models for average developmental trajectories of grey matter volume in the amygdala, nucleus accumbens and PFC across 33 participants, each scanned at least three times between ages 7-30 years. late childhood and early adulthood; dashed lines indicate 95% confidence intervals. **B.** The raw values for each individual are plotted together for comparison. In both panels, the X-axis shows age in years and the Y-axis shows grey matter volume (mm^3). Reproduced from Mills, Goddings, et al. (2014), with permission from S Karger AG.

Furthermore, developmental changes in regulatory and affective-motivational processes, and the neural systems which support them, occur in the context of important and protracted developments in social cognition and the social brain. An adolescent's social world is often unstable and changeable, for example it is only later in adolescence that friendships become more stable and characterised by reciprocity (Burnett Heyes et al., 2015). Self-reported friendship quality predicts mental health resilience and well-being in young people (14-24 years; Van Harmelen et al., 2017), highlighting the importance of social functioning in this period of development. Many of the decisions adolescents make are taken in social contexts and it has been proposed that the risk of social rejection may be weighted more strongly by adolescents than other risks and therefore that engaging in risk-taking behaviour may sometimes be seen as the rational choice (Blakemore, 2018; Blakemore & Mills, 2014). Dual systems models have yet to explicitly incorporate developments in social cognition and the social brain, or the way in which the development of neural systems involved in cognitive control, motivational-affective processing and social cognition during adolescence mutually influence each other within complex and dynamic social contexts.

1.4 Social cognition and the social brain in adolescence

Many social changes occur during adolescence. These include the fact that, compared with children, adolescents form more complex and hierarchical peer relationships and are more sensitive to acceptance and rejection by their peers (Brown, 2004; Steinberg & Morris, 2001). Although the factors that underlie these social changes are likely to be multi-faceted, one possible contributing factor is the development of the 'social brain', a network of brain areas involved in social perception and cognition (Adolphs, 2009; Frith, 2007). Regions within the social brain network include the posterior superior temporal sulcus (pSTS), temporoparietal junction (TPJ), dorsomedial PFC (dmPFC; medial aspects of Brodmann area 10), anterior temporal cortex (ATC), and the IFG (Frith and Frith, 2007; Van Overwalle, 2009; **Figure 1.5**; see

Kilford, Garrett, & Blakemore, 2016 for a more in-depth review of the contributions of different regions to different aspects of social cognition).

In this section I describe how social cognition and the structure and function of the social brain network continue to develop in adolescence.

1.4.1 Social cognition and the social brain

Social cognition refers to the ability to make sense of the world through processing signals generated by other members of the same species (Blakemore & Mills, 2014; Frith, 2007) and encompasses a wide range of cognitive processes that enable individuals to understand and interact with one another (Adolphs, 1999; Frith & Frith, 2007). These include social perceptual processes such as face processing (Farroni et al., 2005), biological motion detection (Pelphrey & Carter, 2008), and joint attention (Carpenter, Nagell, Tomasello, Butterworth, & Moore, 1998), in addition to more complex social cognitive processes involving inference and reasoning, such as mentalising - the process of mental state attribution. Such social cognitive processes enable us to understand and predict the mental states, intentions and actions of others, and to modify our own accordingly (Frith & Frith, 2007). Social cognition thus plays a critical role in the successful negotiation of complex social interactions and decisions (Crone, 2013).

1.4.2 Structural development of the social brain

Areas within the social brain network are among the regions that undergo the most protracted development in humans (Barnea-Goraly et al., 2005; Giedd et al., 1999; Gogtay et al., 2004; Shaw et al., 2008; Sowell et al., 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999), showing changes throughout adolescence before relatively stabilizing in the early to mid-twenties. Mills, Lalonde, et al. (2014) examined the structural developmental trajectories (grey matter volume, cortical thickness and surface area) of brain areas associated with mentalising. In a sample of 288 individuals with at least two brain scans between the ages of 7 and 30

years, they found that grey matter volume and cortical thickness decreased in medial Brodmann area 10 (dmPFC), TPJ, and pSTS from childhood into the early twenties. In contrast, the ATC increased in grey matter volume until early adolescence (around 12 years), decreasing thereafter, whereas cortical thickness increased until early adulthood (around 19 years). Surface area in all four regions followed a cubic trajectory, reaching a peak in late childhood or early adolescence, before decreasing into the early twenties (Mills, Lalonde, et al., 2014; **Figure 1.6**).

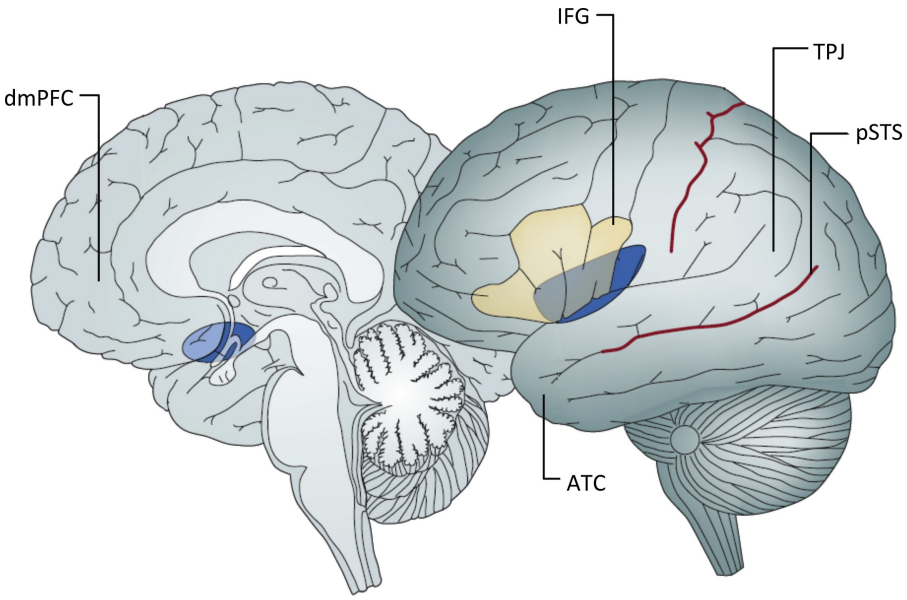

Figure 1.5. The social brain. Regions of the social brain network: areas of the brain that may be sensitive to social cognitive processes necessary to navigate the adolescent social environment. Regions that are involved in social cognition include the dmPFC and TPJ, which are involved in thinking about mental states; the posterior superior temporal sulcus pSTS, which is involved in observing faces and biological motion; the ATC, which is involved in applying social knowledge; and the IFG, which is involved in understanding the actions and emotions of others. Adapted from Blakemore (2008), with permission from Springer Nature.

1.4.3 Development of social cognition and social brain function

While certain social cognitive processes are present from an early age (see Baillargeon et al., 2010). behavioural and neuroimaging studies have shown developments in a number of more complex social cognitive abilities, and functional changes in associated brain networks across adolescence.

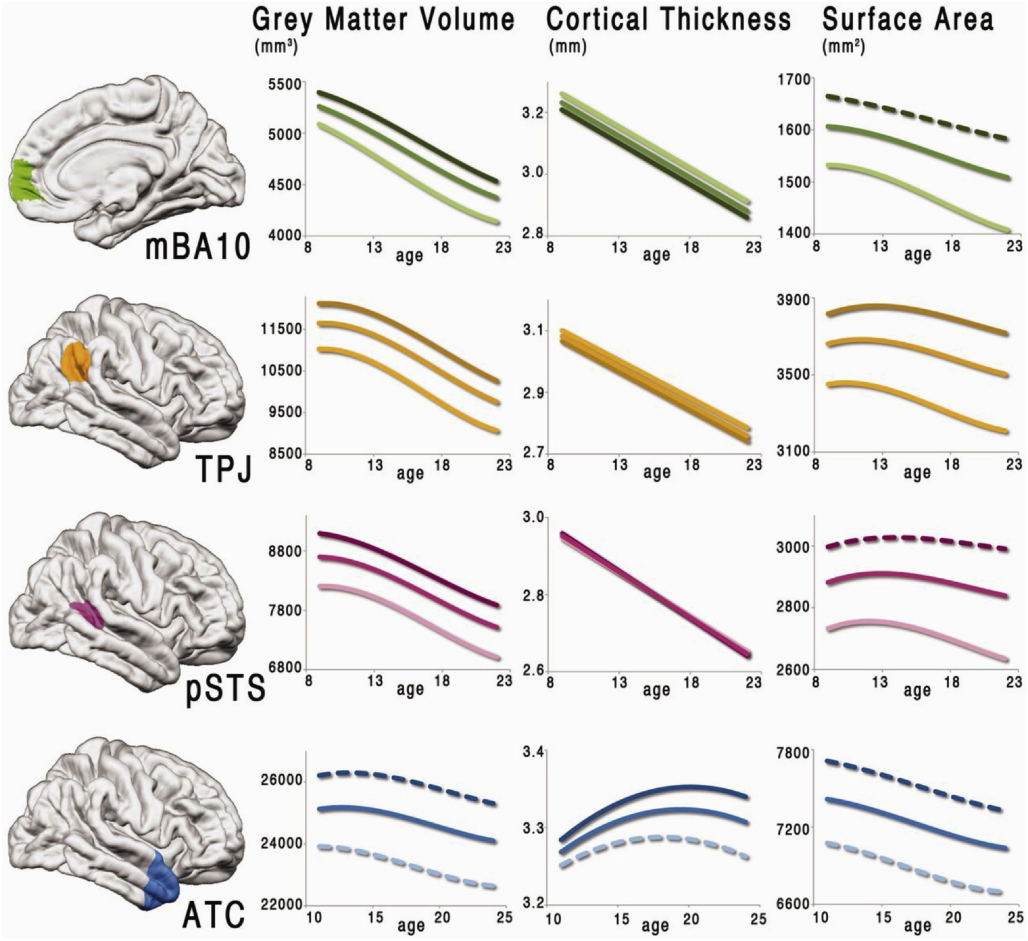

Figure 1.6. Structural development of the social brain. Structural developmental trajectories of brain areas associated with mentalising across adolescence (grey matter volume, cortical thickness, surface area). The best fitting models for all participants are shown for each region of interest (combined hemispheres). Models are fitted to the middle 80% of the sample (ages 9-22 years for medial Brodmann area 10 (dmPFC), TPJ and pSTS; ages 11-24 years for ATC). The lighter lines show the fitted models applied to females only, and the darker lines show the fitted models applied to males only. Solid lines indicate the fitted model was significant (p < .05), whereas dashed lines indicate the fitted model was not significant ($p \geq .05$). Reproduced from Mills, Lalonde, et al. (2014), with permission from Oxford University Press.

1.4.3.1 Mentalising

Mentalising describes the ability to make attributions about the mental states of others, including their beliefs, thoughts, desires, intentions and feelings. There is a rich literature on the development of mentalising in childhood, pointing to changes in the ability to understand others' mental states during the first five years of life (Frith & Frith, 2007). While certain aspects of mentalising are present in infancy (Baillargeon et al., 2010), it is not until around the age of four years that children begin to explicitly understand that someone else can hold a belief that differs from their own, and which can be false (Barresi & Moore, 1996). Until fairly recently, there was a shortage of studies looking into mentalising after childhood, as it was generally assumed that these abilities were already mature by mid-childhood in typically developing children. However, adolescence is marked by substantial changes in social competence and social behaviour, as well as structural development within the social brain (Mills, Lalonde, et al., 2014). These changes may be paralleled by changes in the neural processing of mentalising.

Neuroimaging studies of mentalising have consistently found associations with activity within the dmPFC, TPJ, pSTS, and ATC (**Figure 1.5**), suggesting these regions are key to the process of mental state attribution. A number of developmental fMRI studies of mentalising report decreases in dmPFC recruitment between adolescence and adulthood (reviewed in Blakemore, 2008). These studies have used a variety of tasks that require mental state attribution, such as understanding irony (Wang, Lee, Sigman, & Dapretto, 2006), thinking about social emotions such as guilt (Burnett, Bird, Moll, Frith, & Blakemore, 2009), understanding intentions (Blakemore, den Ouden, Choudhury, & Frith, 2007), thinking about the preferences and dispositions of oneself or a fictitious story character (Pfeifer et al., 2009) and making attributions about the emotional states of others (Gunther Moor et al., 2012; Overgaauw, Van Duijvenvoorde, Moor, & Crone, 2015). An example of such a task is the Reading the Mind in

the Eyes Test (RMET; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Baron-Cohen, Wheelwright, Spong, Scahill, & Lawson, 2001), which assesses the ability to perceive, categorise and make attributions about other people's mental and affective states, based only on photographs of their eyes. Gunther Moor et al. (2012) used fMRI to compare brain activation while performing the RMET between early adolescents (10-12 years), mid adolescents (14-16 years) and young adults (19-23 years), relative to a control condition (age and gender categorisations of the same stimuli). Whereas participants of all ages showed increased activation in the pSTS during the task, participants in the youngest group exhibited additional engagement of the dmPFC (Gunther Moor et al., 2012). A follow-up study in which the same participants were re-tested two years later indicated that these cross-sectional differences reflected longitudinal changes within individuals. Specifically, dmPFC activation during the RMET followed a quadratic developmental trajectory, being lowest during mid-adolescence (Overgaauw et al., 2015).

In some studies, higher activity in more posterior regions of the social brain, such as the pSTS/TPJ (Blakemore et al., 2007), and in the ATC (Burnett et al., 2009), was observed in adults as compared to adolescents. There is also evidence for developmental differences in functional connectivity between dmPFC and other parts of the social brain network, such as the pSTS, ATC and TPJ (Burnett & Blakemore, 2009).

Why younger adolescents recruit the dmPFC more than adults in social cognitive tasks is still an empirical question. It has been suggested that the decrease in recruitment of the dmPFC across adolescence may relate to changes in neuroanatomy or maturing neurocognitive strategies (Blakemore, 2008). It has been hypothesised that developmental changes in brain function may reflect—and/or contribute to—changes in brain structure (Cohen Kadosh, Cohen Kadosh, Dick, & Johnson, 2011; Crone & Richard Ridderinkhof, 2011; Scherf, Behrmann, & Dahl, 2012). However, the relationship between structural and functional changes is currently

not well understood as few studies have directly compared structural and functional data within the same individuals (Cohen Kadosh, Johnson, Dick, Cohen Kadosh, & Blakemore, 2013; Dumontheil, Hassan, Gilbert, & Blakemore, 2010; Lu et al., 2009; Olesen, Nagy, Westerberg, & Klingberg, 2003; van den Bos, Crone, & Güroğlu, 2012). These studies have yielded mixed results, suggesting that age-related changes in blood oxygen level dependent signal do not entirely reflect structural maturation, and may instead reflect the maturation of neurocognitive strategies, such as an increased recruitment of cognitive control systems between adolescence and adulthood during social interactions (Dumontheil, Hillebrandt, Apperly, & Blakemore, 2012; Mills, Dumontheil, Speekenbrink, & Blakemore, 2015; van den Bos, van Dijk, Westenberg, Rombouts, & Crone, 2011; discussed further in **Sections 1.4.3.2** and **1.4.3.3**).

1.4.3.2 Perspective-taking

The ability to take another person's point of view into account, i.e. perspective-taking, is an important determinant of successful social functioning in everyday life (Fett et al., 2011). Fundamental aspects of perspective-taking develop during childhood (Barresi & Moore, 1996; Leslie, 1987; Perner & Davies, 1991). However, the ability to use these social competencies online continues to develop throughout adolescence.

The Director task has been used to investigate the ability to use perspective-taking to guide decisions in a referential communicative context (Apperly, Back, Samson, & France, 2008; Brown-Schmidt & Hanna, 2011; Fett, Shergill, et al., 2014; Keysar, Barr, Balin, & Brauner, 2000; Keysar, Lin, & Barr, 2003). Participants are instructed to move objects around a set of shelves by a director, who cannot see some of the objects that the participant can see (**Figure 1.7;** Apperly et al., 2010; Dumontheil, Apperly, & Blakemore, 2010). Correct interpretation of the instructions requires participants to use the director's perspective and only move objects that the director can see.

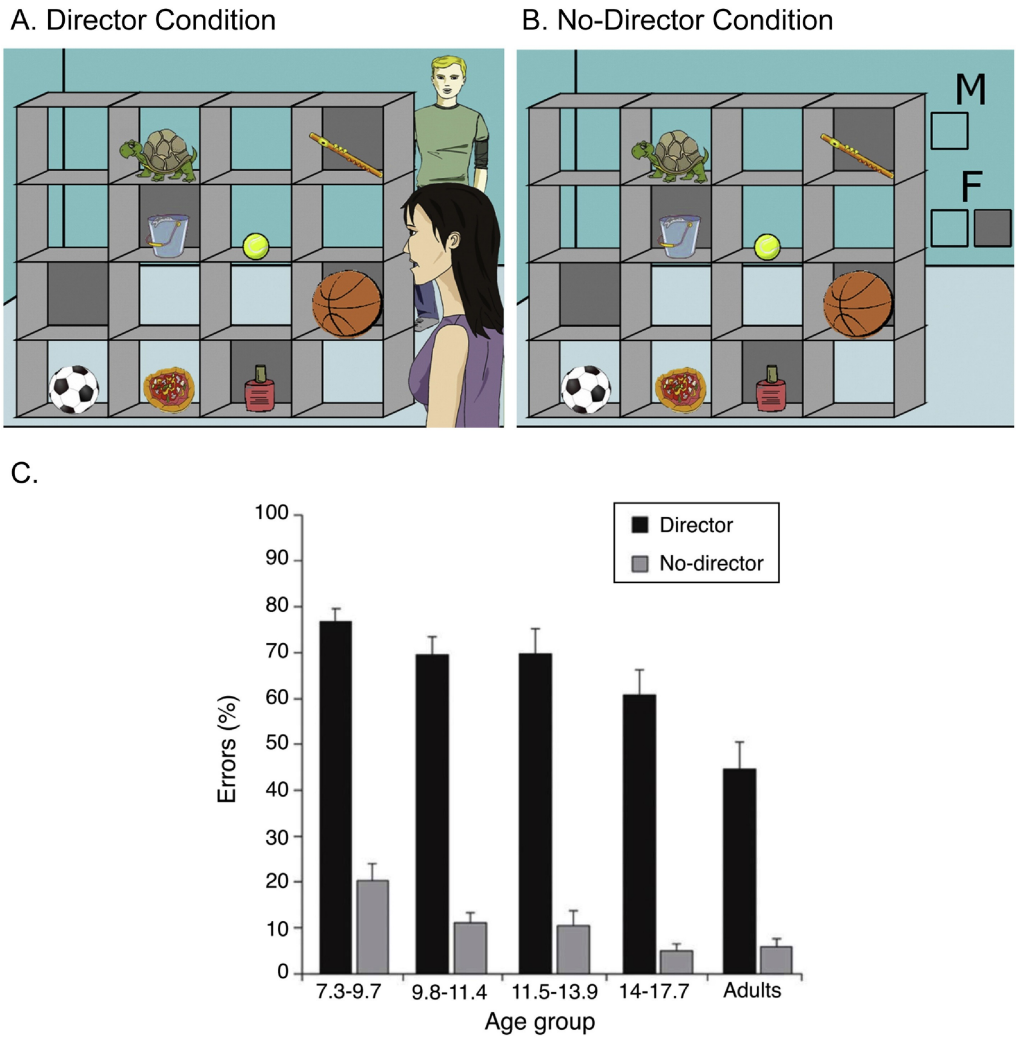

Figure 1.7. The Director task. Example stimuli from the Director task, including a social (**A:** Director) and non-social control condition (**B:** No-Director). In this example, in both conditions participants hear the instruction: 'Move the large ball up' in either a male or a female voice. In both examples, if the voice is female, the correct object to move would be the basketball, because in the Director Present condition **(A)** the female director is standing in front of the shelves and can see all the objects, and in the Director Absent condition **(B)**, the two boxes below the 'F' (for '[female') indicate that all objects can be moved by the participant. If the voice is male, the correct object to move would be the football, because in the Director condition **(A)** the male director is standing behind the shelves and therefore cannot see the larger basketball in the occluded slot, whereas in the No-Director condition **(B)** the single clear box below the 'M' (for 'male') indicates that only objects in open shelves can be moved/that no objects in front of a grey background can be moved. **C.** Adolescents (14-17 years) make more errors than adults in the Director condition, whereas in the No-Director condition no difference is found between these age groups. Adapted from Dumontheil et al. (2012), with permission from John Wiley and Sons, and Dumontheil, Küster, Apperly, & Blakemore (2010), with permission from MIT Press.

Adult participants frequently make errors in this task, suggesting that, despite possessing the ability to use mentalising to understand that the director's perspective differs from their own, they often fail to use this information to guide decisions (Keysar et al., 2000, 2003).

In a sample of participants aged 7 to 27 years, Dumontheil, Apperly, et al. (2010) used a computerised adaptation of the Director task. To differentiate between the general impact of cognitive control demands on task performance and effects that specifically impact the social components of the task, a control condition was included. In this condition the director was absent and participants had to use a non-social rule to guide their decisions while following the (otherwise) identical instructions to the director condition. Although accuracy improved until mid-adolescence (14-17 years) in both conditions, accuracy in the director condition continued to improve after mid-adolescence. Similar findings were also observed in a more recent study (Symeonidou, Dumontheil, Chow, & Breheny, 2015). These findings suggest that the ability to use another's perspective to guide decisions continues to develop in late adolescence, over and above developmental improvements in more general cognitive control processes recruited by both conditions.

However, the improved integration of social cognition and cognitive control systems in adolescence may also contribute to developmental advances in perspective-taking (Dumontheil, Apperly, et al., 2010). Using a variant of the Director task adapted for fMRI (Apperly et al., 2010; Dumontheil, Apperly, et al., 2010), in which the cognitive demands of the task were also manipulated, Dumontheil et al. (2012) demonstrated developmental differences in brain areas associated with both social cognitive and more domain-general cognitive control processes. In both social and non-social conditions, adults recruited fronto-parietal regions associated with cognitive control more than adolescents. When social cues were needed to accurately perform the task both adults and adolescents (11 to 16 years) recruited the dmPFC, however, adolescents also recruited the dmPFC when social cues were

not needed. The authors suggest that this engagement of the dmPFC for irrelevant social stimuli may reflect the use of social brain regions even when they are not necessary, consistent with a pattern of increasing specialisation within networks supporting social cognition.

Developmental improvements in cognitive control likely influence, and are influenced by, developments in social cognitive processing during adolescence. For example, although attending to social cues is largely automatic (Spunt & Lieberman, 2013), taking another person's perspective when it differs from one's own requires the inhibition of our own, egocentric perspective (Surtees & Apperly, 2012), an effortful process that requires cognitive control resources. A behavioural study demonstrated that when under high cognitive load (simultaneously remembering three 2-digit numbers), adults and adolescents were slower at taking another person's perspective in the Director task than when under low cognitive load (remembering one 3-digit number), suggesting that taking another's perspective is cognitively demanding (Mills et al., 2015). Although when under high cognitive load both age groups were less accurate (defined on a trial-by-trial basis as both correctly performing the Director task and remembering the number(s)), multi-tasking accuracy was more greatly impaired in adolescents (11-17 years) than adults (22-30 years). Further evidence for the role of more general cognitive control resources in perspective-taking comes from a developmental study (9-29 years) that found individual differences in inhibitory control ability, measured using a go/no-go task, partly accounted for errors on the director task over and above age-related variance (Symeonidou et al., 2015).

1.4.3.3 Social decision-making

Another line of research into the dynamic and interactive aspects of social cognition has employed tasks from the field of behavioural economics to simulate more complex aspects of social exchanges (Belli, Rogers, & Lau, 2012; Evans & Krueger, 2011; van den Bos et al., 2011;

van den Bos, Westenberg, van Dijk, & Crone, 2010). These paradigms can be used to study the development of social preferences for fairness, trustworthiness, or cooperation, and the cognitive and neural mechanisms that underlie social decision-making.

Even though a basic sense of fairness in bargaining is observed in young children (Fehr, Bernhard, & Rockenbach, 2008; Güroğlu, van den Bos, & Crone, 2009), the understanding of intentionality in social interactions develops gradually over the course of adolescence and early adulthood (Güroğlu et al., 2009; van den Bos et al., 2010). Age-related changes in social behaviour beyond childhood, such as increases in trust and reciprocity during social interactions (Belli et al., 2012; Fett, Gromann, Giampietro, Shergill, & Krabbendam, 2014; van den Bos et al., 2010), may be associated with the increasing tendency to consider others' viewpoints and intentions. Indeed, compared to adults, children and adolescents are less effective in analysing the intentionality of partners' behaviour and mental states during social interaction (Güroğlu et al., 2009; Sutter, 2007).

In an fMRI study, young adolescents (12-14 years), older adolescents (15-17 years), and young adults (18-22 years) played the role of the second player in the Trust Game (van den Bos et al., 2011). An anonymous first player would give them an amount of money as an investment, which the participant could either divide equally between themselves and the investor, or keep the majority for themselves. Participants' tendency to take the perspective of the first player into account was investigated by examining their sensitivity to the degree of risk (i.e. the amount of money that could be lost) taken by the investor. Whereas older adolescents and young adults were more likely to reciprocate when the investor risked losing larger amounts of money by trusting them, the younger adolescents did not differentiate. These findings suggest that adolescence is not necessarily characterised by general increases in prosocial behaviour, but an increase in sensitivity to the perspective of others.

These forms of perspective-taking behaviour were associated with increased involvement of the left TPJ and the right dorsolateral PFC (dlPFC), which the authors suggest indicates a role for both social cognitive and cognitive control systems in the development of social behaviour in adolescence. When participants observed that the first player trusted them, recruitment of the left TPJ increased with age, and this level of activation correlated with participants' sensitivity to the first player. Participants also showed increased engagement of the right dlPFC with age when receiving trust, which the authors speculate may indicate a regulatory role of right dlPFC in social exchange, for example, in the inhibition of more egocentric behaviour, although the precise psychological mechanisms cannot be ascertained from neural activity patterns (van den Bos et al., 2011).

Fett et al. (2014) investigated the relationship between perspective-taking and social processes such as trust and reciprocity in adolescence, using two variants of the Trust Game and the Director task. Adolescents (13-18 years) with a higher perspective-taking tendency (measured as accuracy on the Director task) demonstrated greater trust towards others (initial investment in the Trust Game) and higher levels of trust during co-operative interactions (higher investments). While all adolescents modified their behaviour in response to unfair interactions (decreased investments and more malevolent reciprocity) when they were treated unfairly, high perspective-takers did so more drastically, suggesting a greater decrease in trust. The authors propose that increases in perspective-taking tendencies in adolescence are therefore associated with specific developmental changes in trust and reciprocity, as opposed to simply generalised increases in prosocial behaviour. Although this study did not include adult participants, the behavioural patterns of high perspective-takers were similar to those observed in adults in another study using this paradigm (Fett, Gromann, et al., 2014).

Behavioural findings add support to this conclusion. In a series of resource allocation games, in which the identity of the interaction partner was manipulated (friends; antagonists; neutral

classmates; anonymous peers), younger adolescents (9 and 12 years) showed similar levels of prosocial behaviour to all interaction partners (Güroğlu, van den Bos, & Crone, 2014). However, older adolescents (15 and 18 years) showed increasing differentiation in prosocial behaviour according to their relation with the partner, displaying the most prosocial behaviour (both costly and non-costly) towards friends. This suggests that with age, *who* you are interacting with becomes more important. The age-related increase in non-costly prosocial behaviour towards friends was mediated by self-reported perspective-taking skills..

Behavioural and neuroimaging studies of the development of complex aspects of social cognition such as perspective-taking (**1.4.3.2**) and social decision-making (**1.4.3.3**) suggest that developments in cognitive control and social cognition mutually influence each other. The improved integration of social cognition and cognitive control systems in adolescence may also contribute to developmental advances in other aspects of cognition that require the integration of social cognition with more domain-general cognitive control processes. Social WM, the ability to store and manipulate information about other people, has been shown to be parametrically associated with load-dependent increases in activation in both lateral fronto-parietal systems typically associated with standard, non-social WM tasks and the medial PFC (Meyer et al, 2012; Meyer et al., 2015), suggesting that a domain-general WM system and the social brain may work in parallel to support social WM. In **Chapter 2** I investigate the development of social and non-social WM, and whether this is influenced by dopaminergic genetic variation.

1.5 Interactions between social cognition, cognitive control and affective-motivational processing in adolescence

Adolescence is a time of pronounced social-cognitive and social-affective development (Crone & Dahl, 2012), in which social factors increase in salience and value (Blakemore & Mills, 2014).

While there is a growing body of work investigating the interplay between cognitive control and motivational-affective processing, less is known about the way in which these processes interact with social cognitive processes, social contexts and stimuli. I have already described (see **Sections 1.4.3.2, 1.4.3.3**) the way in which developments in cognitive control and social cognition mutually influence each other. Social interactions are also a key source of elicited motivational-affective responses: social cues can elicit robust affective responses, and those around us can be a salient source of potential rewards and punishments. Socio-affective context, such as the heightened motivational salience of peers or the affective appraisal of the value of an outcome, appears to exert a great influence on the extent to which cognitive control systems are recruited in adolescence (Christakou, 2014). This context can be external, for example, one's social context, or internal, such as one's affective state. Below I present examples of the interactions between social cognition and motivational-affective processing, in the context of several aspects of adolescent typical behaviour, namely social exclusion and peer influence, and discuss experimental studies which illustrate these interactions.

1.5.1 Social cognition and affective processing

The perception, understanding and interpretation of others' emotions is a fundamental aspect of social interaction and requires the integration of a range of perceptual, social cognitive and affective skills (Garcia & Scherf, 2015). These include basic aspects of affective processing, such as emotion perception and recognition, and more complex social cognitive processes, such as the ability to understand the affective states of others, sometimes referred to as affective mentalising.

Affective mentalising requires the integration of both social cognition and affective processing networks. Sebastian et al. (2012) examined the development of affective (understanding emotions) and cognitive mentalising (understanding thoughts, perspectives and intentions)

and their neural substrates during adolescence using cartoon vignettes. Both types of mentalising were associated with activation in social brain network regions (including dmPFC, pSTS/TPJ and ATC), however affective mentalising also elicited activation in the vmPFC, which was greater in adolescents (11-16 years) compared to adults (24-40 years). These findings extend the pattern of decreased dmPFC activation between childhood and adulthood to aspects of medial PFC more typically associated with affective processing and highlight the importance of considering the integration, overlap and interplay of multiple developing brain regions and networks when investigating the development of complex social skills and behaviours during adolescence.

1.5.2 Affective consequences of social interactions

Social affect refers to the interaction between our emotions and our behaviour in the context of communication with others. The highly salient nature of peer interactions during adolescence is believed to increase the impact of both positive and negative aspects of such interactions (Rubia et al., 2006). Social situations can evoke strong emotional responses, and there is evidence this is particularly great in adolescence.

Studies of peer rejection in adolescence, using a range of experimental paradigms, repeatedly find that peer rejection is associated with worsened mood, increased distress and increased anxiety in adolescents compared to child and adult groups, particularly in younger adolescents (reviewed in Platt et al., 2013). Similarly, Silvers et al. (2012) found that, when 11 to 23 year olds viewed socio-affective stimuli, as opposed to non-social affective stimuli, younger adolescents had greater difficulty regulating their emotions than did older adolescents and adults. Studies of the neural bases of emotional regulation in the context of social rejection have implicated prefrontal regions, notably the right ventrolateral PFC (vlPFC). Compared to adults, adolescents show reduced activation of this region during experimental manipulations of social rejection, such as the Cyberball game (Bolling et al., 2011; Masten et al., 2009;

Sebastian et al., 2011; Sebastian & Blakemore, 2011; Sebastian, Viding, Williams, & Blakemore, 2010). It has been suggested that developmental increases in vlPFC activation may be associated with increased regulation of social distress following exclusion. Consistent with this hypothesis, within adolescents, greater right vlPFC activation during exclusion has been associated with higher levels of parent-reported interpersonal competence, lower self-reported distress (Masten et al., 2009), and greater self-reported resistance to peer influence (Sebastian et al., 2011). Furthermore, Bolling et al. (2011) found age-related increases in functional connectivity between the right vlPFC and the ventral anterior cingulate cortex (ACC), an effect which was only found during social exclusion, and not during a similar task in which social expectancies were violated, but participants were not excluded (Bolling et al., 2011).

1.5.3 Social context and peer influence

Social context can impact decision-making, such as the propensity to engage in prosocial or risky behaviours. Studies of social context in adolescence have largely focused on the impact of peer influence on adolescent risk-taking behaviour. The presence of peers affects how likely adolescents are to take risks in a driving-simulation game (Gardner & Steinberg, 2005). While adolescents (13-16 years), young adults (18-22 years), and adults (24+ years) take around the same number of driving risks when alone, in the presence of their friends adolescents take significantly more risks, whereas peer presence had no impact on risk-taking in adults and an intermediate effect in young adults (Gardner & Steinberg, 2005). Adolescents are also sensitive to the presence of peers when performing other experimental tasks involving risky and reward-related decisions (O'Brien, Albert, Chein, & Steinberg, 2011; Smith, Chein, & Steinberg, 2014; Smith, Steinberg, Strang, & Chein, 2015).

Increased sensitivity to the presence of peers found in risky and reward-related decision-making appears to extend to other aspects of cognition. Using a modified version of the Iowa Gambling Task (IGT), Silva et al. (2015) demonstrated that the presence of peers had a

facilitative effect on the ability to learn from rewarding and punishing feedback in late adolescent males (18-22 years). In contrast, another study found that the presence of peers had a detrimental effect on female adolescents' performance on a high-level cognitive task (relational reasoning; Wolf, Bazargani, Kilford, Dumontheil, & Blakemore, 2015). Pairs of female friends were randomly assigned as either a participant or an observer. The participant then performed the task in three social contexts; alone, observed by their friend, or observed by an experimenter. Social context affected adolescent, but not adult, performance, an effect that was also influenced by the participants' age and task difficulty. Older adolescents (14.9-17.8 years) exhibited poorer performance when being observed by their friend relative to the experimenter, independent of task difficulty, while younger adolescents (10.6-14.2 years) only showed this effect for easier reasoning trials (Wolf et al., 2015). Together, these studies suggest that peer presence can result in both enhanced and impaired performance. Further research is needed to understand whether differences between the two studies (e.g. participant age and gender, cognitive task, task difficulty and the presence or absence of feedback) influenced the direction of the performance effects observed. However, the fact that the impact of social context on performance varied according to the identity of the observer (Wolf et al., 2015) suggests that the source of social influence is a critical factor in understanding the effects of social context in adolescence.

Social context can also modulate adolescents' attitudes toward risk (Engelmann, Moore, Capra, & Berns, 2012). A study investigated the development of social influence on risk perception from late childhood to adulthood, by asking participants to rate the riskiness of everyday situations (Knoll, Magis-Weinberg, Speekenbrink, & Blakemore, 2015; **Figure 1.8**). After recording their rating, individuals were informed about the ratings of a social-influence group (teenagers or adults) before rating each situation again. All age groups showed a significant social-influence effect, changing their risk ratings in the direction of the provided ratings, and this social-influence effect decreased with age. Most age groups adjusted their

ratings more to conform to the ratings of the adult social-influence group than to the ratings of the teenage social-influence group. Only young adolescents (aged 12-14) were more strongly influenced by the teenage social-influence group than they were by the adult social-influence group, which suggests that, to early adolescents, the opinions of other teenagers about risk matter more than the opinions of adults.

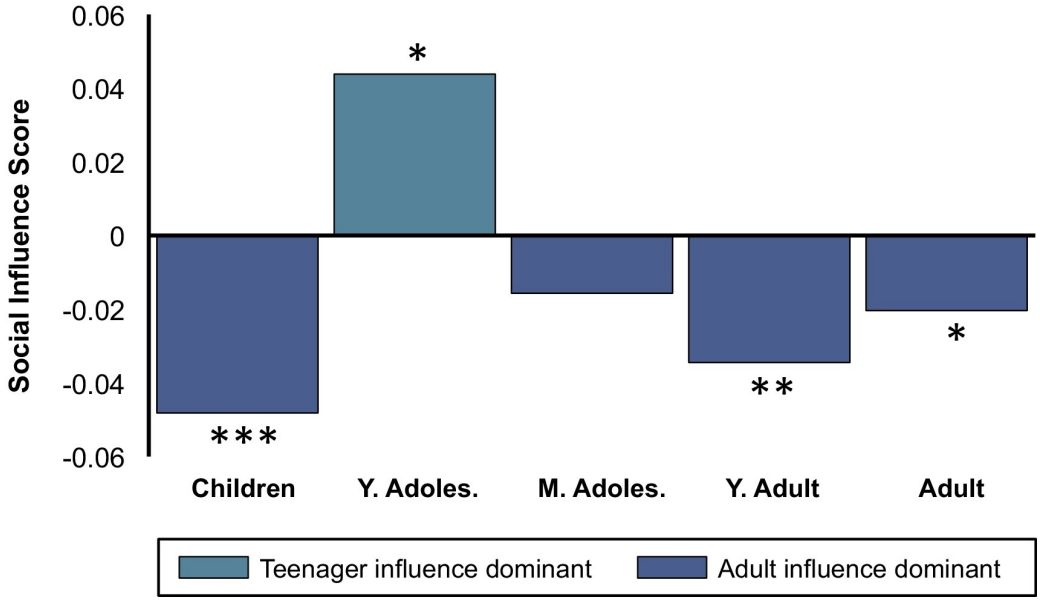

Figure 1.8. Effect of social influence on risk ratings. Participants (*N* = 563) rated the riskiness of everyday situations − before and after they were informed about the ratings of a social influence group (teenagers or adults). Social influence score, an index of conformity to other people's ratings, is shown relative to the source of the social influence for five age groups: children (aged 8-11 years), young adolescents (Y. Adoles., aged 12-14 years), mid-adolescents (M. Adoles., aged 15-18 years), young adults (Y. Adult, aged 19-25 years), and adults (aged 26-59 years). Significant difference in social influence effect between social influence groups (adults vs. teenagers) is shown for each age group. ***$p < .001$; **$p < .01$; *$p < .05$. Adapted from Fuhrmann, Knoll, & Blakemore, (2015), with permission from Elsevier; data published in Knoll et al., 2015).

Research on the mechanisms supporting social influence in adults suggests that social norms and context can influence reward and value signals (Zaki, Schirmer, & Mitchell, 2011), and it has been hypothesised that the presence of peers may be associated with alterations in brain

regions implicated in motivational-affective processing during adolescence, due to increases in the salience of peers (Nelson et al., 2016, 2005; Spear, 2010). In an fMRI version of the driving-simulation game, social context was manipulated by having the participant either play alone, or with two friends present outside of the scanner who communicated with the participant over an intercom. Compared to adolescents (14-18 years) and young adults (19-22 years), adults (24-29 years) showed greater activity in lateral PFC when making decisions in the driving game, regardless of social context. In contrast, relative to both adult groups, adolescents showed increased recruitment of the VS and lateral orbitofrontal cortex when making decisions in the presence of peers compared to when playing alone (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011).

In contrast to the presence of peers, parents can have a protective effect on risk-taking in adolescence. Telzer, Ichien, & Qu (2015) showed that adolescents (aged 14) demonstrated reduced risk-taking behaviour when their mothers were present compared with when alone. Safe decision-making was associated with greater recruitment of the vlPFC and greater functional coupling between the VS and vlPFC, while risky decision-making was associated with decreased activation in the VS. The authors propose that heightened adolescent sensitivity in neural circuitry that is associated with greater risk-taking can also be redirected toward thoughtful, more deliberative and safe decisions.

Peer influence is largely associated with negative outcomes; however peers can also have a positive influence on behaviour. A study demonstrated that prosocial feedback from peers was associated with increased prosocial behaviour in adolescents (12-16 years) compared to either no feedback, or antisocial feedback, which was associated with decreased prosocial behaviour (van Hoorn, van Dijk, Meuwese, Rieffe, & Crone, 2014). The tendency to moderate behaviour in line with the values of the people we are with likely involves both regulatory and social cognitive processes. Greater neural activity within cognitive control regions during a response

inhibition task predicted adolescents (aged 16-17) making safer decisions in the driving game, specifically when in the presence of a peer who expressed risk-averse attitudes, as compared to a risk-promoting peer (Cascio et al., 2014). The authors suggest that the ability to override risky tendencies in the presence of cautious peers may therefore be associated with individual differences in systems involved in top-down cognitive control. In a follow-up fMRI study of the influence of peers on prosocial behaviour, Van Hoorn, Van Dijk, Güroğlu, & Crone, (2016) demonstrated that the presence of peers during decision-making resulted in increased activity in several social brain regions, including the dmPFC, TPJ and pSTS, and that TPJ activity was positively associated with the degree to which peer feedback increased prosocial behaviour. These findings may suggest that individual differences in social cognitive processes, such as perspective-taking, result in variation in the influence of peers on prosocial behaviour.

In everyday life, the attitudes and values of those around us are not always explicitly expressed but must instead be inferred using social cognitive processes. Studies investigating the relationship between risk-taking and social exclusion in adolescence suggest that in addition to cognitive control processes, social cognition processes may also be uniquely implicated in adolescents' vulnerability to peer influence on risk-taking. Falk et al. (2014) used the Cyberball game (Williams, Cheung, & Choi, 2000) to examine whether neural activation during simulated social exclusion predicted peer influence on risky decisions in the driving-game one week later in 16 to 17 year-olds. Activity in the social brain network (dmPFC, right TPJ) during social exclusion was positively associated with increased risk-taking when playing the game in the presence of a peer, relative to alone. In a further study by Peake, Dishion, Stormshak, Moore, & Pfeifer (2013), adolescent participants (14-17 years) completed the driving-game, while in the implied presence of two online peers, before and after being socially excluded by these peers. Exclusion was associated with greater behavioural risk-taking among adolescents with low self-reported resistance to peer influence. When making risky decisions after social exclusion, adolescents who had lower RPI exhibited higher levels of activity in right TPJ, and

this response was a significant mediator of the relationship between RPI and greater risk-taking after social exclusion. Lower RPI was also associated with lower levels of activity in lateral PFC during crashes following social exclusion, but this did not mediate the relationship between RPI and greater risk-taking after social exclusion.

Adolescence is a period of life characterised by increased self-awareness and the emergence of a socially integrated self-identity (Meeus, 2011; Sebastian, Burnett, & Blakemore, 2008). It has been proposed that increased awareness of others' perspectives during adolescence might also be related to the 'imaginary audience'. This term describes the phenomenon whereby adolescents believe that others are constantly observing and evaluating them (Elkind, 1967), even if this is not actually the case. The New Look Theory (Lapsley, 1991, 1993) suggests that the phenomenon may result from a combination of two processes. First, adolescents need to develop their own identity as separate from their parents (separation-individuation). As they begin to question who they are and how they fit in, they may become increasingly self-conscious, leading to the imaginary audience. Second, the development of social perspective taking results in adolescents becoming increasingly aware that others have the capacity to evaluate them. This may subsequently lead them to overestimate the extent to which this actually occurs (Lapsley & Murphy, 1985). It should be noted that more recent studies suggest that the imaginary audience peaks in adolescence but persists into young adulthood, and that even older adults exhibit some phenomena associated with it (Frankenberger, 2000).

Psychology and intervention research highlights the importance of reducing situations in which high-risk behaviours such as gang affiliation and criminal behaviour are rewarded through positive peer feedback (Dishion & Tipsord, 2011). However, social context can also have positive effects on behaviour, such as learning, mental reasoning and engaging in prosocial behaviour (Foulkes et al., 2018).

1.5.4 Social reward processing

Social stimuli are typically pleasurable and rewarding, whether they are simple (e.g. viewing a static picture of a smiling face) or complex (e.g. sharing with a friend, or being liked by others). Reward processing and sensitivity undergoes marked changes in adolescence (see **Section 1.3.4**; see Braams, van Leijenhorst, & Crone, 2014; van Duijvenvoorde, Peters, Braams, & Crone, 2016 for more in-depth reviews). It has been proposed that the heightened effects of social influence in adolescence (reviewed in **Section 1.5.3**) might be due to an increase in the value of socially rewarding stimuli during this period (reviewed in Foulkes & Blakemore, 2016). Research with rodents suggests that social interactions may be more rewarding for adolescent animals compared to adults, with adolescent rats showing a greater preference for social over non-social rewards (Yates, Beckmann, Meyer, & Bardo, 2013), and a more sustained dopaminergic release in response to social interactions (D. L. Robinson, Zitzman, Smith, & Spear, 2011). In humans, behavioural studies indicate that socially rewarding stimuli are more distracting for adolescents (12-14 years) than adults (18-29 years; Cromheeke & Mueller, 2015). However, due to a lack of research investigating social reward processing in pre-adolescence in both rodents and humans, it is not currently possible to conclude that social reward value peaks in adolescence, merely that it may be lower in adulthood. It is also currently difficult to draw conclusions as to whether age differences are due to a general increase in the salience of social stimuli during adolescence (Garcia & Scherf, 2015), or a specific alteration in the hedonic value of social rewards during adolescence.

Imaging studies examining adolescents' neural responses to social stimuli (e.g. happy face stimuli or the presence of peers), have indeed found evidence of heightened activity in brain regions associated with reward processing (e.g. the VS, Chein et al., 2011; Somerville et al., 2011). However, there is also evidence of activation of these regions in response to negatively valenced social stimuli (Dreyfuss et al., 2014; Pfeifer et al., 2011), and that adolescents show

greater sensitivity to social punishment, i.e. peer exclusion (see **Section 1.5.2**). Evidence from the adult literature suggests that the VS is implicated in the signalling of salient information, regardless of valence, and not simply a signal of reward value (Levita et al., 2009). Similarly, the amygdala also shows activation during the anticipation of both positive and negative social feedback (Kohls et al., 2013). Since few behavioural or imaging studies have assessed the subjective value of socially rewarding or punishing stimuli, it is not possible to conclude from differences in neural activation alone that adolescents are more sensitive to this information, as this would merely be reverse inference (Poldrack, 2006).

A related question is to what extent increases in the salience of social information arise from domain-general alterations in sensitivity to motivational-affective stimuli (reviewed in **Sections 1.5.3**, **1.5.4**), or are specific to the social domain. In order to draw conclusions as to whether elevated sensitivity to social rewards occurs during adolescence, and how this may influence adolescent behaviour such as sensitivity to social influence, further research is needed in which social rewards are contrasted with non-social rewards, and the subjective value of these rewards is assessed. In a behavioural study described in **Chapter 5**, I investigate the development of social reward during adolescence using a experimental task assessing both social and non-social reward processing and a questionnaire assessment of social reward sensitivity.

1.6 Individual differences in adolescent development

The successful transition to adulthood requires the rapid refinement of socio-affective and regulatory abilities, social cognition, decision-making and planning in complex social contexts (Nelson et al., 2016, 2005). Many adolescent-typical social behaviours, such as peer influence and sensitivity to social exclusion, involve the co-ordination of social cognition, motivational-affective processes and cognitive control, and the neural systems that support them. The

majority of studies (including those reviewed above) have focused on characterising the development of these systems at the level of average changes during adolescence, which has been an essential step in furthering our understanding of typical trajectories of neurocognitive development during human adolescence. However, adolescence varies greatly between individuals, and while all of these systems described above show profound development during adolescence, the precise timings and trajectories of structural and functional brain development, and how this relates to behaviour, show substantial variation between individuals (reviewed in Foulkes & Blakemore, 2018; Mills, Goddings, Clasen, Giedd, & Blakemore, 2014; see **Figure 1.4**).

A variety of factors influence brain development during adolescence, including biological factors such as pubertal stage, sex, nutrition and genetic variation, and socio-cultural factors such as socio-economic status, culture and peer environment (reviewed in Foulkes & Blakemore, 2018). In this thesis, I focus on the role of genetic variation in individual differences in adolescent neurocognitive development, and associations between variation in cognitive control and socio-affective processing with affective disorder onset and symptomatology.

1.6.1 Genetic influences on adolescent development

An important source of individual differences in neurocognitive function, behaviour, and mental health outcomes is variation in genes involved in the regulation of monoamine neurotransmitter systems. The maturation and functioning of the dopamine system has been implicated in several influential accounts of adolescent development, in part because of the crucial role dopamine plays in prefrontal cognition, including but not limited to motivational-affective processing, value-based decision-making and cognitive control (Caballero, Granberg, & Tseng, 2016; Luciana & Collins, 2012; Luciana et al., 2012; Spear, 2000).

1.6.1.1 Development of the Dopamine System

Animal studies suggest that the dopamine system undergoes significant reorganisation and refinement during adolescence (Luciana et al., 2012; Spear, 2011; Wahlstrom, White, & Luciana, 2010), although less is known regarding the precise developmental trajectories of these systems in humans than is known about the gross structural development of the brain (see Section **1.2**), due to the limited available techniques for assessing monoamine systems in healthy developmental samples (Ernst & Luciana, 2015; Wahlstrom, White, et al., 2010). Dopamine cell density in the rhesus PFC decreases by up to 50% from the onset of adolescent to late adulthood (Goldman-Rakic, 1981), and basal dopamine levels, dopaminergic turnover and dopaminergic input in the PFC peak in early adolescence and decline thereafter in other animal studies (Andersen, Dumont, & Teicher, 1997; Rosenberg & Lewis, 1994, 1995; Teicher et al., 1993). Research has also suggested there are peaks in D1 and D2 dopamine receptors expression around puberty in rats, with a decline in receptor numbers that occurs later in the PFC than in the striatum (see McCutcheon & Marinelli, 2009, for a review).

There are very few studies investigating developmental changes in the dopamine neurotransmitter system in humans. One post-mortem study has shown a very early peak (2 years) in D1 receptors density in the striatum, with a slow decrease in density during subsequent decades (Seeman et al., 1987). Another post-mortem study found that linear decreases with age in mRNA expression and/or protein levels of dopamine receptors (D2, D4 and D5) and enzymes involved in dopamine regulation (tyrosine hydroxylase and catechol-O-methyltransferase) within the dlPFC were driven by early decreases in the first few months or years of life (Rothmond, Weickert, & Webster, 2012). The only differences observed in later development were increases in dopamine receptor D1, monoamine oxidase (MAO)-A and MAO-B protein levels (enzymes that regulate monoamines including dopamine) between 6 to 12 years and 14 to 17 years or adulthood, and an increase in MAO-B mRNA expression

between 14 to 17 years and adulthood (Rothmond et al., 2012). A positron emission tomography study showed a decrease in D1 binding potential during adolescence in the dlPFC, while no changes were observed in the ventral or dorsal striatum (Jucaite, Forssberg, Karlsson, Halldin, & Farde, 2010). Overall, these studies suggest there are changes in the dopamine neurotransmitter system during development, but that the pattern of changes is complex and does not appear to be consistent across species. It has been argued, mostly based on the animal data, that there may be a peak in dopamine availability in the human pubertal period, and that this may explain adolescent specific behaviours (Chambers, Taylor, & Potenza, 2003; Luna et al., 2015; Padmanabhan & Luna, 2014; Wahlstrom, White, et al., 2010). However more research is needed in humans.

1.6.1.2 Genetic variance in dopamine function

In addition to normative developmental changes in the dopamine system, functional genetic polymorphisms can also alter the availability of the enzymes that regulate monoamine systems, by affecting their protein transcription rate or amino-acid sequence, resulting in variation in neurotransmitter availability between individuals. The catechol-O-methyltransferase (COMT) enzyme is a particularly important determinant of prefrontal dopamine levels due to the relatively limited expression of other regulatory proteins that degrade dopamine in this brain region compared to elsewhere in the brain (Lewis et al., 2001; Meyer-Lindenberg & Weinberger, 2006; Tunbridge, Harrison, & Weinberger, 2006). *COMT* Val^{158}Met (rs4680) is a common functional genetic polymorphism that results in a three- to four-fold reduction of COMT enzymatic activity in methionine (Met) homozygotes compared to those homozygous for the ancestral valine (Val) allele (Chen et al., 2004), and consequently increased prefrontal synaptic dopamine levels. Thus, dopaminergic genetic variance at *COMT* can be used as a tool to indirectly investigate prefrontal dopamine function, and how this relates to cognition, without involving drug administration or invasive imagery techniques that would be unethical for use in adolescent populations.

In adults, relative to Val carriers, the lower COMT activity of Met homozygotes has been associated with greater levels of prefrontal extracellular dopamine, and with superior performance on tasks assessing executive function and WM (for reviews see Tunbridge et al., 2006; Dickinson and Elvevåg, 2009; Witte and Flöel, 2012). In contrast to these executive functioning benefits, it has also been proposed that the Met allele is associated with increased reactivity to negative affective stimuli and increased anxious temperament (Goldman, Oroszi, & Ducci, 2005; Mier, Kirsch, & Meyer-Lindenberg, 2010; Montag, Jurkiewicz, & Reuter, 2012). This reciprocal variation in executive function and affective reactivity has been proposed to represent a trade-off between cognitive efficiency and emotional resilience (Dickinson & Elvevåg, 2009; Goldman et al., 2005; Mier et al., 2010; Montag et al., 2012; Papaleo et al., 2008).

1.6.1.3 Developmental influences on genetic variation

The maturation of the neural systems implicated in prefrontal cognition is a critical aspect of adolescent development that shows protracted changes extending into early adulthood (Crone et al., 2006; Luna et al., 2010; Dumontheil, 2014; Luna et al., 2015; see **Section 1.2.1**). In addition to the developmental changes to the dopamine system reviewed above, COMT enzyme activity also increases substantially between birth and adulthood (Tunbridge et al., 2007). However, while the influence of *COMT* genotype on executive function and affective reactivity has been widely studied in adult populations, less is known about its influence in childhood and adolescence.

There is substantial evidence that the relationship between genetic variation in monoamine systems and behavioural/brain phenotypes is moderated by developmental stage. Heritability studies suggest that genetic influence on cognitive and neural markers for affective disorders varies across development (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2016; McGrath,

Weill, Robinson, Macrae, & Smoller, 2012), and studies using rodent models have demonstrated that genetic variation in the serotonin system has opposing effects on behaviour at different stages of development (Holmes, Li, Murphy, Gold, & Crawley, 2003; Lira et al., 2003). Genetic association studies in developmental samples also highlight the importance of studying the influence of genetic variation on cognition, and the mechanisms underlying it, from a developmental perspective (Dumontheil et al., 2011; Lau et al., 2009; Sebastian, Roiser, et al., 2010; Wahlstrom et al., 2007; Wahlstrom, Collins, White, & Luciana, 2010; Wiggins et al., 2014).

Sebastian, Roiser, et al. (2010) found evidence for an interaction between age and MAO-A genotype on the neural processing of rejection-themed affective stimuli in a sample of healthy adult and adolescent participants. In a more recent study, Wiggins et al. (2014) demonstrated that the association typically observed between a common single nucleotide polymorphism (SNP) in the serotonin transporter gene and corticolimbic function during affective processing in adult populations (Hariri, Mattay, Tessitore, & Kolachana, 2002; Pezawas et al., 2005) may not emerge until late adolescence. Although it should be noted that these studies had relatively small sample sizes for genetic research (35 and 49 participants, respectively), they suggest that relationships between genetic variation with neurocognitive function may not necessarily be stable across development, and that to understand the influence of genetic polymorphisms on cognition, a developmental perspective is crucial.

The relationship between dopamine levels and prefrontal function follows an inverted U-shaped curve, whereby both excessive and deficient levels of dopamine result in sub-optimal cognitive performance (Cools & D'Esposito, 2011; Goldman-Rakic, Muly, & Williams, 2000; Williams & Goldman-Rakic, 1995). A variety of factors can influence an individual's dopamine levels, and therefore their position on the dopamine performance curve. In adults, the lower COMT activity of Met homozygotes is thought to place them near the apex of the curve,

resulting in superior prefrontal cognition (Mattay et al., 2003; Meyer-Lindenberg and Weinberger, 2006; Giakoumaki et al., 2008; **Figure 1.9A**). However, the influence of *COMT* genotype on an individual's position on the performance curve can be moderated by more transient changes affecting dopaminergic function. For example, in adults, increasing dopamine availability via pharmacological manipulation reverses baseline *COMT* genotype effects on cognitive performance, suggesting that a rightwards shift along the dopamine curve is beneficial to Val carriers but results in sub-optimally high dopamine levels in Met homozygotes (Farrell, Tunbridge, Braeutigam, & Harrison, 2012; Giakoumaki et al., 2008; Mattay et al., 2003; Tunbridge et al., 2006).

On the basis that variation in basal dopamine levels can influence the effect of *COMT* genotype on performance, it has been hypothesised that the effect of *COMT* genotype on cognition is not fixed during development (Wahlstrom et al., 2007; Wahlstrom, Collins, et al., 2010; Wahlstrom, White, et al., 2010). Instead, developmental changes in the dopamine system are proposed to shift the position of each *COMT* genotype group on the dopamine-performance curve, whereby increases in dopamine availability during adolescence may moderate the association between *COMT* genotype and performance in a similar manner to that observed when dopamine availability is increased pharmacologically in adult populations (Wahlstrom, White, et al., 2010; see **Figure 1.9B**). Thus, a developmental hypothesis of *COMT* effects on cognition predicts relatively poorer cognitive performance in adolescent Met homozygotes, due to developmental increases in extracellular dopamine levels (Tunbridge et al., 2007; Wahlstrom, White, et al., 2010), in contrast to the typically observed adult pattern of superior performance. Furthermore, developmental improvements in prefrontal cognition that occur during adolescence independent of genotype (Crone et al., 2006; Dumontheil, 2014; Luna et al., 2015, 2010) may be greater in Met homozygotes relative to Val carriers, due to their respective shifts toward and away from the apex of the dopamine performance curve. Support for this hypothesis is provided by studies of *COMT* genotype in development which suggest

that the visuospatial WM benefits associated with Met/Met in adulthood emerge during adolescence (Dumontheil et al., 2011; Wahlstrom, Collins, et al., 2010).

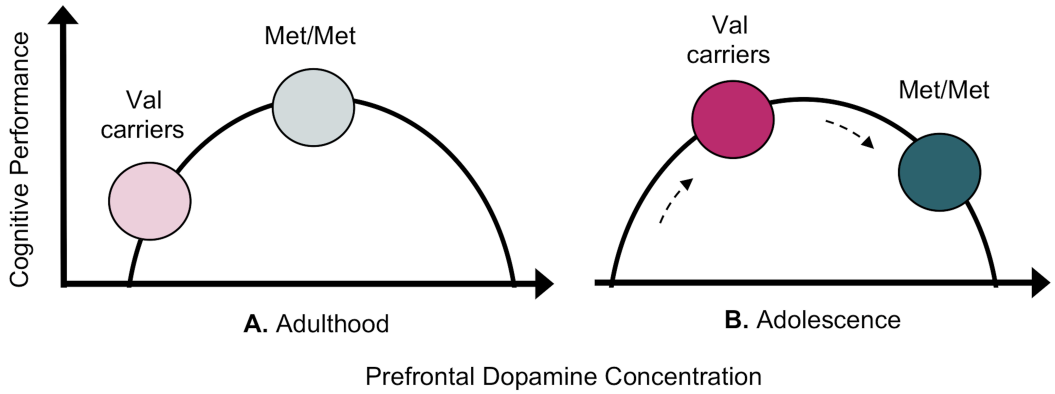

Figure 1.9. Inverted U-shaped relationship between COMT genotype, basal prefrontal dopamine concentration and cognitive performance in adulthood and adolescence. (A) Adulthood. Relative to carriers of the Val allele, Met homozygotes have relatively higher extracellular dopamine levels (due to the lower activity of the COMT enzyme) and show superior performance on tasks assessing prefrontal cognition. **(B) Adolescence.** Greater extracellular prefrontal dopamine levels in childhood and adolescence are proposed to shift the relative position of each *COMT* genotype rightwards along the dopamine-performance curve (as indicated by the dashed arrows). In a similar manner as that observed in adults when dopamine availability is increased via pharmacological manipulation, a rightwards shift along the curve is relatively beneficial to carriers of the Val allele, whereas Met homozygotes experience sub-optimally high dopamine levels and relatively poorer cognitive performance (adapted from Wahlstrom et al., 2007; Wahlstrom, White, et al., 2010).

In contrast to motivational processing (Schultz, 2016), WM and executive function (Cools & D'Esposito, 2011; Goldman-Rakic, 1998), relatively little is known of the role of dopamine in social cognition (Skuse, 2006; Skuse & Gallagher, 2011). In adults, *COMT* genotype has shown an association with variation in social WM, independently of variation in standard verbal and visuospatial WM (Dumontheil et al., 2014), providing preliminary evidence that dopamine may also be involved in supporting social WM processing within prefrontal regions of the social brain network. In **Chapter 2** of this thesis I investigate the development of social, relative to

non-social, WM, and how this is moderated by *COMT* genotype. Based on evidence that *COMT* genotype is associated with reciprocal variation in executive cognition and affective stability in adults (Dickinson & Elvevåg, 2009; Goldman et al., 2005; Mier et al., 2010; Montag et al., 2012; Papaleo et al., 2008), in **Chapter 3** I investigate developmental changes in the association of *COMT* genotype with variation in an aspect of executive function, the ability to flexibly process self-generated information, and in trait anxiety.

1.6.2 Adolescent mental health

Many of the behavioural and cognitive changes associated with adolescence, such as increased exploration, novelty-seeking, emotional lability and social salience assist the transition to an independent adult role. However, they can also confer vulnerability (Eldreth, Hardin, Pavletic, & Ernst, 2013): half of all lifetime cases of mental health disorder appear by age 14 (Kessler et al., 2005, 2007). Indeed, normative individual differences in emotional reactivity in adolescence may put many individuals at increased risk of affective disorders during this period. Self-report studies have found that between 20-50% of adolescents meet conventional adult criteria for clinically significant depression (Kessler, Avenevoli, & Merikangas, 2001; Petersen et al., 1993). While interview-based studies report more modest rates of adolescent depression (Kessler & Walters, 1998), adolescence is unquestionably a period of elevated risk for the onset of mood and anxiety disorders and increased symptomatology (Kim-Cohen et al., 2003; Lewinsohn et al., 1998; Thapar et al., 2012). Experiencing frequent negative affect is particularly common during early adolescence (Larson, Moneta, Richards, & Wilson, 2002), and in addition to low mood, can manifest as anxiety (Abe & Suzuki, 1986), self-consciousness, and low self-esteem (Simmons, Rosenberg, & Rosenberg, 1973; Thornburg & Jones, 1982). Increased intensity of affect or increased emotional reactivity in adolescence may increase the need for top-down cognitive control, placing individuals with lower cognitive control abilities at greater risk for transition into psychiatric disorder. Low mood, anxiety and/or depression is

associated with increased incidence of attempted and completed suicide, self-harm and addiction during adolescence (Mościcki, 2001; Pine, Cohen, & Brook, 2001; Silveri, Tzilos, Pimentel, & Yurgelun-Todd, 2004; Steinberg, 2005).

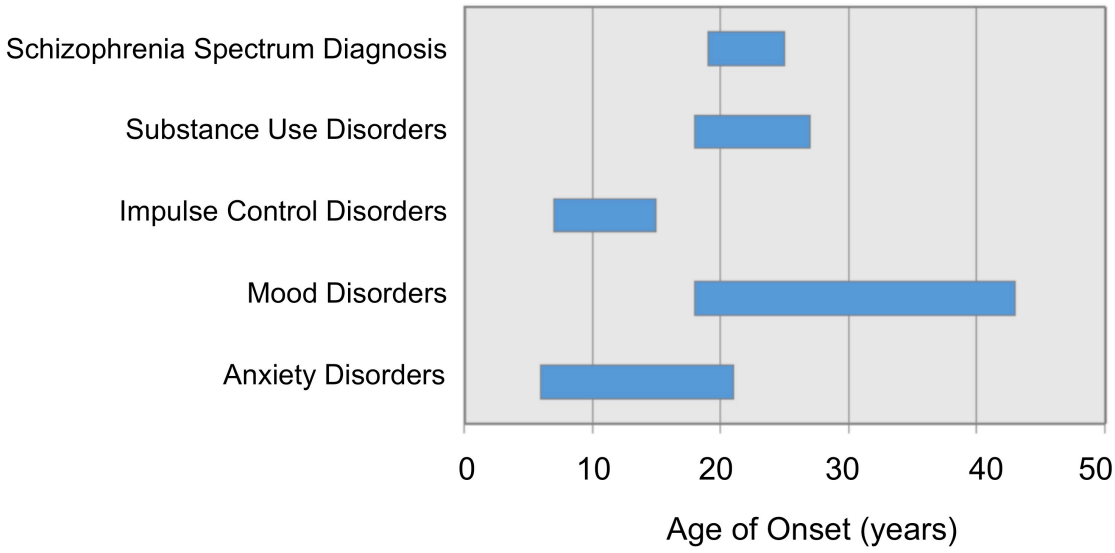

Figure 1.10. Age of onset of mental health disorders. The graph shows the interquartile ranges of the age of onset for common psychiatric disorders, based on nationally representative epidemiological surveys. The majority of diagnosed mental health disorders have their onset in late childhood or adolescence. Data for Schizophrenia Spectrum Diagnosis were adapted from the Early Psychosis Prevention and Intervention Centre in Melbourne, Australia (Kessler et al., 2007). Data for the remaining disorders stems from the National Comorbidity Survey Replication in the United States (Kessler et al., 2005). Reproduced with permission from Fuhrmann (2017).

Cognitive control is compromised in many psychiatric disorders (Luna & Sweeney, 2004; Sweeney, Takarae, Macmillan, Luna, & Minshew, 2004). Depressed patients consistently show deficits in cognitive control (see Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008 for review), and it has been hypothesised that cognitive control deficits could contribute to affective biases associated with the development and maintenance of depression (Roiser, Elliott, & Sahakian, 2012). Studies using the Affective Go/No-Go task (AGN; Murphy et al., 1999), an inhibitory control paradigm, have found that currently depressed adults respond

faster to sad targets than happy targets, and miss more happy than sad targets (Erickson et al., 2005; Murphy et al., 1999), suggesting the presence of affective biases. Furthermore, alterations in amygdala-PFC connectivity have been implicated in the pathophysiology of mood and anxiety disorders in adults (Blair et al., 2008; Drevets, 2003; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007) and adolescent populations (Guyer et al., 2008; McClure et al., 2007; Monk et al., 2008; Pine, 2007; Rich et al., 2006). Individuals with, or at risk of, affective disorders indicate greater amygdala relative to prefrontal activity, and reduced recruitment of the vmPFC, a key region for emotional regulation (Ochsner & Gross, 2005; see **Section 1.3.3**). However, due to neurocognitive differences between adults and adolescents, and potential cumulative effects of repeated depressive episodes, it is difficult to generalise findings from studies of adult-onset disorder to adolescent populations.

1.6.2.1 Emotional regulation and adolescent mental health

Some studies have investigated the interplay between affective processing and cognitive control in adolescents with or at risk of mood and anxiety disorders. While these studies provide evidence of affective bias, they do not precisely mirror those reported in adult studies. Han et al. (2012) found a moderate association between depressive symptom severity and the cognitive control of affective processing in an emotional go/no-go task. Similarly, relative to healthy controls, anxious and depressed adolescents showed overall deficits in inhibitory control (Hardin et al., 2009; Hardin, Schroth, Pine, & Ernst, 2007), which were further moderated by socio-affective properties of the stimuli: typically developing adolescents exhibited enhanced inhibitory control for positive stimuli, whereas anxious adolescents showed enhanced control for threat related stimuli (Hardin et al., 2009). When sad, as opposed to threatening, negative stimuli have been used, currently depressed adolescents showed poorer performance when they had to orient to happy stimuli (Kyte, Goodyer, & Sahakian, 2005; Maalouf et al., 2012), which was not found for adolescents with remitted

depression, suggesting the existence of state-dependent affective biases (Maalouf et al., 2012).

Whilst it is clear that depressive symptoms and affective biases *co-occur*, the precise role of affective biases in the *onset* of depression and the role of prior depression on later affective processing is unclear (Jacobs, Reinecke, Gollan, & Kane, 2008; Roiser et al., 2012). Longitudinal studies are required in order to determine whether affective biases are state markers associated with current depression, or 'trait' markers of risk that precede depression onset or persist after remission. In **Chapter 7**, I describe a one-year longitudinal study of affective bias measured with an affective go/no-go task in a sample of adolescents at high familial risk of developing depression, aimed at assessing the relationship between affective bias and depression both concurrently and across time.

1.6.2.2 Motivational processing and adolescent mental health

Adult depression has been associated with reward hyposensitivity and reduced reward-seeking behaviour (Eshel & Roiser, 2010). Studies of non-social rewards in adolescents with depressive disorder also suggest that reward processing, and associated decision-making behaviours, may also be altered in adolescents with depression compared with non-depressed adolescents. Adolescents with depression are less likely to differentiate between small and large monetary reward outcomes when making choices on probabilistic reward tasks with favourable odds, suggesting reduced reward-seeking behaviours (Forbes, Shaw, & Dahl, 2007; Rawal et al., 2014; Rawal, Collishaw, Thapar, & Rice, 2013). This pattern of choice behaviour has also been associated with greater prevalence of depressive symptoms and onset of depressive disorder one year later (Forbes et al., 2007) and, conversely, depressive symptoms also predict a greater prevalence of this pattern of choice behaviour one year later (Rawal et al., 2014).

There is also evidence of alterations in neural activity during reward processing in adolescents with depression. Neuroimaging studies using monetary reward paradigms have shown that compared to healthy controls, currently depressed adolescents exhibit reduced striatal activation during both the anticipation and receipt of monetary rewards (Forbes et al., 2006, 2009; Olino et al., 2011; Sharp et al., 2014), and that striatal activity was negatively correlated with depressive symptoms and positively correlated with positive affect (Forbes et al., 2009). There is also evidence that decreased VS response to the receipt of monetary rewards in adolescence is associated with longitudinal increases in depressive symptoms (Hanson, Hariri, & Williamson, 2015; Telzer, Fuligni, Lieberman, & Galvan, 2014).

1.6.2.3 Social processing and adolescent mental health

Social processing and context may be particularly relevant in understanding adolescent mental health risk. Silk, Davis, McMakin, Dahl, & Forbes (2012) propose that sensitivity to social threat is a core vulnerability that predisposes adolescents to early anxiety and later depression. Using a simulated peer interaction neuroimaging paradigm, Silk et al. (2013) demonstrated that adolescents with depression showed greater activation of the amygdala, nucleus accumbens, anterior insula and subgenual ACC during peer rejection compared to age and gender matched healthy controls. Furthermore, many, although not all, longitudinal studies suggest that peer rejection temporally precedes the onset of depressive symptoms during adolescence (reviewed in Platt et al., 2013). Social reward processing has also been emphasised as an important factor in the development of adolescent depression (Davey et al., 2008; 2011), as well as in social anxiety disorder (SAD; Caouette & Guyer, 2014). The age-of-onset distribution for SAD differs notably from other anxiety disorders. SAD onset rates increase considerably at age 10, with approximately 50% of cases beginning by age 13, and 90% of cases beginning by age 23 (Beesdo, Pine, Lieb, & Wittchen, 2010; Stein, 2006). It has been hypothesised that the normative cognitive, socio-affective and environmental changes of adolescence place

individuals at elevated vulnerability to SAD, especially when these changes interact with existing risk factors (Caouette & Guyer, 2014).

Experimental studies suggest that adolescents with or at risk of SAD exhibit atypical activity and connectivity in reward-related brain circuits during the anticipation of social rewards (Guyer et al., 2008, 2014). While adolescence is typically associated with increased salience of social reward and motivation to approach peers to gain social affiliation, individuals at increased risk for SAD may experience approach-avoidance conflict in these situations, due to being simultaneously highly invested in what their peers think of them and extremely fearful of humiliation or rejection (Caouette & Guyer, 2014; Lucock & Salkovskis, 1988). In **Chapter 6** I investigate the relationship between social anxiety and social reward sensitivity, and whether this changes during development.

Increasing our understanding of the development of cognitive control, motivational-affective processing and social cognition, and the way in which they interact dynamically with each other, may give insight as to why some adolescents are successful in making the transition to adulthood, while others experience difficulties. It may also allow the identification of developmental 'windows' in which individuals may be particularly vulnerable, knowledge which is vital for understanding who is at greatest risk, and how to design effective early interventions (Andersen, 2016). Indeed, it has been suggested that adolescence may represent a period of heightened neural plasticity, during which time the brain is particularly amenable to change and the effects of experience and intervention (Fuhrmann et al., 2015).

1.7 Summary and thesis overview

This thesis focuses on investigating how interactions between social cognition, motivational-affective processing, and cognitive control change over adolescent development, and how this is influenced by individual differences in affective reactivity and genetics.

The studies described in the first two experimental chapters use a behavioural genetics approach to investigate the influence of dopaminergic variation during development on social cognition, WM, executive function and affective reactivity in a sample of children, adolescents and adults. **Chapter 2** explores the association of *COMT* genotype with both social and non-social WM across development, and the extent to which these cognitive processes are: 1) independent from each other; and 2) influenced by dopamine function. In **Chapter 3**, I investigate whether reciprocal associations of *COMT* with an aspect of executive function, specifically the flexible processing of self-generated information, and trait anxiety are moderated by developmental stage. Taken together, these studies demonstrate the importance of taking a developmental approach when investigating the influence of genetic variation on cognition.

The next two experimental chapters focus on two different aspects of reward processing in adolescence. **Chapter 4** uses a combination of computational modelling and behavioural analyses to investigate how adolescents (12-17 years) learn from reward versus punishment, and from counterfactual feedback about their decisions, and whether this differs between adolescents and adults. **Chapter 5** examines developmental changes in social reward sensitivity using a combination of self-report questionnaire assessment and a behavioural task that compares the processing of social and non-social rewards.

In **Chapters 3**, **5** and **6** I investigate how individual differences in genetics (**Chapter 3**), reward processing (**Chapter 5**) and cognitive control of affective information (**Chapter 6**) relate to the development of mood and anxiety disorders during adolescence using a combination of behavioural tasks, self-report questionnaires and psychiatric interview methods. While **Chapters 3** and **5** are cross-sectional studies and therefore cannot assess conclusions the directionality of these relationships, **Chapter 6** used a 1-year longitudinal design to investigate whether variation in affective control is predictive of depression onset in adolescents at high familial risk of depression.

CHAPTER 2: Development of dopaminergic genetic associations with visuospatial, verbal and social WM

Dopamine transmission in the PFC supports WM, the temporary holding, processing and manipulation of information in one's mind. The gene coding the COMT enzyme, which degrades dopamine, has a common polymorphism leading to two versions of the COMT enzyme that vary in their enzymatic activity. In a previous study of adults, COMT genotype was associated with performance on verbal and visuospatial WM tasks, and performance on a novel social WM paradigm that requires participants to maintain and manipulate information about the traits of others over a delay. Here, children and adolescents (N = 202) were compared to the adult sample (N = 131) to investigate possible age differences in genetic associations, and also age-related changes in social, relative to non-social WM. Adults performed significantly better than adolescents on all three measures of WM, and the effect of age group on social WM performance was not accounted for by variation in non-social WM. Developmentally moderated genetic effects were observed for both visuospatial and social WM, even when controlling for non-social WM performance, suggesting that the maintenance and manipulation of social information may also recruit the dopamine neurotransmitter system. The results replicate and extend previous work showing that the pattern of superior WM performance observed in Met/Met adults emerges during development, providing indirect evidence that prefrontal dopamine levels decrease during adolescence.

The study presented in this chapter has been submitted for publication as:

Dumontheil, I., **Kilford, E.J.** & Blakemore, S-J. Development of dopaminergic genetic associations with visuospatial, verbal and social working memory.

This chapter also refers to the following published paper:

Kilford, E.J., Dumontheil. I., Wood, N.W., Blakemore, S-J. (2015) Influence of *COMT* genotype and affective distractors on the processing of self-generated thought. *Social Cognitive and Affective Neuroscience, 6,* 777-82.

2.1 Introduction

Working memory (WM) refers to the temporary holding, processing and manipulation of information in one's mind. Research in the past has typically distinguished between verbal and visuospatial WM, referring to the nature of the information being maintained. Social WM is the ability to store and manipulate information *about other people* (Meyer, Spunt, Berkman, Taylor, & Lieberman, 2012; Meyer, Taylor, & Lieberman, 2015). While verbal and visuospatial WM tasks are associated with increased activation in the lateral fronto-parietal cortex (Owen, McMillan, Laird, & Bullmore, 2005; Rottschy et al., 2012; Van Overwalle, 2009), social cognition tasks are associated with increased activation of the social brain network (reviewed in **Section 1.4**), including medial regions of the frontal-parietal cortex. Using neuroimaging, Meyer and colleagues (Meyer et al., 2012, 2015) demonstrated that, during a social WM task, both medial and lateral fronto-parietal systems show WM load-dependent increases in activation, suggesting that the social brain and typical WM systems work in parallel to support social WM.

Dopamine transmission in the PFC is critically involved in WM, as evidenced from electrophysiological and pharmacological studies in animals (Brozoski, Brown, Rosvold, & Goldman, 1979; Levy & Goldman-Rakic, 2000) and neuroimaging (Cropley, Fujita, Innis, & Nathan, 2006; H. Fischer et al., 2010; McNab et al., 2009) and pharmacological studies in humans (e.g. Mehta et al., 2000; Müller, von Cramon, & Pollmann, 1998). This research has led to the suggestion that prefrontal dopamine facilitates the stabilisation of information in WM (Cools & D'Esposito, 2011; de Frias et al., 2010), and that PFC functioning and WM performance follow an inverted U-shaped function, whereby both deficient and excessive amounts of prefrontal dopamine activity predict poor task performance (Cools & D'Esposito, 2011; Goldman-Rakic, Muly, & Williams, 2000; Williams & Goldman-Rakic, 1995; see **Figure 1.9A**).

COMT Val^{158}Met (rs4680) is a common functional genetic polymorphism that results in individuals differences in prefrontal dopamine levels, and thus can be used to indirectly investigate prefrontal dopamine function and its association with cognition (see **Section 1.6.2**). The Met allele has been shown to be associated with superior WM performance (Diaz-Asper et al., 2008; Dumontheil et al., 2011; Goldberg & Egan, 2003), and reduced PFC activation during executive function tasks (de Frias et al., 2010; Dickinson & Elvevåg, 2009; Mier et al., 2010; Tunbridge et al., 2006; Witte & Flöel, 2012). However, the association between rs4680 genotype and WM performance has not always been consistently observed (e.g. Blanchard, Chamberlain, Roiser, Robbins, & Müller, 2011) and depends on the population studied and the specific paradigm used (see Barnett, Scoriels, & Munafò, 2008 for meta-analysis, Dickinson & Elvevåg, 2009; Witte & Flöel, 2012, for reviews).

In contrast to WM, relatively little is known of the role of dopamine in social cognition (Skuse, 2006; Skuse & Gallagher, 2011). However, previous research in adults has shown that the rs4680 variant of *COMT* was associated with individual differences in performance of a social WM task (Dumontheil et al., 2014), with superior performance observed in Met homozygotes. Importantly, the association was maintained when performance on standard verbal and visuospatial WM tasks was covaried out. These results, in parallel with the neuroimaging studies by Meyer and colleagues (Meyer et al., 2012, 2015), provide tentative evidence that the dopamine neurotransmitter system may also be involved in supporting social WM processing within the social brain.

As reviewed in **Chapter 1,** the PFC undergoes prolonged structural and functional changes during adolescence, and is associated with the continued maturation of a range of PFC-mediated cognitive processes, including both WM and social cognition. Furthermore, behavioural and neuroimaging studies of the development of complex aspects of social cognition such as perspective-taking (**Section 1.4.3.2**) and social decision-making (**Section**

1.4.3.3) suggest that developments in executive functions and social cognition mutually influence each other. Thus the improved integration of social cognitive and frontal-parietal systems in adolescence may also contribute to developmental advances in other aspects of cognition that require the integration of social cognition with more domain-general cognitive control processes, such as social WM.

Research has shown that the dopamine system undergoes significant reorganisation and refinement during development (**Section 1.6.1**). Furthermore, there is converging evidence that associations between monoaminergic genetic variation and neurocognitive function may not necessarily be stable over development (**Section 1.6.3**). For example, Wahlstrom et al., (2007) estimated WM in 9-17 year olds using a composite score combining performance in digit and spatial forward and backward span tasks and a delayed visuospatial response task. In contrast to previous findings in adult samples (e.g. Diaz-Asper et al., 2008; Goldberg et al., 2003), *COMT* Val carriers showed poorer WM performance than Met/Met homozygotes. Dumontheil et al. (2011) later demonstrated in a longitudinal sample that the adult pattern of lower WM capacity and higher lateral PFC recruitment during a visuospatial WM task in Val carriers emerged during development, rather than being stable over childhood, adolescence and early adulthood. These data were considered to support the presence of higher levels of basal dopamine in late childhood and adolescence than in adulthood, leading to a shift of the position of the *COMT* genotypes on the inverted U-shape function linking PFC functioning and dopamine levels (Dumontheil et al., 2011; Wahlstrom et al., 2007; Wahlstrom, Collins, et al., 2010; Wahlstrom, White, et al., 2010; see **Figure 1.9B**).

The current study used genetic variation in *COMT* to investigate the dopamine neurotransmitter system, and its role in different types of WM, during development. Data were collected from a sample of children and adolescents aged 9-18 years old and compared to previously collected and published data from a sample of adults aged 20-39 years old

(Dumontheil et al., 2014; Kilford, Dumontheil, Wood, & Blakemore, 2015; Magis-Weinberg, Blakemore, & Dumontheil, 2017). The first aim of this study was to investigate developmental differences in social, relative to non-social, WM. The second was to replicate previous findings of an interaction between age and *COMT* genotype on the performance of a visuospatial WM task (Dumontheil et al., 2011), and investigate whether this interaction was also observed in a verbal WM task, as suggested by results in a sample of 9-17 year olds (Wahlstrom et al., 2007), following up the genetic effects previously observed in an adult sample (Dumontheil et al., 2014; Kilford et al., 2015). The final study aim was to investigate whether a similar pattern would be observed in a social WM task, over and above genetic effects on standard WM, as this would suggest that the influence of dopaminergic genetic variation on social WM also changes between childhood and adolescence and adulthood.

2.2 Methods

2.2.1 Participants

Healthy adult participants were recruited via University College London (UCL) volunteer databases (*N* = 161, 20-39 years old, 78 females); child and adolescent participants (*N* = 218, 9-18 years old, 121 females) were recruited in schools in and around London. The study was approved by the UCL Research Ethics Committee, all adult participants gave written informed consent, while written informed consent was obtained from the parent or guardian of the child and adolescent participants and verbal assent was obtained from these participants themselves. All participants were healthy according to self-report.

Participants were individually tested in a quiet room either in the laboratory or at their school on a battery of behavioural tasks (see **Section 2.2.4**) and subsequently provided a saliva sample, which was genotyped for the rs4680 Val^{158}Met substitution on the *COMT* gene (see **Section 2.2.2**). Two adolescent participants were tested but excluded from all analyses due to being diagnosed with developmental disorders (one participant had Asperger Syndrome and

did not complete the testing session and one had Turner Syndrome). Six adolescent participants were unable to provide saliva samples, giving a total of 371 participants for genotyping.

2.2.2 Genetic Sampling and Analysis

Saliva samples were collected using Oragene DNA Self-Collection Kit (DNA Genotek Inc., Ottawa, Ontario, Canada), in accordance with the manufacturer instructions. Adult DNA was extracted from saliva samples at the Department of Molecular Neuroscience at the Institute of Neurology, UCL, while child and adolescent DNA was extracted at the Molecular Psychiatry Laboratory, UCL. DNA was extracted using the OG-L2P DNA extraction kit, as per the protocol suggested by the manufacturer (DNA Genotek Inc., Ottawa, Ontario, Canada).

Analysis of the SNP was carried out by AROS, University of Aarhus, Denmark. The *COMT* rs4680 SNP in exon 4 of the gene is characterised by an A/G substitution, which causes the $Val^{158}Met$ polymorphism. The SNP was determined using the TaqMan genotyping platform (Applied Biosystems, Foster City, California). Reactions and analysis were performed in a 384-well plate format. All samples were normalized to 5ng/µl of DNA. The reaction components for each genotyping reaction were as follows: 2.5 µl TaqMan master mix, 0.25 µl TaqMan assay X20, 1.25 µl water resulting in a total volume of 4.0 µl + 1 µl template genomic DNA with a concentration of 5ng/µl. The reaction was analysed using an Applied Biosystems 7900 Fast Real-Time Polymerase Chain Reaction instrument. Included in the analysis were three negative controls (no template control) and five positive controls (known DNA samples and known SNP assays).

2.2.2.1 Data quality control and participant exclusions

The genotyping was validated using a set of five control samples with genotype data available through the Coriell Institute for Medical Research. There was a 100% concordance with the data from Coriell Institute for Medical Research. Of the 371 participants that provided DNA

samples, genotyping was unsuccessful for 10 (2.7%) participants due to poor quality of the sample: DNA extraction failed for two participants (2 adolescents) and genotyping was unsuccessful for eight participants (1 adolescent, 7 adults).

The frequency of many genetic variants, including *COMT,* varies considerably across populations (Palmatier, Kang, & Kidd, 1999). Global allele frequency distributions reveal that the Val allele at *COMT* is significantly more frequent in East Asian populations (including China and Japan) compared to European, African and Southwest Asian populations (Palmatier et al., 1999). Thus East Asian populations may have a different ancestral haplotype of *COMT* (DeMille et al., 2002). Here, East Asian participants (*n*=6 adolescents, *n*=22 adults) had indeed a greater frequency of the *COMT* Val allele than the other ethnicities, and were therefore excluded to make the distribution of genotypes more homogeneous. After exclusions based on ethnicity (*n* = 28), failed genotyping (*n* = 10), analyses included 333 participants (202 adolescents, 131 adults; see **Table 2.1**), although final sample sizes were slightly smaller for individual tasks and measures because of task-specific exclusions (detailed in **Section 2.2.4**).

Genetic analysis identified 93 participants (27.9%) with the Val/Val genotype, 153 with Met/Val (45.9%) and 87 with Met/Met (26.1%). This gave an allele frequency distribution of .51 Val and .49 Met (adolescents: .52 Val, .48 Met; adults: .48 Val, .52 Met), which is comparable to previously reported allele frequency distributions of .52 Val and .48 Met (Hapmap European sample: http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4680/, n.d.). The Hardy-Weinberg equilibrium test indicated that the *COMT* genotypic frequency distribution was in equilibrium across the sample ($X^2(1) = 2.17$, $p = .140$; adolescents: $X^2(1) = 0.91$, $p = .341$; adults: $X^2(1) = 1.27$, $p = .260$).

2.2.3 Matching of age and genotypic groups

Effects of *COMT* genotype were investigated using the Val allele dominant genotype grouping (Met/Met vs. Val carriers) that was found to show association with performance in previous analyses of the adult data (Dumontheil et al., 2014; Kilford et al., 2015), and has been shown in previous studies to be the most effective model for explaining the influence of *COMT* variance on behaviour (Barnett et al., 2008; Dumontheil et al., 2011). Effects of age were explored by comparing adolescent (age range: 9.0-18.0 years) and adult (age range: 20.3-39.4 years) participant groups. Analyses were performed on the final sample with genetic data but without considering task-specific exclusions (n = 333), which resulted in slightly smaller n's for individual tasks (see **2.2.4**).

Table 2.1. Participant demographics.

	Val carriers				Met/Met			
	n	**Age** *M* (*SD*)	**Verbal IQ** [a] *M* (*SD*)	**Sex** (%F)	***n***	**Age** *M* (*SD*)	**Verbal IQ** [a] *M* (*SD*)	**Sex** (%F)
Adolescents	153	13.3 (2.1)	115.2 (11.8)	51.0%	49	13.1 (2.0)	113.7 (12.7)	61.2%
Adults	93	26.9 (4.1)	112.7 (12.9)	55.9%	38	25.2 (3.2)	113.6 (12.0)	39.5%
All	246	18.4 (7.3)	114.2 (12.3)	52.9%	87	18.4 (6.6)	113.6 (12.3)	51.7%

Note. %F: Percentage female; *M*: Mean; *SD*: Standard deviation.
[a] Four adults were missing Verbal IQ data (1 Met/Met, 3 Val carrier).

Univariate analysis of variance (ANOVA) on mean age indicated that the *COMT* genotype groups (Met/Met vs. Val carrier) were matched in the adolescent group ($F(1,200) = 0.20$, p = .653), whereas Val carriers were significantly older than Met/Met individuals in the adult group ($F(1,129) = 5.12$, p =.025; **Table 2.1**), as was the case in previous analyses of only the adult sample (Kilford et al., 2015; Dumontheil et al., 2014). Sex distribution did not differ significantly between *COMT* genotype groups ($\chi^2(1) = .032$, p = .857) or age groups ($\chi^2(1)$ =

0.17, p = .679), and within each age group there was no difference in sex distribution between the *COMT* groups (adolescents: $\chi^2(1) = 1.57$, p = .211; adults: $\chi^2(1) = 2.92$, p = .088).

A 2 x 2 ANOVA with age group (adolescent, adult) and *COMT* genotype (Met/Met, Val carrier) as between subjects factors indicated that there were no significant main effects of *COMT* genotype ($F(1,325) = 0.03$, p = .854) or age group ($F(1,325) = 0.70$, p = .404) on verbal IQ (Wechsler, 1999) and no significant interaction between age group and *COMT* ($F(1,325) = 0.62$, p = .431). Note this was also the case within the slightly different backwards digit span, visuospatial, and social WM tasks samples (p's > .260). Therefore, the age and genotype groups were considered sufficiently matched and verbal IQ was not included in further analyses.

In terms of ethnicity, 154 of the adolescents were Caucasian, 44 were not (7 Black (African or Caribbean), 26 Asian (not East Asian), 10 Mixed Asian (not East Asian) and Caucasian, 2 Other (not specified) and 3 did not provide ethnicity information (2 Met/Met, 1 Val carrier). In the adult sample, 87 were Caucasian, 43 were not (13 Black (African or Caribbean), 3 Mixed Black and Caucasian, 21 Asian (not East Asian), 2 Mixed Asian (not East Asian) and Caucasian, 4 Other (not specified) and 1 did not provide ethnicity information (Val carrier). Chi-square analyses indicated that ethnicity (Caucasian vs. non-Caucasian) differed significantly between *COMT* genotype groups ($\chi^2(1) = 7.67$, p = .006), due to a significantly higher proportion of Caucasian individuals within Met homozygotes (84.7%) relative to Val carriers (69.3%). There was also a significantly greater proportion of Caucasians in the adolescent (77.4%) than the adult sample (66.9%; $X^2(1) = 4.394$, p = .036). Analyses were therefore repeated with the inclusion of ethnicity (Caucasian vs. non-Caucasian) as a covariate (the four participants with missing ethnicity information were not included in these analyses).

2.2.4 Behavioural assessments

Participants performed a Social WM task (Meyer et al., 2012), a visuospatial WM grid task (Dumontheil et al., 2011) and a verbal WM backwards digit span task in the first, fourth and final position of a series of five cognitive tasks. Two additional computerised tasks and a series of questionnaire assessments, not described here, were also performed by participants. The second task, focused on the processing of self-generated information and is described in detail in Kilford et al. (2015), and **Chapter 3** of this thesis along with the questionnaire assessments. The third task focused on social and non-social relational reasoning and is described in detail in Magis-Weinberg et al. (2017). Verbal IQ was assessed at the end of the testing session using the vocabulary subtest of the Wechsler's Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). The entire testing session lasted approximately 1 hour.

2.2.4.1 Backwards digit span task

The backwards digit span task measures verbal WM for numerical information. Participants were presented with sequences of digits of increasing load (number of digits in the sequence), which they had to repeat in the reverse order. There was a maximum of four trials at loads 3, 4, and 5 and two trials at load 7. Correct reversal of three out of four trials was required to start the next load level. The score was the total number of correct reversals, out of a total of 14. One adult participant had a score of 0, which was further than 3 *SD* away from the sample mean, and was therefore excluded from analyses including this measure (final n = 332).

2.2.4.2 Visuospatial WM task

The visuospatial WM task measures spatial WM for visually presented stimuli, and was adapted from the Dot Matrix test of the Automated WM Assessment (Alloway, 2007). The task required participants to remember and replicate the order and location of sequences of dots presented one by one in a four by four grid, and was programmed in MatLab with experimental stimuli designed using Cogent graphics (http://www.vislab.ucl.ac.uk/cogent_graphics.php). Each dot was presented for 600 ms, with a

300 ms interval between dots. Each sequence of dots was followed by a short delay (1.5 s), after which participants reproduced the sequence using a computer mouse. Trials varied in load depending on the number of dots in a sequence (between three and eight). There were four trials of each load condition and correct reversal of three trials was required to start the next load level. The score was the total number of correct sequence reproductions, out of a total of 24. Reaction time (RT) was recorded from the beginning of the response phase to the last response and divided by the number of dots in the trial. Data were overwritten and lost for one adolescent participant. There were no outliers on the visuospatial WM score (final *n* = 332), however three participants (2 adolescents, 1 adult) were slower than 3 *SD* above the mean visuospatial WM RT and were therefore excluded from analyses including this measure (final *n* = 329).

2.2.4.3 Social trait-ranking WM task

The social trait-ranking WM task is a recently developed task that uses social stimuli within a standard WM task paradigm (Meyer et al., 2012). The adapted version of the task used here was programmed in MatLab with experimental stimuli designed using Cogent Graphics (http://www.vislab.ucl.ac.uk/cogent_graphics.php). Prior to the study, participants completed a questionnaire in which they named and rated 10 friends on 10 predefined personality traits (e.g., funny, clever, stubborn), using a rating scale from 0 to 100. Forty trials were generated by combining the names of friends whose ratings varied by at least five points on a given personality trait. Trials were equally distributed between load 2 (two names) and load 3 (three names). On each trial, participants were first presented with a list of names, followed by a personality trait (e.g., 'happy'). During a delay period, participants were asked to order, in a decreasing manner, in their head, the names on the list according to how much the personality trait applied to each of the names (i.e., the happiest friend is at the top of the list; see **Figure 2.1**). A measure of participants' WM manipulation was collected by presenting a question such as 'Second happy? Jane', which required a yes/no response using a right/left index finger key

press. Participants were asked to answer as quickly and accurately as possible. Measures of accuracy (consistency between questionnaire and responses in the task) and RT (response time to the final question) were calculated. Data were lost for 15 adolescent participants, not collected for six adolescent participants who did not complete the necessary initial questionnaire (one of whom also did not provide a saliva sample), and incomplete for one adolescent participant because of a computer malfunction (*n* = 312). There were no outliers on accuracy, but two adult participants responded on average faster than 3 *SD* below the mean RT and were excluded from analyses including this measure (final *n* = 310).

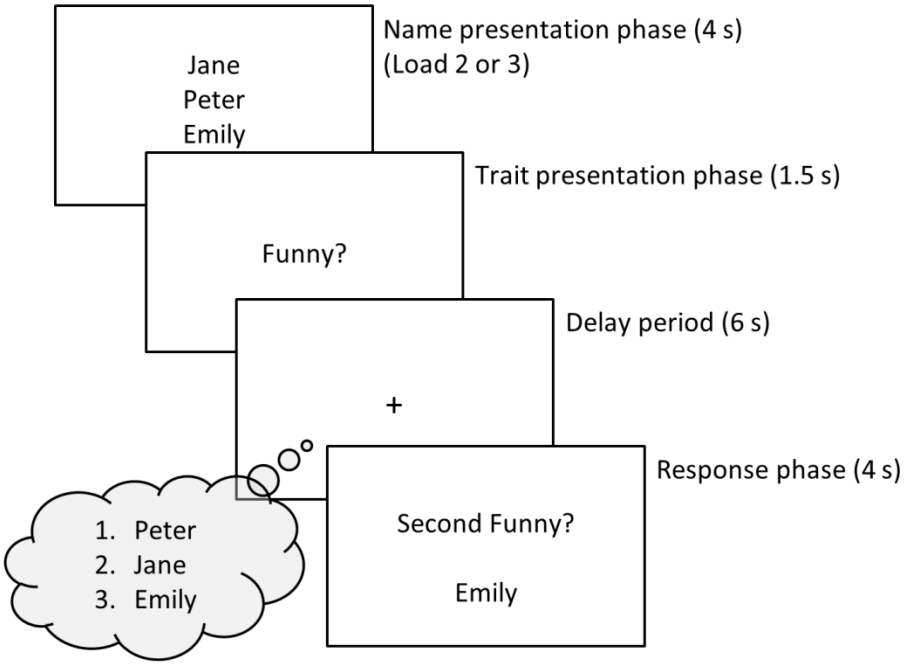

Figure 2.1. Social trait-ranking WM paradigm. Schematic description of the four phases of a load 3 trial, including timings. Adapted from Dumontheil et al. (2014).

2.2.5 Statistical analyses

Statistical analysis was carried out in SPSS (version 21), using Greenhouse-Geisser correction when assumptions for sphericity were not met. Univariate analyses of variance (ANOVA) was performed to investigate the effects of *COMT* genotype (Met/Met, Val carriers) and age group

(adolescents, adults) on task performance. The dependent variables were the backwards digits span score, visuospatial WM score, and social WM mean RT averaged across loads 2 and 3. Sex was included as a between subject factor in all analyses. In addition, analyses were repeated by including ethnicity (Caucasian/non-Caucasian) as a covariate. All genetic effects remained significant, therefore the estimated standardized means and standard errors obtained from the original ANOVAs are reported in the text and plotted in relevant figures ($M \pm SE$).

Two-way interactions between age group and *COMT* genotype, the interaction of interest, were followed up using simple effects analysis (Howell, 1997), with the prediction of an absent or inverted direction of the genotype effect in the developmental sample compared to the adult sample. The sample was also split by genotype to explore whether there were differences between age groups for each genotype. Finally, in order to investigate whether genetic effects on the social WM mean RT could be accounted by genetic effects on standard WM tasks, the social WM mean RT analyses were repeated entering backwards digit score, visuospatial WM score and visuospatial WM RT as covariates (Dumontheil et al., 2014).

2.3 Results

2.3.1 Backwards digit span task

A univariate ANOVA with backwards digit score as the dependent variable and age group, *COMT* genotype and sex as independent variables revealed main effects of age group ($F(1,324) = 67.00$, $p < .001$, $\eta_p^2 = .171$) and sex ($F(1,324) = 4.24$, $p = .040$, $\eta_p^2 = .013$). Adults scored higher (10.82 ± 0.26) than adolescents (8.06 ± 0.22), and females scored higher (9.79 ± 0.24) than males (9.09 ± 0.24). There was no significant main effect of *COMT* genotype and the interaction between age group and genotype was not significant (**Table 2.2**).

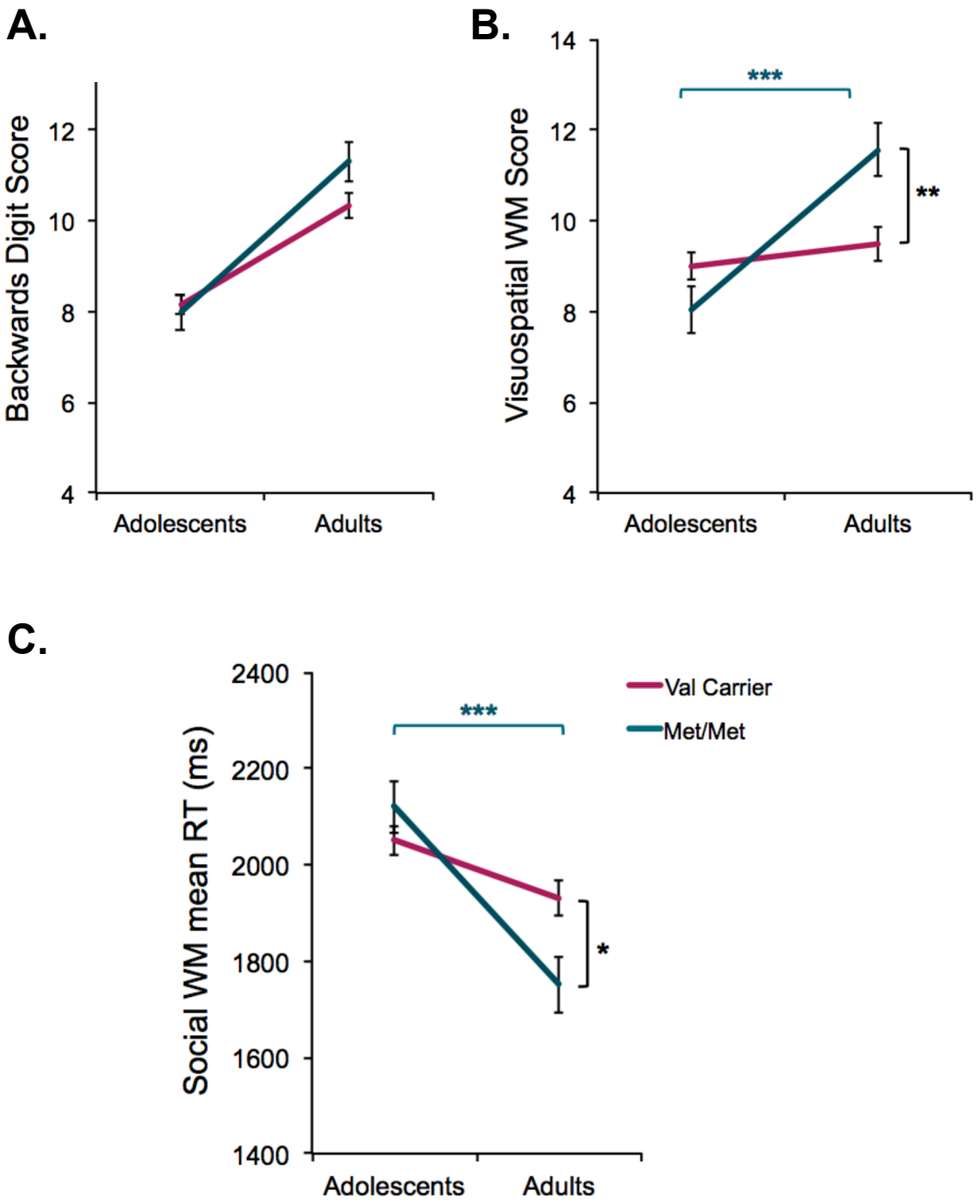

Figure 2.2. Performance on the (A) backwards digit span task, (B) visuospatial WM task and (C) social trait-ranking WM task as a function of age group and *COMT* genotype (*M*±*SE*). The interaction between age group and *COMT* genotype was significant for the visuospatial **(B)** and social **(C)** WM tasks. Significant interactions were followed up by analysing the simple effects. On both the visuospatial **(B)** and social **(C)** WM tasks, Met/Met adolescents were significantly less accurate than Met/Met adults, whereas adolescent and adult Val carriers did not significantly differ. In addition, adult Met/Met individuals significantly outperformed Val carriers, whereas this effect was not observed in adolescents. *$p < .05$, **$p < .01$, *** $p < .001$.

2.3.2 Visuospatial WM task

The same analysis was performed for the visuospatial WM task data. Results showed again a significant main effect of age group, with better performance in adults (10.52 ± 0.35) than adolescents (8.51 ± .30) but no main effect of sex. The predicted interaction between age group and *COMT* genotype was significant (**Table 2.2**). Simple effects analysis, in which the sample was split by age group, indicated the effect of genotype was significant in adults ($F(1,324) = 8.95$, $p = .003$, $\eta_p^2 = .027$, see Dumontheil et al., 2014), with better performance in Met/Met individuals than Val carriers, but not in adolescents ($F(1,324) = 2.64$, $p = .106$), where the direction of effects was in the opposite direction (**Figure 2B**). When the sample was split by genotype, analysis of simple effects indicated that Met/Met adults had higher visuospatial WM scores and Met/Met adolescents ($F(1,324) = 20.14$, $p < .001$, $\eta_p^2 = .059$) whereas adult Val carriers did not significantly differ from adolescent Val carriers ($F(1,324) = 1.04$, $p = 308$).

2.3.3 Social trait-ranking WM task

Analyses of mean RT on the social trait-ranking WM task showed very similar results to the analysis of the visuospatial WM task. There was a main effect of age group (**Table 2.2**), with faster RT in adults (1840 ms ± 34) than adolescents (2085 ms ± 31), and a significant interaction between age group and genotype (**Table 2.2**). Similar to the visuospatial WM task, analysis of simple effects indicated that the effect of genotype was significant in adults ($F(1,302) = 7.12$, $p = .008$, $\eta_p^2 = .023$, see also Dumontheil et al., 2014), with faster RTs in Met/Met individuals than Val carriers, but not in adolescents ($F(1,302) = 1.30$, $p = .255$), where the pattern was in the opposite direction (**Figure 2.2C**). Simple effects analyses also indicated that the difference in social WM RT between Met/Met adults and Met/Met adolescents was greater ($F(1,302) = 22.10$, $p < .001$, $\eta_p^2 = .068$), than between adult and adolescent Val carriers ($F(1,302) = 6.60$, $p = .011$, $\eta_p^2 = .021$) (**Figure 2.2C**), a pattern similar to that observed in the visuospatial WM task. The interaction between genotype and age group remained significant when covarying for backwards digit score ($F(1,300) = 6.73$, $p = .010$, $\eta_p^2 = .022$), visuospatial

WM score (F(1,300) = 490, p = .028, η_p^2 = .016) and visuospatial WM mean RT (F(1,297) = 7.68, p = .006, η_p^2 = .025), as did the main effect of age group (p's < .001).

Table 2.2. Effects of age group, *COMT* genotype and sex on WM tasks.

	Backwards digit score (n = 332)	**Visuospatial WM score** (n = 332)	**Social WM mean RT** (n = 310)
Age group	**F(1,324) = 67.00, p < .001, η_p^2 = .171**	**F(1,324) = 19.16, p < .001, η_p^2 = .056**	**F(1,302) = 28.67, p < .001, η_p^2 = .087**
Genotype	*ns.* p = .242	*ns.* p = .223	*ns.* p = .230
Sex	**F (1,324) = 4.24, p = .040, η_p^2 = .013**	*ns.* p = .804	*ns.* p = .517
Age group x Genotype	*ns.* p = .091	**F(1,324) = 11.09, p = .001, η_p^2 = .033**	**F(1,302) = 7.51, p = .007, η_p^2 = .024**
Age group x Sex	*ns.* p = .411	*ns.* p = .571	*ns.* p = .812
Genotype x Sex	*ns.* p = .430	*ns.* p = .562	*ns.* p = .980
Age group x Genotype x Sex	*ns.* p = .808	*ns.* p = .927	*ns.* p = .134

ns., p > .05.

2.4 Discussion

This is the first study using a common genetic polymorphism affecting the function of the COMT enzyme to probe the development the dopamine neurotransmitter system, through its involvement in social and non-social WM. In a previous study, variation at *COMT* was associated with performance on verbal and visuospatial WM tasks in adults (Dumontheil et al., 2014), findings consistent with the suggestion that Met/Met individuals have levels of dopamine in the PFC suitable for optimal WM performance (Meyer-Lindenberg & Weinberger, 2006). Using a novel social WM paradigm, which requires participants to maintain and manipulate information about the traits of their family and friends over a delay, the previous study of Dumontheil et al. (2014) further demonstrated that social WM performance was also

associated with variation at *COMT*, and that this association was not fully accounted for by individual differences in verbal or visuospatial WM (Dumontheil et al., 2014). Here, data collected in children and adolescents were compared with the data from this adult sample to investigate whether the genetic associations were observed across ages. The results of this study replicate and extend previous work showing that the pattern of better WM performance in Met/Met individuals observed in adulthood emerges during development, suggesting that the levels of PFC dopamine decrease during adolescence (Dumontheil et al., 2011; Jucaite et al., 2010; Wahlstrom et al., 2007).

Our first aim was to investigate developmental changes in social, relative to non-social WM. Both WM and social cognition show develop throughout adolescence, and there are extensive changes in the structure and function of the brain networks that support the processes (reviewed in **Chapter 1**). Consistent with these developmental improvements, adults performed significantly better than adolescents on all three assessments of WM. Of particular interest however, the effect of age on social WM performance was not accounted for by age-related variation in non-social measures of WM. While these results are behavioural in nature, they are consistent with neuroimaging evidence suggesting that in adults the effortful processing of social information is supported by regions of the social brain network, as well as traditional WM networks (Meyer et al. 2012; 2015).

Our second aim was to replicate the finding that the association between *COMT* genotype and visuospatial WM performance is not stable throughout childhood, adolescence and adulthood (Dumontheil et al., 2011; Wahlstrom et al., 2007; Wahlstrom, Collins, et al., 2010; Wahlstrom, White, et al., 2010), reflecting underlying changes in the dopamine neurotransmitter system (Jucaite et al., 2010; Wahlstrom, White, et al., 2010). Indeed, an interaction was observed between *COMT* genotype and age group on the visuospatial WM task score, whereby while the Val allele was associated with poorer visuospatial WM in adulthood, this was not the case in

childhood and adolescence. While performance of Val carriers did not differ between age groups, visuospatial WM performance was better in Met/Met adults than Met/Met children and adolescents. These results replicate those observed in a previous study using the same task in a longitudinal and cross-sectional sample of participants aged 6-25 years old (Dumontheil et al., 2011), where steeper improvements in performance with age were observed in Met/Met individuals than Val carriers, leading to the emergence of the adult pattern of better visuospatial WM performance in Met/Met individuals. It is also consistent with the neuroimaging results from that study, which again showed an interaction between genotype and age, and a gradual emergence of the adult pattern of *COMT* genotype differences in brain activation during executive functions task (e.g. de Frias et al., 2010; Dickinson & Elvevåg, 2009; Mier et al., 2010; Tunbridge et al., 2006; Witte & Flöel, 2012). In this case, older participants started showing the pattern of increased PFC (and in this case, lateral parietal cortex) activation in Val/Val individuals compared to Met carriers during a simpler version of the visuospatial Dot Matrix WM task (Dumontheil et al., 2011). The pattern of findings observed in the current study, consistent with previous findings (Dumontheil et al., 2011; Wahlstrom et al., 2007), is that children and adolescents who are Val carriers do not show deficits in visuospatial WM, in line with the improvement in performance observed in Val/Val adults administered amphetamine (Mattay et al., 2003). These results are therefore consistent with a decrease in prefrontal basal dopamine levels during adolescence (see **Section 1.6.1.1**).

This study also aimed to assess whether a similar developmental difference in *COMT* genotype effects could be observed for a verbal WM task. Although the pattern was similar overall, the genotype by age group interaction was not significant for the backwards digit span task. This weaker effect may reflect the fact that these two tasks rely on partially distinct aspects of the PFC, which may differ in their dopaminergic innervation. A meta-analysis of neuroimaging studies of WM has shown that the caudal superior frontal sulcus appeared specifically sensitive

to spatial content, while a left mid-lateral IFG region was more sensitive to nonspatial, in particular verbal, content (Nee et al., 2013). Alternatively, as both human pharmacological studies (reviewed in **Section 1.6.3.1**) used verbal n-back WM tasks to demonstrate differential effects of tolcapone or amphetamine as a function of *COMT* genotype (Giakoumaki et al., 2008; Mattay et al., 2003), it is possible that *updating* verbal information in WM, which is necessary in n-back tasks, may be more dependent on the dopaminergic system than the maintenance and manipulation (with no updating) of verbal information, which is required in the backwards digit span task.

Finally, this study aimed to assess whether the association between social WM performance and *COMT* genotype also changed with age, and whether these changes were explained by genetic associations with domain-general WM skills. The results show that there was indeed an interaction between *COMT* genotype and age group in the social trait-ranking WM task, with the adult pattern of faster RT in Met/Met individuals (Dumontheil et al., 2014) emerging with age. As in the visuospatial WM task, this result reflected steeper improvements over development in Met/Met individuals than Val carriers, which may be limited by their basal dopamine levels. Importantly, the interaction between genotype and age group in the social WM task was not fully mediated by individual differences in verbal or visuospatial WM, which is similar to what was observed in the adult sample (Dumontheil et al., 2014). The social WM trait-ranking task has been shown to recruit regions of the social brain, in particular the medial PFC, precuneus, and TPJ (Meyer et al., 2012, 2015), in addition to the typical lateral fronto-parietal regions typically observed in standard verbal or visuospatial WM tasks (Nee et al., 2013; Owen et al., 2005; Rottschy et al., 2012; Van Overwalle, 2009). The results of this study therefore suggest that similar changes in basal dopamine levels are occurring in the social WM specific brain regions, in particular the medial PFC, as those occurring in the lateral PFC regions supporting non-social WM. The present finding of parallel developmental changes in WM and social cognition fits with the observation of the prolonged development of cognitive control

and social cognition during adolescence (see **Chapter 1**). More specifically, these findings are in line with evidence suggesting that the social and non-social higher cognitive brain systems tend to be recruited in parallel rather than showing interactions during development (e.g. Dumontheil et al., 2012; Magis-Weinberg et al., 2017).

There was a main effect of sex on performance in the verbal WM task, however no other main effect and no interaction with age group or genotype was observed. There is some evidence that rs4680 associations with behaviour, brain structure and the incidence of psychiatric disorders may interact with sex (Gogos et al., 1998; Harrison & Tunbridge, 2008). Oestrogens, which are thought to down-regulate COMT activity, may be behind these sex differences (Gogos et al., 1998; Harrison & Tunbridge, 2008). Studies with larger numbers and puberty measures may be needed to detect sex differences and to further our understanding of the possible role of sex differences in the development of the dopamine neurotransmitter system. Future studies could also demonstrate a greater specificity of the association between *COMT* genotype and social WM by including a non-social WM task more closely matched to the social trait-ranking task (Meyer et al., 2015). By including an updating verbal WM task, such as the n-back task, they could also assess whether updating verbal information in WM is more dependent on the dopamine neurotransmitter system than the maintenance and manipulation of verbal information measured in the backwards digit span task. The results of the present study suggest that the range of WM tasks used in the literature, as well as differences in the age of participants, may account for some of the inconsistencies in findings previously obtained (Barnett et al., 2008; Dickinson & Elvevåg, 2009; Witte & Flöel, 2012).

In sum, the present study shows that associations between *COMT* genotype and task performance change during development in a range of WM measures. Met/Met individuals show steeper improvements in performance between age groups than Val carriers, suggesting that the progress of Val carriers may be limited by their basal dopamine levels. In line with this,

previous neuroimaging data suggest that top-down excitation from frontal to parietal cortex may be increased during adolescence in Val/Val individuals to compensate for suboptimal levels of dopamine and parietal functioning (Dumontheil et al., 2011; Edin et al., 2009), leading to the increased PFC activation observed in executive function tasks in Val carriers compared to Met/Met individuals in adulthood (de Frias et al., 2010; Dickinson & Elvevåg, 2009; Mier et al., 2010; Tunbridge et al., 2006; Witte & Flöel, 2012). Many psychiatric conditions first appear during adolescence (see **Section 1.7**) and have been associated with atypical functioning of the dopamine neurotransmitter system and genotypic variation in dopamine-related genes (Meyer-Lindenberg & Weinberger, 2006). It is therefore important to better understand how genetic variation affects the development of brain and cognition during adolescence, as this could in turn inform our understanding of adolescent behaviour as well as the emergence of psychiatric disorders. Indeed the findings presented here show that development should be considered when trying to understand the impact of genetic polymorphisms on the mature higher cognition of healthy adult or psychiatric populations (Dumontheil et al., 2011).

CHAPTER 3: Developmental changes in the influence of *COMT* genotype on self-generated thought and trait anxiety

Developmental changes in the dopamine system during adolescence are hypothesized to moderate the association of COMT genotype with reciprocal variation in executive function and anxiety. A cross-sectional sample of healthy adults and adolescents (N=307, aged 9-37 years) performed a behavioural task assessing the flexible processing of self-generated and perceptual information, of which a sub-sample also completed a measure of self-reported trait anxiety. Adolescents showed poorer task performance, particularly for self-generated information. Associations of COMT genotype with both task accuracy and trait anxiety were moderated by age group, with adolescents showing the opposite pattern of association to adults. Variation in self-generated information processing was partially accounted for by visuospatial WM performance, however this did not account for variation in overall task performance. The results of this study extend findings of developmental changes in the association between COMT and WM to other aspects of executive function as well as trait anxiety. Associations of COMT with cognition are not static over the course of the lifespan, therefore a developmental perspective is crucial in understanding the influence of genetic variation on cognition.

[2] The study presented in this chapter has been submitted for publication as:

Kilford E.J. Dumontheil. I., & Blakemore, S-J. Developmental changes in the influence of COMT genotype on self-generated thought and trait anxiety.

This chapter also refers to the following published paper:

Kilford, E.J., Dumontheil. I., Wood, N.W., Blakemore, S-J. (2015) Influence of COMT genotype and affective distractors on the processing of self-generated thought. *Social Cognitive and Affective Neuroscience, 6,* 777-782. doi:10.1093/scan/nsu118

3.1 Introduction

The PFC plays a key role in a diverse range of cognitive processes (Fuster, 2015) and converging evidence implicates the dopaminergic system as an important influence on prefrontal cognition (Cools & D'Esposito, 2011; Goldman-Rakic, 1998). A common genetic polymorphism at rs4680 (*COMT* Val^{158}Met) results in variation in the activity of COMT, an enzyme which degrades extracellular dopamine, and thus can be used to indirectly investigate variation in cognitive processes that are associated with prefrontal dopamine function. In adults, *COMT* genotype has been associated with reciprocal variation in executive function and affective reactivity, which has been proposed to represent a trade-off between cognitive efficiency and emotional resilience (reviewed in **Section 1.6.1.2**).

While the influence of *COMT* genotype on executive function and affective reactivity has been widely studied in adult populations, less is known about its influence in childhood and adolescence. There is converging evidence from rodent models, heritability studies and genetic association studies in developmental samples that the relationship between genetic variation in monoamine systems and neurocognitive phenotypes are not necessarily stable across the lifespan, but instead are moderated by developmental stage (see **Section 1.6.1.3**). These studies highlight the importance of investigating the way in which dopaminergic systems are influenced by genetic variation from a developmental perspective, to understand how these systems mature, and how this varies between individuals.

In adults, the lower COMT activity of Met homozygotes is thought to place them near the apex of the inverted U-shape curve characterising the relationship between dopamine and performance, resulting in superior prefrontal cognition (Mattay *et al.*, 2003; Meyer-Lindenberg and Weinberger, 2006; Giakoumaki *et al.*, 2008; **Figure 1.9A**). However, the dopamine system develops substantially between childhood and adulthood (see **Section 1.6.1.1**), with

dopaminergic synaptic input to the PFC peaking during adolescence (reviewed in Wahlstrom, White, *et al.*, 2010) and *COMT* enzyme activity increasing substantially between birth and adulthood (Tunbridge et al., 2007). Basal dopamine levels can influence associations between *COMT* genotype and cognitive performance, and thus it has been hypothesised that developmental changes in the dopamine system shift the position of each *COMT* genotype group on the dopamine-performance curve (Wahlstrom, White, *et al.*, 2010; **Figure 1.9**).

As discussed in **Section 1.6.1.3**, and **Chapter 3**, a developmental hypothesis of *COMT* effects on cognition would predict that, in contrast to the pattern of superior cognitive performance in Met homozygotes typically observed in adult studies, developmental increases in baseline extracellular dopamine would result in relatively poorer performance in Met/Met adolescents. Furthermore, developmental improvements in prefrontal cognition that occur during adolescence (Crone et al., 2006; Dumontheil, 2014; Luna et al., 2015, 2010) would be predicted to be greater in Met homozygotes, relative to Val carriers, due to their respective shifts toward and away from the apex of the dopamine performance curve. This hypothesis is supported by studies of *COMT* genotype in developmental populations that suggest the WM benefits associated with Met/Met in adulthood emerge during adolescence (Dumontheil et al., 2011; Wahlstrom, Collins, et al., 2010; **Chapter 2**).

The current study set out to investigate developmental changes in the association of *COMT* genotype with variation in executive function and in affective reactivity, based on evidence that *COMT* genotype is associated with reciprocal variation in executive cognition and affective stability in adults (see **Section 1.6.1.2**). Specifically, this study examined the flexible processing of self-generated and perceptually-derived information, an aspect of executive function that can be measured using the Alphabet task (Gilbert, Frith, & Burgess, 2005) and that has previously shown to be more accurate in adult Met homozygotes relative to Val carriers (Kilford et al., 2015). This study also explored whether individual variation in trait anxiety

would be characterised by reciprocal age-moderated genetic associations in a sub-sample of participants for who provided self-report questionnaire data.

The first hypothesis of this study was that, independent of genotype, adults would show superior task performance to adolescents, as the ability to flexibly select and manipulate self-generated information shows developmental improvements late into adolescence (Dumontheil *et al.*, 2010; *Age Hypothesis*). Following the proposal that genetic associations are not necessarily stable across development, and the developmental model of *COMT* influence on cognition (see **Section 1.6.1.3**), the second hypothesis was that the influence of *COMT* genotype on task accuracy would be moderated by age group (*Age x COMT Hypothesis: Executive Function*). The third hypothesis was that the variation in the processing of self-generated information would show overlap with variation in visuospatial WM, which has previously been found to be associated with *COMT* genotype (Dickinson & Elvevåg, 2009; Dumontheil et al., 2011; Mier et al., 2010; Tunbridge et al., 2006; Witte & Flöel, 2012), and may be closely related to as the ability to maintain and manipulate self-generated information (Kilford *et al.*, 2015; *Visuospatial WM Hypothesis*). The final hypothesis was that, in addition to variation in executive function (as measured by the Alphabet task), there may also be developmentally moderated reciprocal effects of *COMT* genotype on trait anxiety (*Age x COMT Hypothesis: Affective Reactivity*).

3.2 Methods and Materials

3.2.1 Participants

As described in **Section 2.2.1**, 379 adult and adolescent participants were recruited. The study was approved by the UCL Research Ethics Committee, and all adult participants, or the parent or guardian of those under 18 years old, gave written informed consent. Participants were tested individually on a series of behavioural tasks and questionnaire assessments (see **Section**

3.2.3) and then provided a saliva sample, which was genotyped for the rs4680 Val^{158}Met substitution on the *COMT* gene (see **Section 2.2.2** for details of the genetic analysis).

As detailed in **Chapter 2**, after exclusions based on developmental disorders (*n* = 2), inability to provide a saliva sample (*n* = 6), failed genotyping (*n* = 10), and ethnicity (*n* = 28; see **Sections 2.2.1**, **2.2.2** for details) genetic data was available for 333 participants. Due to lost behavioural data (*n*=15 and poor performance on the Alphabet task (*n* = 11; see **Section 3.2.3.1**) the final sample included 307 participants (184 adolescents, 123 adults).

3.2.2 Matching of age and genotypic groups

As in **Chapter 2**, effects of *COMT* genotype were explored using a Val dominant model (Met/Met vs. Val carrier; see **Section 2.2.3** for further details) and effects of age were explored by comparing adult (age range: 20.3-39.4 years) and adolescent (age range: 9.0-18.0 years) participant groups (**Table 3.1**). Matching of age and genotype groups was assessed as in **Section 2.2.3**, for the final sample of 307 participants analysed in the current study. Of this sample, there were 84 participants with the Val/Val genotype (27.4%), 143 with Met/Val (46.6%) and 80 participants (26.1%) with Met/Met. This gave an allele frequency distribution of .51 Val and .49 Met (adolescents: .52 Val, .48 Met; adults: .48 Val, .52 Met), which is comparable to previously reported allele frequency distributions of .48 Met and .52 Val (Hapmap European sample). The Hardy-Weinberg equilibrium test indicated that the *COMT* genotypic frequency distribution was in equilibrium across the sample ($X^2(1) = 1.43$, $p = .232$; adolescents: $X^2(1) = 0.50$, $p = .480$; adults: $X^2(1) = 0.95$, $p = .330$).

Univariate ANOVAs on mean age indicated that *COMT* genotype groups were matched for the adolescent group ($F(1,182) = 0.52$, $p = .471$), whereas Val carriers were significantly older than Met/Met individuals in the adult group ($F(1,121) = 4.89$, $p = .029$; **Table 3.1**), as was the case in our previous analysis of only the adult sample (Kilford et al., 2015; Dumontheil et a., 2014). Sex

distribution did not differ significantly between *COMT* genotype groups ($\chi^2(1) < .001$, $p = .992$) or age groups ($\chi^2(1) = 1.22$, $p = .270$), and within each age group there was no difference in sex distribution between the *COMT* groups (adults: $\chi^2(1) = 1.86$, $p = .173$; adolescents: $\chi^2(1) = 1.63$, $p = .202$). There were no significant differences in verbal IQ (Wechsler, 1999) between *COMT* genotype groups ($F(1,299) = 0.04$, $p = .839$) or age groups ($F(1,299) = 0.43$, $p = .513$) and no significant interaction between age group and *COMT* ($F(1,299) = 0.54$, $p = .463$). Therefore, the age and genotype groups were considered sufficiently matched and verbal IQ was not included in further analyses.

Table 3.1. Participant demographics.

	Val carriers				Met/Met			
	N	**Age** *M* (*SD*)	**Verbal IQ**[a] *M* (*SD*)	**Sex** (%F)	***N***	**Age** *M* (*SD*)	**Verbal IQ**[a] *M* (*SD*)	**Sex** (%F)
Adolescents	140	13.2 (2.1)	115.4 (12.0)	55.0%	44	13.0 (2.0)	113.9 (12.2)	65.9%
Adults	87	27.0 (4.2)	113.1 (12.8)	55.2%	36	25.3 (3.2)	114.0 (11.8)	41.7%
All	227	18.5 (7.4)	114.5 (12.3)	55.1%	80	18.5 (6.7)	113.9 (12.0)	55.0%

N=307; %F: Percentage female; *M*: Mean; *SD*: Standard deviation.

[a]Four participants were missing verbal IQ data (4 adults: 1 Met/Met, 3 Val carrier).

In terms of ethnicity, 138 of the adolescents were Caucasian, 43 were not (7 Black (African or Caribbean), 24 Asian (not East Asian), 10 Mixed Asian (not East Asian) and Caucasian, 2 Other (not specified) and 3 did not provide ethnicity information: 2 Met/Met, 1 Val carrier). In the adult sample, 84 were Caucasians, 38 were not (11 Black (African or Caribbean), 3 Mixed Black and Caucasian, 18 Asian (not East Asian), 2 Mixed Asian (not East Asian) and Caucasian, 4 Other (not specified) and 1 did not provide ethnicity information: Val carrier). Chi-square analyses indicated that ethnicity (Caucasian vs. non-Caucasian) differed significantly between *COMT* genotype groups ($\chi^2(1) = 6.91$, $p = .009$), due to a significantly higher proportion of Caucasian individuals within Met homozygotes (84.6%) relative to Val carriers (69.3%). Chi-

square analyses performed on each age group indicated that this difference was particularly driven by the adolescents ($\chi^2(1) = 6.12$, $p = .013$; Val carriers: 65.1% Caucasian; Met/Met 77.7% Caucasian; adults: $\chi^2(1) = 1.80$, $p = .168$).

Due to the fact that there were significant differences in age and ethnicity between *COMT* groups, analyses were repeated including both age and ethnicity (Caucasian vs. non-Caucasian) as covariates to assess whether differences in age or ethnicity accounted for any genotype effects. All genetic effects remained significant, therefore I report in the text and plot in relevant figures the estimated standardized means and standard errors obtained from the original ANOVAs.

3.2.3 Behavioural assessments

Participants performed the Emotional Alphabet task and a standard measure of visuospatial WM (described in detail in **2.2.4.2**), in the second and final position of a series of five cognitive tasks. Two of the other tasks assessed social and verbal WM (described in detail in **Section 2.2.4**), while the third assessed social and non-social relational reasoning and is not analysed in this thesis (see Magis-Weinberg *et al.*, 2017 for analysis of this task in adults). Verbal IQ was assessed using the vocabulary subtest of the WASI (Wechsler, 1999). The entire testing session lasted approximately 1 hour.

3.2.3.1 Emotional Alphabet task

This task was adapted from the Alphabet task (Gilbert et al., 2005), which tests the control of the allocation of attention between perceptually-derived (stimulus-oriented, SO) and self-generated (stimulus-independent, SI) information. SO phases of the task require participants to attend to and process information presented on a computer screen, while SI phases of the require participants to ignore this information and instead attend to and process self-generated information. The adapted task had a factorial design, with two within-subjects factors: block type (SO, SI) and distractor type (no distractor, fearful faces, happy faces).

In SO blocks, participants performed a shape judgement about a green letter presented on a screen. After each response, a new letter was presented, following the sequence of the alphabet. During SI blocks, participants were asked to continue to go through the alphabet in their head and perform the requested judgement on the letter in their head, while ignoring a distracting random blue letter that was presented on the screen (**Figure 3.2**). The specific shape judgement varied across each of three sessions, in order to reduce the likelihood of participants learning the correct series of button presses. Participants judged whether the letters contained either: (1) a curve, (2) a straight vertical line and (3) a straight horizontal line. SO and SI blocks alternated and lasted on average 4.5 trials (range, 3–7 trials).

The task variant used here included the additional factor of distractor type, to explore the effect of distracting socio-affective stimuli on the control and allocation of attention. All trials were pseudo-randomly allocated to one of three distractor conditions: no distractor (50% of the trials), fearful faces (25%) and happy faces (25%). In the latter conditions, the image of either a fearful or happy face was presented centrally behind the letter stimuli. Faces were selected from the NimStim (Tottenham et al., 2009) and NIMH Child Emotional Faces Picture Set (Egger et al., 2011) stimulus sets, from 24 models (12 adult males, 2 adolescent males; 12 adult females, 2 adolescent females), with each model providing both happy and fearful face stimuli. In the no distractor condition the letter was presented directly on a black background (**Figure 3.1**). Faces were 8.1cm x 6cm (H x W) in size, and letters measured 2cm in height (width varied). Participants viewed the screen from approximately 45cm away, giving approximate visual angles of 10.29° (face) and 2.55° (letter). The task was self-paced and, including training and testing phases, lasted on average 9.9 min. The first trial in each block was excluded, as the task included too few of these 'switch' trials to analyse them separately, giving a total of 70 SO and 70 SI trials per participant. Participants with accuracy scores that fell

outside of 3 *SD*'s from the mean in either SO, SI or both trials were considered outliers and excluded from all analyses (*n* = 11; 3 adolescents, 8 adults).

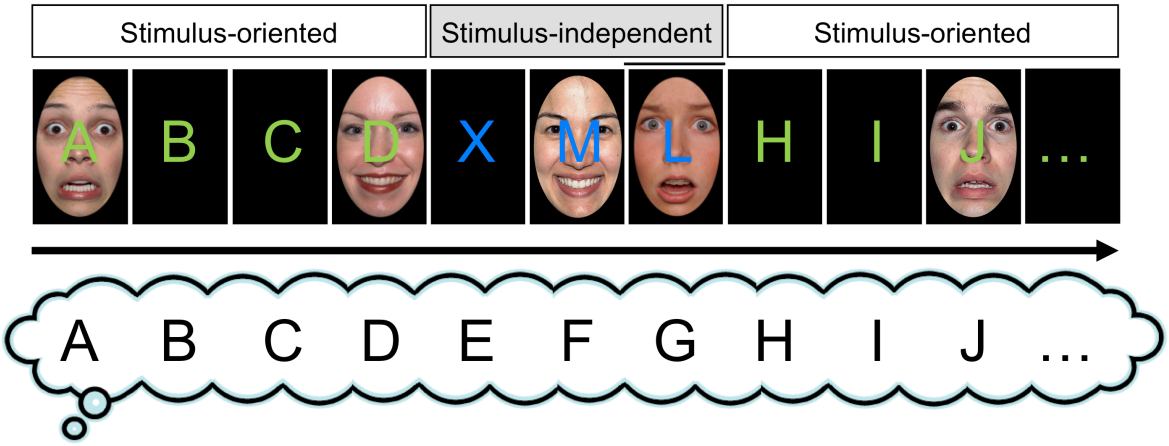

Figure 3.1. Emotional Alphabet task. In stimulus-oriented (SO) blocks, participants made 'yes'/'no' judgements about the shape of green letters presented on the screen in alphabetical order. In stimulus-independent (SI) blocks, participants had to ignore the blue letters on the screen, continue the alphabet sequence in their head (e.g. 'E', 'F', 'G', bottom row) and make the judgement about the letter in their head. In half of all trials, an emotional distractor was present: either a fearful face or a happy face was presented behind the letter.

3.2.3.2 Trait anxiety

Trait anxiety was assessed with either the trait section of the State-Trait Anxiety Inventory for Adults (STAI; Spielberger, 1983) or the State-Trait Anxiety Inventory for Children (STAIC; Spielberger, 1973) in participants aged ≤ 12 years. Adults completed the questionnaire at the end of the testing session, whereas, due to time constraints, adolescents completed it at home and returned it by post. Age and sex appropriate norms included in the STAI and STAIC manuals were used to standardise anxiety scores for adolescents and adults.

3.2.4 Statistical analyses

Statistical analysis was carried out in SPSS (version 21), using Greenhouse-Geisser correction when assumptions for sphericity were not met. Three-way interactions were followed up by

conducting separate repeated measures ANOVAs for each *COMT* genotype group. Two-way interactions were followed up using simple effects analysis (Howell, 1997). Analyses were repeated with age and ethnicity included as covariates to assess whether differences in age or ethnicity accounted for significant genotype effects. All genetic effects remained significant, therefore the estimated standardized means and standard errors obtained from the original ANOVAs are reported in the text and plotted in relevant figures.

Effects of age group and *COMT* genotype on Emotional Alphabet task performance were modelled using mixed-design repeated measures ANOVA, with age group (adolescent, adult), *COMT* genotype (Met/Met, Val carrier) and sex as between subject factors, and block type (SO, SI) and distractor type (no distractor, fearful face, happy face) as within-subject factors. Of specific interest was whether the significant effects of *COMT* genotype effects observed in adults on task accuracy (Kilford et al., 2015) were moderated by developmental stage. In the previous analysis of only the adult sample (Kilford et al., 2015) there was a complex four-way interaction between block type, distractor type, *COMT* genotype and sex, but no straightforward effects of *COMT* genotype on sensitivity to emotional face distractors. Thus, although this factor is included the model for consistency, it was not strongly predicted that there would be associations of age group and *COMT* on the influence of emotional distractors on performance. Effects of age group on RT in correct trials are also presented, although it was not predicted that there would be any effects of *COMT* genotype on RT.

To assess the extent to which significant genetic effects on Emotional Alphabet task performance could be accounted for by *COMT* genetic variation on visuospatial WM performance, analyses were run including visuospatial WM score as a covariate in the model. The study of Kilford et al. (2015) previously found evidence of an overlap between the influence of *COMT* genotype on the ability to select and manipulate SI information and variation in visuospatial WM ability in adults. While a standard measure of verbal WM

(described in **Section 2.2.4.1**) also showed an association with *COMT* genotype, only visuospatial WM showed shared variance with task performance and therefore here only visuospatial WM is included in analyses.

Trait anxiety data was only available for a sub-sample of participants, due to missing data from 1 adult (Met/Met) and 64 adolescents (38.6% of Met/Met; 33.6% of Val carriers; the difference in completion rate between age groups was due to different methods of data collection; see **Section 3.2.3.2**). For this sub-sample, between-subjects ANOVA was used to assess the influence of *COMT* genotype and age group, on variation in self-reported trait anxiety (STAI Spielberger, 1983; STAIC, Spielberger, 1973).

3.3 Results

3.3.1 Genotype-independent age effects on the Emotional Alphabet task

There was a significant main effect of block type ($F(1,299) = 153.21$, $p < .001$, $\eta_p^2 = .339$) on task accuracy: participants were less accurate in SI blocks than SO blocks (see **Table 3.2**). There was a significant main effect of age group on task accuracy ($F(1,299) = 18.97$, $p < .001$, $\eta_p^2 = .060$), with adolescents being less accurate than adults (**Table 3.2**), which was moderated by block type ($F(1,299) = 7.91$, $p = .005$, $\eta_p^2 = .026$). Simple effects analysis indicated that age groups differed significantly on both SO ($F(1,299) = 12.01$, $p = .001$, $\eta_p^2 = .039$) and SI blocks ($F(1,299) = 15.41$, $p < .001$, $\eta_p^2 = .049$; **Figure 3.2A**), however the difference between age groups was greater in SI than SO blocks. There was no main effect of distractor type on accuracy ($F(1.80, 537.58) = 0.03$, $p = .969$).

There was a significant main effect of block type on mean RT ($F(1,299) = 380.73$, $p < .001$, $\eta_p^2 = .560$): participants were slower in SI blocks than SO blocks (**Table 3.2**). There was also a significant main effect of age group ($F(1,299) = 44.18$, $p < .001$, $\eta_p^2 = .129$), whereby

adolescents were slower than adults (**Table 3.2**), which was further modified by block type ($F(1,299) = 51.82$, $p < .001$, $\eta_p^2 = .148$; **Figure 3.2B**). Simple effects analysis indicated that age groups differed significantly on both SO ($F(1,299) = 24.21$, $p < .001$, $\eta_p^2 = .075$) and SI blocks ($F(1,299) = 52.91$, $p < .001$, $\eta_p^2 = .150$), but similar to accuracy the age effect was greater in SI blocks (**Figure 3.2B**). There was a main effect of distractor type on RT ($F(1.81, 570.68) = 3.30$, $p = .040$, $\eta_p^2 = .011$), whereby participants were faster on no distractor trials, than on fearful or happy face trials (**Table 3.2**; p's < .036). This effect of distractor type was not moderated by age group ($p = .512$).

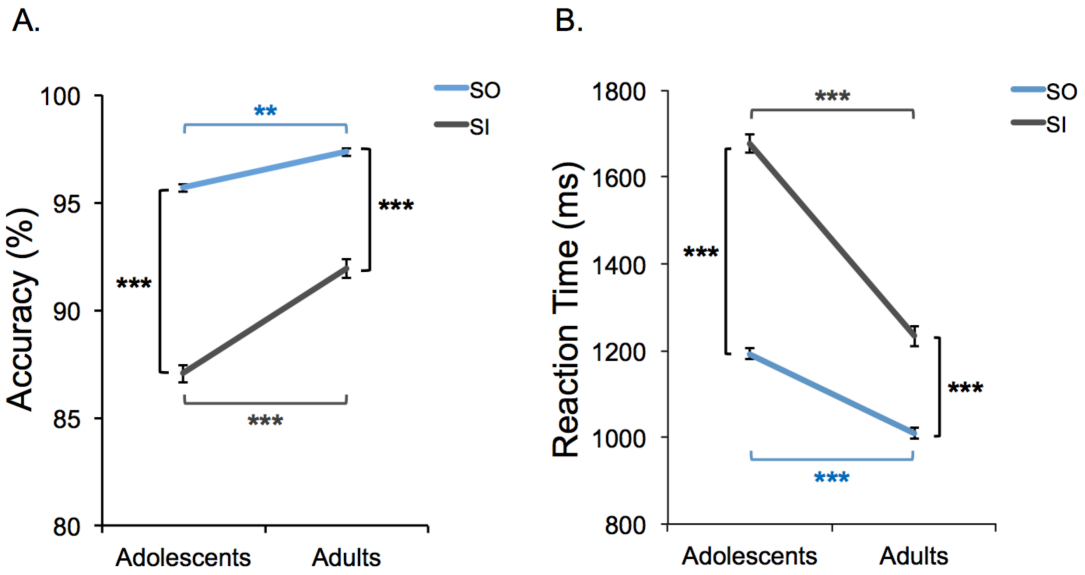

Figure 3.2. Interaction between age group and block type on (A) accuracy and (B) RT in the Emotional Alphabet task (*M* ± *SE*). Simple effects analyses indicated that adolescents were significantly less accurate **(A)** and significantly slower **(B)** than adults on both stimulus-oriented (SO) and stimulus-independent (SI) blocks. ***$p < .001$; **$p < .01$.

Table 3.2. Mean accuracy and RT on the Emotional Alphabet task.

	Age Group		Block Type		Distractor Type		
	Adolescents	Adults	SO	SI	No Face	Fearful	Happy
Accuracy (%)	91.37	94.64	96.51	89.50	93.04	93.02	92.95
M (*SE*)	(0.50)	(0.56)	(0.24)	(0.62)	(0.38)	(0.48)	(0.43)
RT (ms)	1434	1121	1100	1454	1261	1289	1282
M (*SE*)	(31)	(35)	(19)	(31)	(23)	(25)	(25)

Note: SO: Stimulus-oriented; SI: Stimulus-independent.

3.3.2 Genetic effects on the Emotional Alphabet task

As expected, there was no significant main effect or interactions with *COMT* genotype in the RT data (*p*'s > .183). Analysis of genetic effects therefore focused on the accuracy measure. There was no significant main effect of *COMT* genotype on task accuracy (*p* =. 809). However, there was a significant interaction between age group and *COMT* genotype ($F(1,299) = 8.29$, $p = .004$, $\eta_p^2 = .027$; **Figure 3.3A**). Simple main effects analysis indicated significant differences between age groups for Met homozygotes ($F(1,299) = 17.66$, $p < .001$, $\eta_p^2 = .056$) but not for Val carriers ($F(1,299) = 2.10$, $p = .148$, $\eta_p^2 = .007$). Additionally, there were significant differences between *COMT* genotypes in both the adolescent ($F(1,299) = 3.89$, $p = .049$, $\eta_p^2 = .013$) and adult group ($F(1,299) = 4.40$, $p = .037$, $\eta_p^2 = .015$) that occurred in opposite directions: adolescent Val carriers were more accurate than Met/Met adolescents, whereas Met/Met adults were more accurate than adult Val carriers.

The interaction between age group and *COMT* genotype was further moderated by block type ($F(1,299) = 5.48$, $p = .020$, $\eta_p^2 = .018$; **Figure 3.3C**). To understand this interaction, the sample was split by *COMT* genotype and separate follow-up ANOVAs were run for Met/Met participants and Val carriers. For the Met/Met participants, there was a significant interaction between block type and age group ($F(1,76) = 9.68$ $p = .003$, $\eta_p^2 = .113$; **Figure 3.3C**). Simple

effects analysis indicated significant differences between age groups on both SO (F(1,76) = 10.15, p = .002, η_p^2 = .118) and SI blocks (F(1,76) = 16.88, p < .001, η_p^2 = .182), however with a larger age group effect in SI blocks. In Val carriers, there was no significant interaction between age group and block type (p = .648). In the previous analysis of only the adult sample (Kilford et al., 2015), there was a four-way interaction between block type, distractor type, *COMT* genotype and sex. Here this interaction was not significant (F(1.84,548.55) = 2.92, p = .059, η_p^2 = .010), nor was it moderated by age group (p = .544).

3.3.3 Role of visuospatial WM in genetic effects

The significant interaction between age group and *COMT* genotype on visuospatial WM performance reported in **Chapter 2** remained significant in the smaller participant sample considered here (F(1, 298) = 12.46, p < .001, η_p^2 = .040), again with only Met/Met participants showing an effect of age group (F(1,298) = 23.27, p < .001, η_p^2 = .072; Val carriers: F(1,298) = 1.49, p = .224). When the sample was split by age group, as in **Chapter 2** adult Met homozygotes performed better than adult Val carriers (F(1,298) = 7.19, p = .008, η_p^2 = .024), whereas in adolescents the direction of effects occurred in the opposite direction, a difference which reached significance in the sample considered here (F(1,298) = 5.28, p = .022, η_p^2 = .017).

Analyses of significant genotype effects in the Emotional Alphabet task were therefore repeated including visuospatial WM score as a covariate in the model. When visuospatial WM score was included, the interaction between age group and *COMT* genotype was reduced but remained significant (F(1, 297) = 4.36, p = .037, η_p^2 = .015). However, there was no longer a significant interaction between age group, *COMT* and block type (F(1, 297) = 2.30, p = .130). The main effect of age was not altered (F(1, 297) = 10.15, p = .002, η_p^2 = .033), however the interaction between age and block was no longer significant (F(1, 297) = 2.76, p = .098).

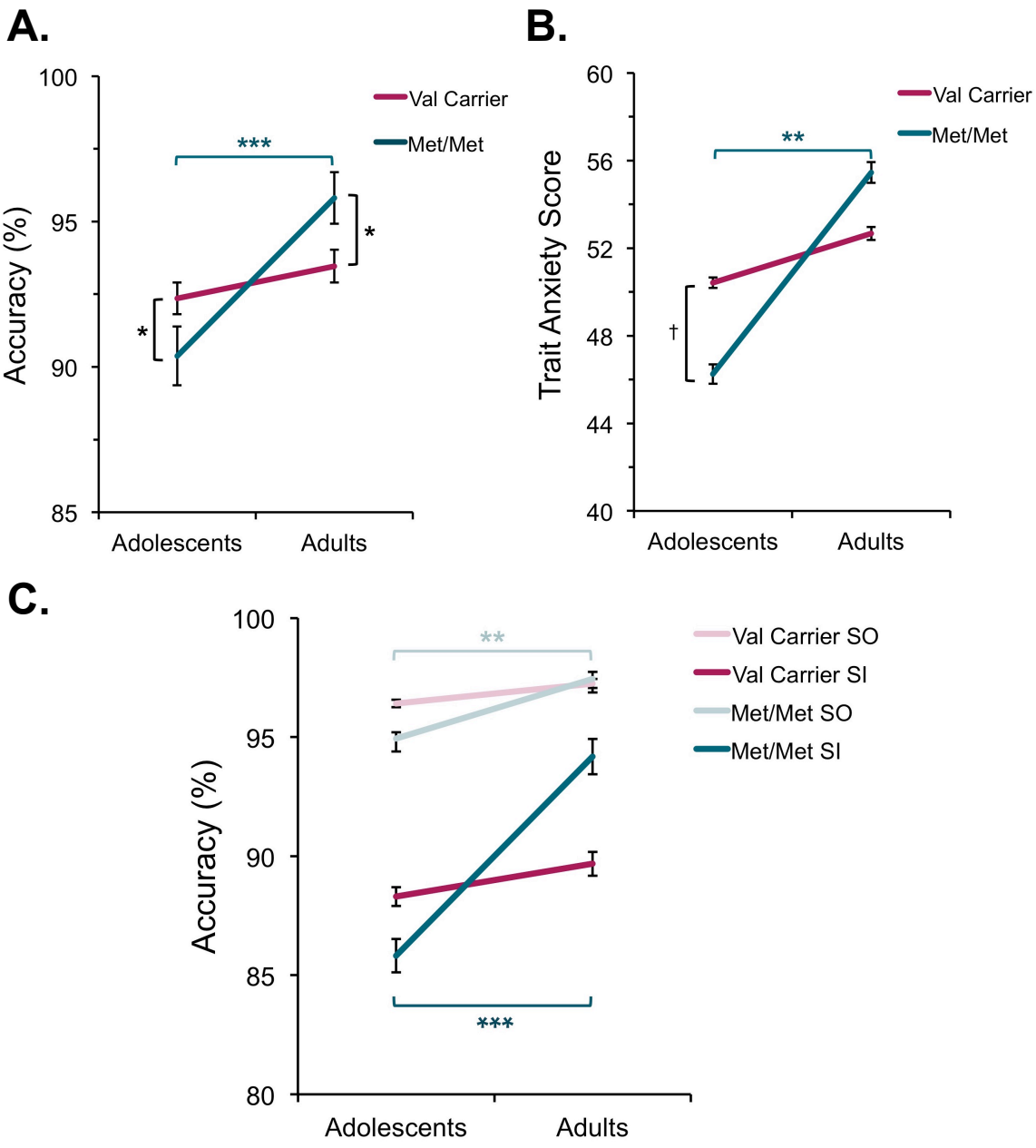

Figure 3.3 Performance on the Emotional Alphabet task and trait anxiety scores as a function of age group and *COMT* genotype (*M* ± *SE*). (A) Interaction between age group and *COMT* genotype on % accuracy. Met/Met adolescents were significantly less accurate than Met/Met adults, whereas adolescent and adult Val carriers did not significantly differ. *COMT* genotypes differed significantly in both age groups. **(B)** Interaction between age group and *COMT* genotype on trait anxiety (normed scores). Met/Met adolescents had significantly lower trait anxiety than Met/Met adults, whereas adolescent and adult Val carriers did not significantly differ. Met/Met adolescents also had marginally lower trait anxiety than adolescent Val carriers. **(C)** Three-way interaction between age group, block type and *COMT* genotype on % accuracy. Met/Met adolescents were significantly less accurate than Met/Met adults on both

stimulus-oriented (SO) and stimulus-independent (SI) blocks, but more so on SI blocks. In Val carriers adolescents and adults did not significantly differ from each other on either.

***$p < .001$;**$p < .01$; *$p < .05$; †$p < .1$.

3.3.4 Developmental genetic effects on trait anxiety

There was no main effect of *COMT* genotype on trait anxiety ($F(1,238) = 0.20$, $p = .657$). However, there was a main effect of age group ($F(1, 238) = 13.57$, $p < .001$, $\eta_p^2 = .054$), whereby adults had higher trait anxiety ($M = 54.06$, $SE = 1.05$) than adolescents ($M = 48.34$, $SE = 1.15$). There was also an interaction between age group and *COMT* genotype ($F(1,238) = 5.01$, $p = .026$, $\eta_p^2 = .021$; **Figure 3.3B**). Simple effects analysis showed that in Met/Met participants there was an effect of age group ($F(1,238) = 11.74$, $p = .001$, $\eta_p^2 = .047$), which was not found in Val carriers ($F(1,238) = 2.07$, $p = .152$). In addition, in adolescents there was a trend effect of *COMT* genotype ($F(1,238) = 3.31$, $p = .070$, $\eta_p^2 = .014$), with Met/Met adolescents reporting lower trait anxiety than adolescent Val carriers (adults: $F(1,238) = 1.76$, $p = .186$).

3.4 Discussion

This study investigated developmental changes in the association of *COMT* genotype with variation in executive function and in affective reactivity, specifically, the flexible processing of self-generated and perceptually-derived information, an ability that continues to develop in late adolescence. This aspect of executive function was examined using an emotional variant of the Alphabet task (Gilbert et al., 2005), which requires participants to flexibly select perceptually-derived or self-generated information, in the presence or absence of socio-affective perceptual distractors. Results indicated effects of age group, and age group by *COMT* genotype interactions, on executive function. Independent of genotype, adolescents were less accurate and slower at the task, particularly for self-generated information.

Furthermore, the association between genotype and task was modulated by age group, with the adolescents showing the opposite pattern of genetic association to the adults. While task-general effects were not accounted for by shared variance with visuospatial WM, task-specific effects were, to some extent. There was also evidence that self-reported trait anxiety showed an age group by *COMT* interaction, providing preliminary evidence that the trade-off pattern of *COMT* genotype effects on executive function and affective reactivity may be moderated by developmental stage.

3.4.1 Genotype-independent age effects on the Emotional Alphabet task

It was hypothesised that, relative to adolescent participants, adults would show superior performance on the Emotional Alphabet task, particularly during the processing of self-generated (SI) relative to perceptually-derived (SO) information (*Age Hypothesis*). Main effects of age group on task performance were found for both accuracy and RT, whereby adolescents were both less accurate and slower to make correct responses. Although adolescents were less accurate and slower in both SO and SI blocks of the task, this was particularly pronounced in SI blocks, in which participants were required to ignore perceptually-derived (SO) information and instead process self-generated (SI) information.

Our findings are broadly in line with previous research (Dumontheil, Hassan, et al., 2010), in which participants aged between 7 and 27 showed developmental improvements (both accuracy and RT) in the ability to resist visual distractors (presence vs. absence of distracting SO information during SI blocks) and in the ability to attend to and manipulate SI, relative to SO, information (RT only). Here, there were effects of age group on both task accuracy and RT when comparing SI blocks to SO blocks, in addition to age-related effects on both block types. There are several possible reasons that age group moderated the effect of block type (SO vs. SI) on both task accuracy and RT in the present study, while Dumontheil et al. (2010) only found developmental effects of RT on this factor. First, the modification of the task to include

emotional distractors might have made the task more difficult. However, this seems unlikely as effects of distractors on task accuracy were not found, and while participants were slower to respond accurately in the presence of emotional distractors, this was not moderated by age. Second, in this study, all SI blocks featured distracting SO information, which was not the case previously. Third, in the adaptation of the paradigm used here, the specific shape judgement to be made varied across the task, which would have reduced the likelihood of participants learning the sequence of button presses and increased the general task demands, as the rule would need to be both remembered and updated.

3.4.2 Developmental genetic effects on the Emotional Alphabet task

It was hypothesised that the influence of *COMT* genotype on the Emotional Alphabet task would be moderated by age group, as genetic associations are not necessarily stable across development (*Age x COMT Hypothesis: Executive Function*). Based on the developmental model of the influence of *COMT* genotype on cognition (Wahlstrom, White, et al., 2010), it was hypothesised that adult Met homozygotes would show superior task performance, particularly on SI blocks, due to their greater levels of prefrontal dopamine. In contrast, due to developmental increases in dopamine concentration during adolescence, relative to childhood and adulthood (reviewed in Wahlstrom, White, *et al.*, 2010), it was hypothesised that adolescent Met homozygotes would show poorer performance due to having excessively high dopamine levels.

In line with these predictions, there were no main effects of *COMT* genotype on task performance. However, there were significant interactions between *COMT* and age group for accuracy on the Emotional Alphabet task (**Figure 3.3A**). Adolescent Met homozygotes were less accurate than Met/Met adults, whereas adolescent Val carriers did not differ from the adult Val carriers. The interaction also reflected the fact that there was a significant effect of *COMT* genotype within the adolescent and adult groups, the direction of which differed

between the groups. While adult Met homozygotes showed superior task performance to adult Val carriers, in the adolescents the opposite pattern was found, whereby adolescent Met homozygotes were less accurate than their Val carrier counterparts. The finding of an interaction between *COMT* and age group is consistent with the predictions of the developmental model of the influence of *COMT* genotype on cognition (Wahlstrom, White, et al., 2010), which hypothesises that Met homozygotes would show greater developmental improvements between adolescence and adulthood as they transition from a position on the dopamine curve characterised by excess dopamine, towards the curve apex (See **Figure 1.9**). On the other hand, Val carriers are likely to show smaller developmental improvements as the reduction in dopamine levels that occurs upon entering adulthood shifts their relative position down the curve. The findings of this study are also consistent with other evidence suggesting that Met allele benefits on prefrontal cognition emerge during adolescence (Dumontheil et al., 2011; Wahlstrom, Collins, et al., 2010).

The interaction between *COMT* and age group was further moderated by the task-specific factor of block type (**Figure 3.3C**). Follow-up analyses of this 3-way interaction indicated that, for Met/Met participants, the difference between adolescent and adult task accuracy was modified by the nature of the task block, that is whether they were processing self-generated (SI) or perceptually-derived (SO) information. Met/Met adults performed significantly better than Met/Met adolescents on both SO and SI blocks of the task, but this difference was more pronounced for SI blocks. In contrast, significant differences in accuracy between age groups were not found for either block type for Val carriers.

3.4.3 Role of visuospatial WM in genetic effects

To evaluate the extent to which age-moderated effects of *COMT* genotype on the Emotional Alphabet task were accounted for by shared genetic variation in visuospatial WM ability, analyses were repeated while controlling for performance on a standard measure of

visuospatial WM. It was hypothesised that genetic variance at *COMT* in the ability to maintain and manipulate self-generated information accurately would show overlap with variation visuospatial WM (*Visuospatial WM Hypothesis*), in line with findings from the previous study of adults (Kilford et al., 2015). Including visuospatial WM as a covariate in the model accounted for at least some of the variance in the ability to select and manipulate SI information. While the interaction between age group and *COMT* on overall task performance remained significant, the task-specific 3-way interaction between age group, *COMT* and block type was no longer significant. The main effect of age group on task accuracy also remained significant after controlling for variation in visuospatial WM, whereas the interaction between age group and block was no longer significant. These findings suggest that variation in visuospatial WM ability, either due to age-moderated effects of *COMT* genotype on prefrontal dopamine or genotype-independent developmental improvements in prefrontal cognition, may to some extent account for variation in the ability to select and manipulate SI information.

Taken together, the above genetic effects (**Sections 3.4.2** and the present section) are consistent with the idea that developmentally-moderated effects of *COMT* on prefrontal dopamine are associated with variation in the ability to select and manipulate SI information. In line with hypotheses, Met/Met individuals showed more pronounced age-related improvements in this ability relative to Val carriers (**Figure 3.3C**). Furthermore, there was evidence of shared genetic variance on both the processing of SI information and visuospatial WM. However, Met homozygotes also showed more pronounced age-related improvements on the task in general, which were not accounted for by variation in visuospatial WM. This may reflect more general improvements in executive function, that facilitate more general task performance, for example, the ability to keep task goals active, and/or update the current shape-rule.

3.4.4 Developmental Genetic effects on Trait Anxiety

It was hypothesised that, in addition to effects on executive function, there may be reciprocal, developmentally moderated effects of *COMT* genotype on trait anxiety (*Age x COMT Hypothesis: Affective Reactivity*). While adults reported generally higher anxiety than adolescents, Met/Met adults had significantly higher trait anxiety than Met/Met adolescents, an effect which was not found in Val carriers (**Figure 3.3B**). Similar to the finding that age group moderated the association between *COMT* genotype and executive function, this suggests greater age-related changes in associations between *COMT* and cognition in Met homozygotes than Val carriers.

Our finding that age group moderated the association of *COMT* genotype with both executive function and trait anxiety are consistent with a developmental model of *COMT* effects on cognition, as well as evidence suggesting *COMT* is associated with reciprocal variation in cognitive efficiency and affective reactivity (Dickinson & Elvevåg, 2009; Goldman et al., 2005; Mier et al., 2010; Papaleo et al., 2008). In adults, the lower COMT activity of Met homozygotes has been associated with superior executive function but increased affective reactivity and anxious temperament (Mier et al., 2010; Montag et al., 2012). The opposite pattern of associations was observed in adolescents, whereby adolescent Met homozygotes displayed relatively poorer executive functioning and lower trait anxiety than their Val counterparts.

3.4.5 Implications and Conclusions

Association studies of *COMT* genotype can provide a useful tool for furthering our understanding of the association between prefrontal dopaminergic variance and cognition during development, without involving drug administration or invasive imagery techniques. While this study was cross-sectional, and looked at age in a categorical rather than a continuous manner, it was nevertheless able to demonstrate evidence that developmental stage moderates the associations between *COMT* genotype and cognition and that different

genotype groups show a different pattern of age-related effects. However, longitudinal studies are needed to examine the way in which trajectories of cognitive development vary between each *COMT* genotype group. The findings of this study underline the importance of taking developmental stage into account when studying the influence of genetic variation on behaviour and cognition, consistent with previous genetic association studies in developmental samples (Lau et al., 2009; Sebastian, Roiser, et al., 2010; Wiggins et al., 2014) and heritability studies (Hannigan et al., 2016; McGrath et al., 2012). In this study, had adolescents and adults been studied as a single population, no effects of *COMT* would have been observed as opposing patterns of associations were observed for different age groups. Relationships between *COMT* genotype and cognition have not always been replicated (Barnett et al., 2008; Dickinson & Elvevåg, 2009; Montag et al., 2012; Witte & Flöel, 2012), and one factor contributing to this may be a failure to consider the impact of individual differences such as developmental stage and sex on the baseline functioning of the prefrontal dopamine system.

CHAPTER 4: The computational development of reinforcement learning during adolescence

Adolescence is a period of life characterised by changes in learning and decision-making, processes which do not rely on a unitary system, but instead require the coordination of different cognitive processes that can be mathematically formalised as dissociable computational modules. This study aimed to trace the developmental time-course of the computational modules responsible for learning from reward or punishment, and learning from counterfactual feedback. Adolescents and adults carried out a novel RL paradigm in which participants learned the association between cues and probabilistic outcomes, where the outcomes differed in valence (reward versus punishment) and feedback was either partial or complete (either the outcome of the chosen option only, or the outcomes of both the chosen and unchosen option, were displayed). Computational strategies changed during development: whereas adolescents' behaviour was better explained by a basic RL algorithm, adults' behaviour integrated increasingly complex computational features, namely a counterfactual learning module (enabling enhanced performance in the presence of complete feedback) and a value contextualisation module (enabling symmetrical reward and punishment learning). Unlike adults, adolescent performance did not benefit from counterfactual (complete) feedback. In addition, while adults learned symmetrically from both reward and punishment, adolescents learned from reward but were less likely to learn from punishment. This tendency to rely on rewards and not to consider alternative consequences of actions might contribute to our understanding of decision-making in adolescence.

The study presented in this chapter has been previously published as:

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4.1 Introduction

The computational framework of RL formally captures value-based decision-making, using mathematical models of varying levels of complexity to characterise the way in which individuals learn from their environment and use this information improve future choices by maximising the expected value of future outcomes (Daw, 2014; Rangel et al., 2008). The simplest RL algorithm (Q-learning) learns action-outcome associations directly from experienced rewards on a trial and error basis (Rescorla & Wagner, 1972; Watkins & Dayan, 1992). However, more complex behaviours, such as counterfactual learning and punishment avoidance learning cannot be explained using this basic RL algorithm, due to its computational simplicity.

Counterfactual learning refers to the ability to learn not only from direct experience, but also from hypothetical outcomes (the outcomes of the option(s) that were not chosen; (Boorman, Behrens, & Rushworth, 2011; A. G. Fischer & Ullsperger, 2013). Punishment avoidance, compared to reward seeking, requires an additional computational step in which outcomes are considered relative to a reference point (i.e. outcome valuation is contextualised; Maia, 2010; Palminteri, Khamassi, Joffily, & Coricelli, 2015). Thus, compared to simple reward seeking, counterfactual and avoidance learning are more computationally demanding. Accordingly, whereas simple reward learning has been largely and robustly associated with the striatum (Kahnt, Heinzle, Park, & Haynes, 2011; O'Doherty, 2004; Palminteri et al., 2013), punishment and counterfactual processing have been consistently associated with the dorsal prefrontal system and the insula, areas that are classically associated with cognitive control (Boorman et al., 2011; Casey, Galvan, & Hare, 2005; Koechlin, 2014; Palminteri et al., 2012; Ullsperger, Fischer, Nigbur, & Endrass, 2014).

Significant changes in value-based decision-making are observed during adolescence (reviewed in **Section 1.3.4**). Thus, investigating the RL strategies that characterise learning and decision making, and how these may differ according to developmental stage, has the potential to increase our understanding of adolescent value-directed behaviour. Dual systems theories of adolescent brain development have pointed to differential functional and anatomical development of limbic regions, such as the striatum, and cognitive control regions and there is some evidence to support this notion (see **Sections 1.3.2 - 1.3.4)**. It was hypothesised that differences in the developmental trajectories of limbic and prefrontal regions, and their associated cognitive functions, might be translated into a difference in the computational strategies used by adolescents compared with adults, with more complex computational strategies emerging as the PFC and cognitive control processes mature and become increasingly integrated with motivational processing systems.

To test this hypothesis, adults and adolescents performed an instrumental probabilistic learning task in which they had to learn which stimuli had the greatest likelihood of resulting in an advantageous outcome through trial and error. Both outcome valence (Reward vs. Punishment) and feedback type (Partial vs. Complete) were manipulated using a within-subjects factorial design (**Figure 4.1A**), enabling the investigation of both punishment avoidance learning and counterfactual learning within the same paradigm. In a previous study using this task, model comparison indicated that adult task performance was best explained by a computational model in which basic RL was augmented by a counterfactual learning module (to account for learning from outcomes of unchosen options) and a value contextualisation module (to account for learning efficiently to avoid punishments; **Figure 4.2A**; Palminteri et al., 2015). Here, it was hypothesised that while adults would integrate more sophisticated computations, such as counterfactual learning and value contextualisation, a basic RL algorithm would successfully encapsulate value-based decision-making in adolescence.

4.2 Material and Methods

4.2.1 Participants

A sample of 50 participants aged between 12 and 32 years were recruited for this study. Adolescents (*N* = 26; 12-17 years) were recruited from a local Community Theatre and UCL volunteer databases; adults (*N* = 24; 18-32 years) were recruited from UCL volunteer databases. The study was approved by the UCL Research Ethics Committee, and participants, or their legal guardians (adolescents), gave written informed consent. All participants were native English speakers and non-verbal IQ was assessed using the matrix reasoning subset of the WASI (Wechsler, 1999). Due to group differences in non-verbal *T* scores ($t(48) = 4.59$, $p < .001$), analysis was restricted to those participants with scores falling within the range shared by both groups. This gave a final sample of 38 participants, in which age groups (20 adults; 18 adolescents) were matched in non-verbal IQ ($t(36) = 2.01$, $p > .05$) and gender composition ($\chi^2(1) = 0.08$, $p = .782$; see **Table 4.1**).

Table 4.1. Sample demographics.

Age Group	*N*	Gender Ratio (Male : Female)	Age (years) *M* ± *SE* (range)	Matrix Reasoning *T* score *M* ± *SE* (range)
Adolescents	18	8 : 10	14.27 ± 0.30 (12 - 16)	98.5 ± 1.1 (46 - 61)
Adults	20	8 : 12	22.35 ± 0.83 (18 - 32)	101.4 ± 1.0 (43 - 61)

4.2.2 Behavioural task

Participants performed a probabilistic instrumental learning task adapted from a previous neuroimaging study (Palminteri et al., 2015). The task had two phases, a learning task and a post-learning test. The learning task was designed to manipulate both outcome valence (Reward vs. Punishment) and feedback information (Partial vs. Complete; **Figure 4.1**) using a 2 x 2 factorial design. In the learning task, participants viewed pairs of abstract symbol cues

(characters from the Agathodaimon alphabet) on a computer screen and had to choose one of the two. There were eight different cues, divided into four fixed pairs so that a given cue was always presented with the same counterpart. As such, the cue pairs represented stable choice contexts. Each of the four pairs corresponded to one of four context conditions (Reward/Partial, Reward/Complete, Punishment/Partial and Punishment/Complete). In Reward contexts, the 'good' outcome was gaining a point and a 'bad' outcome was not gaining a point, whereas in Punishment contexts, a 'good' outcome was not losing a point, while a 'bad' outcome was the loss of a point. Within each pair, one cue had a higher probability of resulting in a 'good' outcome (75%; the 'correct' option; G75 and L25 cues) than the other (25%; the 'incorrect' option; G25 and L75 cues). Depending on the pair of cues (i.e. choice context), participants were presented with only the outcome of the chosen cue (Partial feedback) or the outcomes of both the chosen and unchosen cues (Complete feedback). Each cue pair was presented 20 times in a pseudo-randomised order, giving a total of 80 trials. Cue pairs were presented either side of a central fixation cross, with side of presentation pseudo-randomised so that each cue was presented an equal number of times on each side.

Participants were instructed to acquire as many points as possible, as this would determine their final payment. Participants were informed that only their chosen outcome counted toward their points score, even if sometimes both outcomes were presented, and that both winning points and avoiding losing points were equally important to maximise payoff. After hearing the task instructions, participants performed a training session, before starting the learning task. Each trial started with a fixation cross (1 second), followed by presentation of the cue pairs (2 seconds), during which participants had to select either the left or right cue by pressing the corresponding button. After the choice window, a red arrow indicated the chosen option (0.5 seconds), before the cues disappeared and the chosen cue was replaced by the outcome (2 seconds; '+ 1 point' and a happy smiley, '0 points' and no image, or '- 1 point' and an unhappy smiley; **Figure 4.1B**). In Complete feedback contexts, the outcome corresponding

to the unchosen option (counterfactual feedback) was also displayed. Note that while, on average, outcomes for each cue pair were anti-correlated on an individual trial, the outcomes of each cue were independent from one another. Thus, for example, in Complete feedback contexts participants could observe the same outcome for each cue (37.5% of trials).

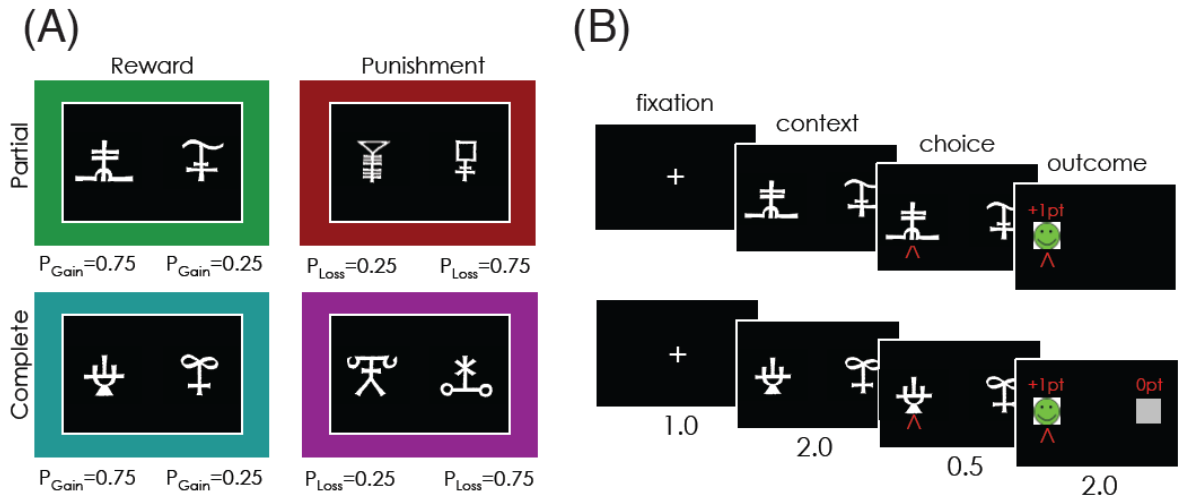

Figure 4.1. Learning task design. (A) The learning task 2 x 2 factorial design. Different symbols were used as cues in each context, and symbol to context attribution was randomised across participants. The coloured frames are purely illustrative and represent each of the four context conditions throughout all figures. Reward: gain maximisation context; Punishment: loss minimisation context; Partial: counterfactual feedback was not provided; Complete: counterfactual feedback was provided; P_{Gain}: probability of gaining 1 point; P_{Loss}: probability of losing 1 point. **(B)** Time course of example trials in the Reward/Partial (top) and Reward/Complete (bottom) conditions. Durations are given in seconds.

After the learning task, participants completed a post-learning test of cue value. Here, the eight cues from the learning task were presented as unfixed pairs of all 28 possible pair-wise combinations (Frank, 2004; Palminteri et al., 2015; Wimmer & Shohamy, 2012). Each pair was presented 4 times in a pseudo-random order, giving a total of 112 trials. For each cue pair, participants had to indicate the option with the highest value during the preceding learning session (i.e. the cue with the highest likelihood of resulting in a 'good' outcome). Unlike the learning task, choice was self-paced and no feedback was presented. Instructions for this task

were given after the learning task, to prevent participants from explicitly memorising cue values. Participants were informed that cues would not necessarily be shown in pairings that had been presented previously during the learning task. While participants could not earn points in this assessment, they were encouraged to respond as if points were at stake.

All participants received a fixed amount of £5 for taking part, plus an additional amount (£0 - £10) that varied according to their performance on the learning task (their average correct choice rate). A correct response was defined as a choice directed toward the 'correct' stimulus (i.e., the most rewarding or the least punishing cue of the pair). For correct choice rate ≤ 0.50 participants received no bonus, for 0.50 > correct choice rate ≥ 0.75 participants received a £5 bonus, and for correct choice rate > 0.75 participants received a £10 bonus. As a result of this payoff scheme, on average adults received £11.75 ± 0.9 and adolescents received £9.72 ± 0.9. Payoff did not significantly differ between age groups ($t(36) = 1.8$, $p > .08$).

4.2.3 Behavioural analyses

Correct choice rate and RT were extracted from the learning task as dependent variables. Learning curves were computed from the trial-by-trial cumulative average of correct responses during the learning session. The cumulative average in a given trial 't' was calculated by averaging the correct choice rate from trial 1 to trial 't'. Statistical analyses were performed on the learning curves, using a mixed-design ANOVA, with trial (1 : 20), valence (Reward, Punishment) and feedback information (Partial, Complete), as within-subjects factors, and age group (adolescents, adults) as the between-subjects factor. Inclusion of trial as a factor is important to enable the assessment of whether or not observed effects are due to learning, i.e. 'learning-dependent' (Palminteri et al., 2011). Between-group post hoc comparisons were performed on final correct choice rate (which is directly proportional to the final number of points earned) and on the correct choice rate improvement (i.e. correct choice rate at trial 20 minus correct choice rate at trial 1) using independent-samples *t*-tests. Examining both the

final, and the improvement in, correct choice rate is important in being able to draw conclusions regarding differences in learning.

Although RL models and paradigms are primarily concerned with choice data, RTs are also supposed to carry relevant information concerning both option and decision values (Guitart-Masip, Duzel, Dolan, & Dayan, 2014; Shenhav, Straccia, Cohen, & Botvinick, 2014). Therefore RTs were also extracted from the learning task, smoothed with a three trial sliding window and submitted to the same statistical model used for the correct choice rate. For RTs, between-group post hoc comparisons were performed on the RT improvement (i.e. RTs at trial 1 minus RTs at trial 20) and the final RT (RTs at trial 20).

Post-learning choice rate (i.e. the number of time a cues was chosen in the post-learning test, divided by the total number of trials the cue was presented in) indirectly reflects instrumental learning and should be higher for the more advantageous (Correct) cues of the learning task (G75 for Reward contexts; L25 Punishment contexts). Post-learning choice rate was extracted for each of the eight cues and analysed using a mixed-design ANOVA with age group (adolescents, adults) as a between-subjects factor, and cue valence (Reward, Punishment), feedback information (Partial, Complete), and cue correctness (Correct, Incorrect) as within-subject factors. Between-group post hoc comparisons were performed on the decision value, that is the difference between Correct and Incorrect cues (i.e. G75 minus G25, in Reward contexts; L25 minus L75 in Punishment contexts) using independent samples t-tests (2-sided). This difference provides a measure of cue discrimination: a significant and positive value indexes the participant's tendency to prefer the optimal option during the preceding learning task. Statistical analyses were performed using Matlab (www.mathworks.com) and R (www.r-project.org).

4.2.4 Computational models

Participants' performance was analysed with RL models (Sutton & Barto, 1998). The goal of all models was to find the option that maximises the cumulative future reward (R) in each choice context (state: s). The model space included three nested and increasingly sophisticated models (**Figure 4.2A**). Model 1 was a standard Q-learning model, which instantiates learning from direct experience by updating the value of the chosen option according to the outcome of each trial. Counterfactual information and the context in which choices are presented are not taken into account. In Model 2, the standard Q-learning model was augmented by a computational module enabling learning from counterfactual information(A. G. Fischer & Ullsperger, 2013). Finally, in Model 3, Model 2 was further augmented by a contextual learning module, enabling the updating of option values relative to the choice context in which they were presented (Louie & Glimcher, 2012). Model 3, has recently been proposed to account for: i) the ability to perform similarity in both Punishment and Reward contexts; ii) counterfactual learning; and iii) inverted preferences for intermediate value cues (i.e. small gains and small losses) when assessed post-learning (Palminteri et al., 2015). Since Model 1 and Model 2 can be considered as special cases of Model 3, only Model 3 is described.

These models were deliberately kept as simple and parsimonious as possible. Model 3 tracks the mean of the distribution of values of the choice context and uses it to centre option values. Notably, this model represents a minimal departure from standard RL algorithms that imply context or option values are updated with a delta rule, such as Q-learning and actor–critic algorithms (Sutton & Barto, 1998). Given that the focus of this study was the computational (dynamic) processes of learning, and also given that outcome variance and valence were not independently modulated in the task, the model space did not include descriptive and aggregate economic models, such as cumulative prospect theory (CPT; Hsu, Krajbich, Zhao, & Camerer, 2009). Furthermore, exploratory simulations showed that models with different

learning rates for positive and negative prediction errors were not capable of discriminating between the task factors and were therefore not included (see **Appendix A.1** for further details).

At trial t the chosen (c) and the unchosen (u) option values of the current context (s) are updated with the Rescorla-Wagner rule (also called delta-rule; Rescorla & Wagner, 1972):

$$Q_{t+1}(s,c) = Q_t(s,c) + \alpha_1 \delta_{C,t}$$

and

$$Q_{t+1}(s,u) = Q_t(s,u) + \alpha_2 \, \delta_{U,t},$$

The key idea behind Model 3 is that it separately learns and tracks the choice context value V(s). Crucially, the state value (V(s)) is not merely the sum of the option values, but rather it actively affects (controls) them. In fact V(s) is used to centre option prediction errors δ_C and δ_U as follows:

$$\delta_{C,t} = R_{C,t} - V(s) - Q_t(s,c)$$

and

$$\delta_{U,t} = R_{U,t} - V(s) - Q_t(s,u)$$

(in the Complete feedback contexts only, in the Partial feedback condition no counterfactual prediction error is calculated: $\delta_{U,t} = 0$). Consequently, the option values are no longer calculated on an absolute scale, but are relative to their choice context value V(s). V(s) itself is learnt with a delta rule:

$$V_{t+1}(s) = V_t(s) + \alpha_3 * \delta_{V,t}$$

where α_3 is the context value learning rate and $\delta_{V,t}$ the context value prediction error, which is calculated as follows:

$$\delta_{V,t} = R_{Tot,t} - V_t(s)$$

where R_{Tot} is the average outcome of a trial and is calculated in the Complete feedback contexts as the average of the factual and the counterfactual outcomes as follows:

$$R_{Tot,t} = (R_{C,t} + R_{U,t}) / 2$$

Given that R_{Tot} is designed to be a measure that encompasses the value of both chosen and unchosen options, in order to incorporate the unchosen option in the Partial feedback trials $R_{Tot,t}$ is calculated as follows:

$$R_{Tot,t} = (R_{C,t} + Q_t(s,u)) / 2$$

Model 2 can be derived from Model 3 by assuming no context value learning (α_3 =0). Model 1 can be derived from Model 2 by assuming no counterfactual learning ($\alpha_2 = \alpha_3 = 0$). In all models decision-making relies on a softmax function. The probability of choosing the option 'a' over the option 'b' is given by:

$$P_t(s,a) = (1 + exp(\beta*(Q_t(s,b) - Q_t(s,a))))^{-1}$$

where β is the inverse temperature parameter.

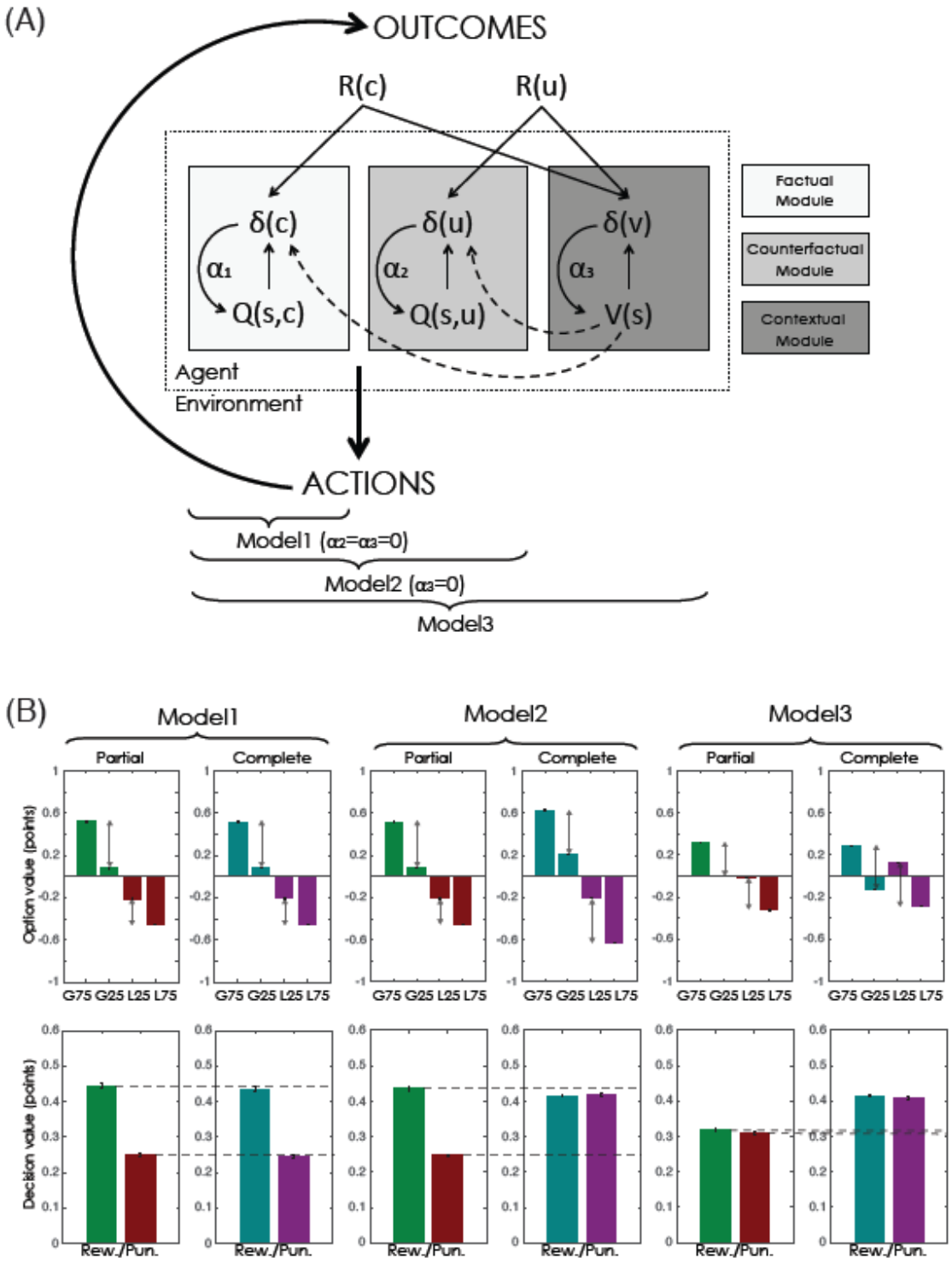

Figure 4.2. Computational models and ex-ante model simulations. (A) The schematic illustrates the computational architecture of the model space. For each context (or state, 's'), the agent tracks option values (Q(s,:)), which are used to decide amongst alternative courses of action. In all contexts, the agent is informed about the outcome corresponding to the chosen option (R(c)), which is used to update the chosen option value (Q(s,c)) via a prediction error (δ(c)). This computational module ('factual module') requires a learning rate (α_1). In the

presence of Complete feedback, the agent is also informed about the outcome of the unchosen option (R(u)), which is used to update the unchosen option value (Q(s,u)) via a prediction error (δ(u)). This computational module ('counterfactual module') requires a specific learning rate (α_2). In addition to tracking option value, the agent also tracks the value of the context (V(s)), which is also updated via a prediction error (δ(v)), integrating over all available feedback information (R(c) and, where applicable, R(u)). This computational module ('contextual module') requires a specific learning rate (α_3). The full model (Model 3) can be reduced to Model 2 by suppressing the contextual module (i.e. assuming $\alpha_3 = 0$). Model 2 can be reduced to Model 1 (basic Q-learning) by suppressing the counterfactual module (i.e. assuming $\alpha_2 = \alpha_3 = 0$). (**B**). Bars represent the model estimates of option values (top row) and decision values (bottom row), plotted as a function of the computational models and task contexts. G75 and G25: options associated with 75% and 25% chance of gaining a point, respectively; L75 and L25: options associated with 75% and 25% chance of losing a point, respectively. Decision value represents the difference in value between the correct and incorrect options (G75 minus G25 in Reward contexts; L25 minus L75 in Punishment contexts).

It should be noted that the model space did not include a model in which standard Q-learning (Model 1) was augmented with value contextualisation ($\alpha_3 > 0$) but not counterfactual learning $\alpha_2 = 0$). The first reason for this was that previous studies involving counterfactual feedback have already proposed models implementing counterfactual learning and thus the counterfactual learning module did not represent a novel approach, but rather a benchmark by which to compare to the value contextualisation module(Boorman et al., 2011; A. G. Fischer & Ullsperger, 2013; Li & Daw, 2011). The second reason was conceptual. Since the counterfactual learning module learns value in a manner that is independent from participants' actual choices, when feedback is complete its update rule requires the integration of information from both the chosen (R_C) and the unchosen outcomes (R_U). A model that integrates (R_U) information to update context value but does not use this information to update the unchosen option value would be conceptually unsound, and thus was not included. However, for the sake of completeness, a post-hoc additional model comparison analysis

involving such a model was run, the inclusion of which did not alter the results (see **Appendix A.2**).

4.2.5 Parameter optimisation and model selection procedure

In a first analysis, model parameters were optimised by minimising the negative log-likelihood of the data, given different parameter settings, using Matlab's fmincon function initialised at different starting points, as described in Palminteri et al. (2015; ranges: $0 < \beta <$ infinite, and $0 < \alpha_n < 1$). Note that model fitting and parameter optimisation involved the learning, and not the post-learning, data. Negative log-likelihoods and inverse temperature parameters (β) were submitted to a mixed-design ANOVA with group (adolescents, adults) as the between-subjects factor and Model (1 : 3) as the within-subjects factor, in order to compare the between-group baseline quality of fit (without taking into account the model complexity; see **Section 4.3.2**).

In a second analysis, model parameters were optimised by minimising the Laplace approximation to the model evidence (LPP):

$$LPP = log(\Sigma P(D|M,\vartheta)),$$

where D, M and θ represent the data, model and model parameters, respectively.

The LPP increases with the likelihood (a measure of quality of fit) and is penalised by the size of the parameter space (a measure of model complexity). Thus, the LPP represents a trade-off between accuracy and complexity and can guide model selection. In addition, LPP maximisation, by including priors over the parameters, avoids degenerate parameter estimates, due to the small number of trials and the noisiness of the data. To avoid bias in model selection the same priors were used for the adolescent and adult group. In a control

analysis, w the model was fitted to maximise the negative log-likelihood and the LPP, assuming a single set of parameters for each group (group-level optimisation; see **Tables 4.1, 4.2, 4.3**).

Individual LPPs were fed into the mbb-vb-toolbox (https://code.google.com/p/mbb-vb-toolbox/; Daunizeau et al., 2014), a procedure that estimates the expected frequency and the exceedance probability for each model within a set of models, given the data gathered from all participants (summarised in **Table 4.4**). Expected frequency is a quantification of the posterior probability of the model (PP), i.e. the probability of the model generating the data obtained from any randomly selected participant. Exceedance probability (XP) is the probability that a given model fits the data better than all other models in the set, i.e. has the highest PP. The more recently introduced LPP-derived PP criterion was chosen, as opposed to the more frequently used Bayesian Information Criterion (BIC; Schwarz, 1978), based on the results of a priori model simulations which suggested that for this dataset and model set the former was the more sensitive model selection criterion (see **Appendix A.3**). Furthermore, PP has an advantage over likelihood ratios as it can be directly compared between subjects (log-likelihood ratios are calculated within subjects), which was necessary in order to compare model fitting between age groups, a key aim of this study. To do so, the PP of the models was submitted to a mixed-design ANOVA with group (adolescents, adults) as the between-subjects factor and Model (1 : 3) as the within-subjects factor (see **Section 4.3.2**).

4.2.6 Model simulations

Both ex-ante and ex-post model simulations were performed. Ex-ante model simulations, in which data was simulated from 1000 virtual participants, were used to illustrate the properties of each model. The parameter values used in these simulation were $\beta = 5.0$, $\alpha_n = 0.3$, similar to values observed in previous studies (Li & Daw, 2011; Palminteri et al., 2012). Note that using different parameter values led to very similar results. For each model, the model estimates of the option values (Q(s, :)) and decision values (ΔQ(s); **Figure 4.2B**) were analysed, both of

which are associated with different aspects of task performance. In the learning task, performance is a function of the learned difference in Q-values (ΔQ(s)) between the correct and incorrect option (decision value); in contrast, preference in the post-learning test allows inferences to be made about the value of individual options, which cannot be directly inferred from learning performance. Ex-ante model simulations were not submitted to statistical testing because the *N* was arbitrary.

Once the model parameters were optimised, ex-post model simulations of the data were used to assess their generative performance by analysing the model simulation of the data (Corrado, Sugrue, Brown, & Newsome, 2009). Model estimates of choice probability were generated on a trial-by-trial basis using the individual history of choices and outcomes, using the best fitting set of model parameters from each participant's age group's best fitting model (i.e. Model 1 for adolescents; Model 3 for adults). Model-simulated correct choice probability was then submitted to the same statistical analysis that was used to assess the actual choices made by participants in the learning task and in the post-learning test. Note that qualitative discrepancies between actual and simulated data at the beginning of the learning curves should be interpreted with caution. In fact, in the behavioural data, the variance is higher in the early trials and then progressively decreases due to integrating over the past trials, whereas in model simulations the variance follows a different trajectory. By definition, the variance is 0 in the first trial, in which the probability of a correct response is 0.5 for all virtual participants/contexts and then progressively increases following individual histories of choice and outcomes, as well as individual differences in free parameters.

4.3 Results

4.3.1 Ex-ante model simulations: Learning task

To describe the properties of the three models and illustrate how their performances differ across the different choice contexts (states, 's'), ex-ante model simulations were run and the model estimates of option values (Q(s,:)) and decision values (ΔQ(s); **Figure 4.2B**) were analysed. Decision value is defined for each context as the difference in value between the correct and incorrect option. Decision values ultimately determine the percentage of correct choices during the learning task. Model 1 (basic Q-learning) predicts higher performance in the Reward compared to the Punishment contexts, a learning asymmetry predicted by the punishment avoidance learning paradox (Seymour, Maruyama, & De Martino, 2015), and similar performance in the Partial and Complete feedback contexts. Model 2 (Model 1 plus the counterfactual learning module) permits an improvement in performance in the Punishment/Complete context, however still predicts a learning asymmetry in the Partial feedback contexts. Finally, Model 3 (Model 2 plus the value contextualisation module) predicts similar performance in the Reward and Punishment contexts and increased performance in the Complete compared to the Partial feedback contexts: this is the behavioural pattern that was expected for the adult group, based on the findings of a previous study (Palminteri et al., 2015).

4.3.2 Model fitting: Baseline quality of fit did not differ between adolescents and adults

The three models were fitted to individual histories of choices and outcomes, in order to obtain, for each participant and each model, the parameters that maximised the negative log-likelihood of participants' choices during the learning task (see **Table 4.2**).

To assess whether baseline model fitting differed between adolescents and adults, the negative log-likelihood and the inverse temperature parameter (β) were submitted to a mixed-design ANOVA with age group (adolescents, adults) as the between-subjects factor and model as the within-subjects factor. For negative log-likelihood (a measure of model quality of fit), there was no main effect of group ($F(1,36) = 1.3$, $p > .2$) and the interaction between group and model did not reach significance ($F(2,72) = 2.7$, $p < .08$). Note that the main effect of model cannot be tested since the models are nested and therefore the negative log-likelihood can only decrease. Analysis of the inverse temperature (β) parameter supported these results. This parameter can be taken as a measure of how well choices are predicted by the model and strongly correlates with the model likelihood (for all models: $r > 0.93$; $p < .001$). There was no main effect of group ($F(1,36) = 2.3$, $p > .1$), but there was a significant interaction between group and model ($F(2,72) = 5.0$, $p < .01$; **Figure 4.3A**). Post hoc comparisons showed that this interaction was driven by adults showing increases in inverse temperature when comparing Model 1 to Model 2 ($t(19) = 3.2$, $p < .01$) and Model 2 to Model 3 ($t(19) = 2.2$, $p < .05$). Baseline (Model 1) inverse temperature did not differ between adults and adolescents ($t(36) = 0.4$, $p > .70$). The absence of main effects of group indicates that baseline quality of fit was not different between age groups, thus allowing further model comparison analyses.

Table 4.2. Negative log-likelihood maximisation.

	Random	**Model 1**	**Model 2**	**Model 3**
Subject-level				
Adolescents	998.1	817.1	772.6	771.2
Adults	1109.0	865.2	752.3	733.1
Group-level				
Adolescents	998.1	922.9	922.9	922.9
Adults	1109.0	962.2	897.2	895.9

Note: Random refers to a model that assumed chance performance for all trials: P(correct choice) = 0.5. Subject-level: parameters were optimised assuming a set of free parameters per

subject. Group-level: parameters were optimised assuming a single set of free parameters per age group.

4.3.3 Model comparison: Different computational models explained learning in adolescents compared to adults

In a second analysis, model parameters (presented in **Table 4.3**) were optimised by minimising the LPP, from which model PP and XP was then computed (see **Section 4.2.5**). To compare model fitting between age group, as above the PP of the three models was submitted to a mixed-design ANOVA with group as the between-subjects factor and model as the within-subjects factor (**Figure 4.3B**).

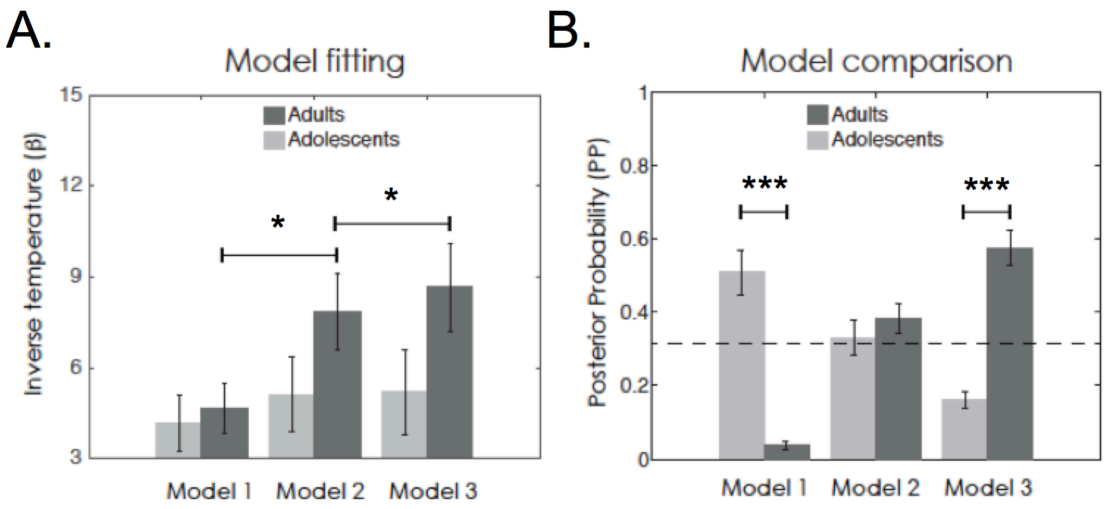

Figure 4.3. Baseline model fitting and model comparison. (A) Choice inverse temperature (β) of each model for adults and adolescents. (**B**). Posterior probability (PP) of each model for adults and adolescents. The dotted line indicates chance level (PP = .33). Error bars represent *SE*. *p < .05; one-sample *t*-test (2-sided), ***p < .001; independent-samples *t*-test (2-sided).

This analysis indicated a significant interaction between group and model ($F(2,72) = 38.9$, p < .001). The main effect of model did not reach significance ($F(2,72) = 3.0$, p < .06). Note that the main effect of group cannot be tested, since the model PP's by definition must sum to one, thus creating equal group means. Post hoc comparisons showed that in the adolescent group,

the posterior probability of Model 1 was significantly greater than chance level ($t(17) = 3.0$, $p < .01$; exceedance probability = .77) and greater than that of the adult group ($t(36) = 8.0$, $p < .001$). Conversely, in adults, the PP of Model 3 was significantly greater than chance level ($t(19) = 5.2$, $p < .001$; XP = .79) and greater than that of the adolescents ($t(36) = 7.8$, $p < .001$; see also **Table 4.4**, **Figure 4.3B**). This result indicates that different computational models explained learning behaviour in the two groups. More precisely, a simple RL model better described adolescents' behaviour, whereas a more complex model, which integrates counterfactual and contextual learning processes, better accounted for adults' behaviour.

Table 4.3. Model Parameters.

	Model 1		**Model 2**			**Model 3**			
	β	α^1	β	α^1	α^2	β	α^1	α^2	α^3
Subject-Level									
Adolescents	4.18 ± .91	.45 ± .06	5.19 ± 1.22	.36 ± .05	.29 ± .05	5.20 ± 1.39	.33 ± .04	.38 ± .05	.42 ± .06
Adults	4.66 ± .81	.49 ± .06	7.85 ± 1.28	.36 ± .05	.29 ± .04	8.65 ± 1.45	.35 ± .06	.28 ± .04	.39 ± .07
Group-Level									
Adolescents	2.73	.38	2.73	.38	.00	2.73	.38	.00	.00
Adults	3.90	.39	5.69	.24	.23	6.09	.21	.21	.04

Note: Parameters were optimised by minimising the LPP. Subject-level parameters ($M \pm SE$) were optimised assuming a set of free parameters per subject. Group-level parameters (M) were optimised assuming a single set of free parameters per age group. Adolescents were systematically fitted with $\alpha^2 = \alpha^3 = 0$ (basic Q-learning), whereas adults were fitted with $\alpha^2 > 0$ and $\alpha^3 > 0$ when these parameters were permitted by the model to deviate from 0.
β: inverse temperature; α^1: factual learning rate; α^2: counterfactual learning rate; α^3: contextual learning rate.

4.3.4 Behavioural analyses: correct choice rate

Our model comparison analyses suggest that adults and adolescents do not use the same computational strategy (**Figure 4.3B**). If this is the case, this computational result should be reflected in behavioural differences between the two groups. To verify this, the correct choice rate learning curves were analysed using a mixed-design ANOVA with group (adolescents, adults) as the between-subjects factor and trial (1 : 20), valence (Reward, Punishment) and feedback information (Partial, Complete) as within-subjects factors (**Figure 4.4A**). There was a significant main effect of trial on correct choice rate ($F(19,684) = 26.8$, $p < .001$), in which the rate of correct choices increased over the course of the learning task. There was also a significant interaction between group and trial ($F(19,684) = 5.7$ $p < .001$), which was further moderated by valence ($F(19,684) = 2.0$, $p < .01$). This suggests that adults and adolescents differed in the way their correct choice rate evolved during learning and that this difference was moderated by the valence of the outcome (Reward vs. Punishment). Post hoc comparisons performed on the correct choice rate improvement (the difference between the first and last trials) indicated that, compared to adults, adolescents showed lower correct choice rate improvement in the Punishment/Partial context ($t(36) = 2.9$, $p < .01$; **Figure 4.4B**).

Table 4.4. Bayesian model comparison.

	Model 1		**Model 2**		**Model 3**	
	PP	**XP**	**PP**	**XP**	**PP**	**XP**
Subject-Level						
Adolescents	**.51 ± .06**	**.77**	.33 ± .05	.02	.16 ± .02	.02
Adults	.04 ± .01	.00	.38 ± .04	.20	**.57 ± .05**	**.79**
Group-Level						
Adolescents	.70	.48	.21	.28	.08	.24
Adults	.00	.21	.31	.32	.68	.47

Note: Subject-level: Parameter optimisation assumed a set of free parameters per subject. Group-level: Parameter optimisation assumed a single set of free parameters per age group. PPs are reported as $M \pm SE$ at the subject-level.

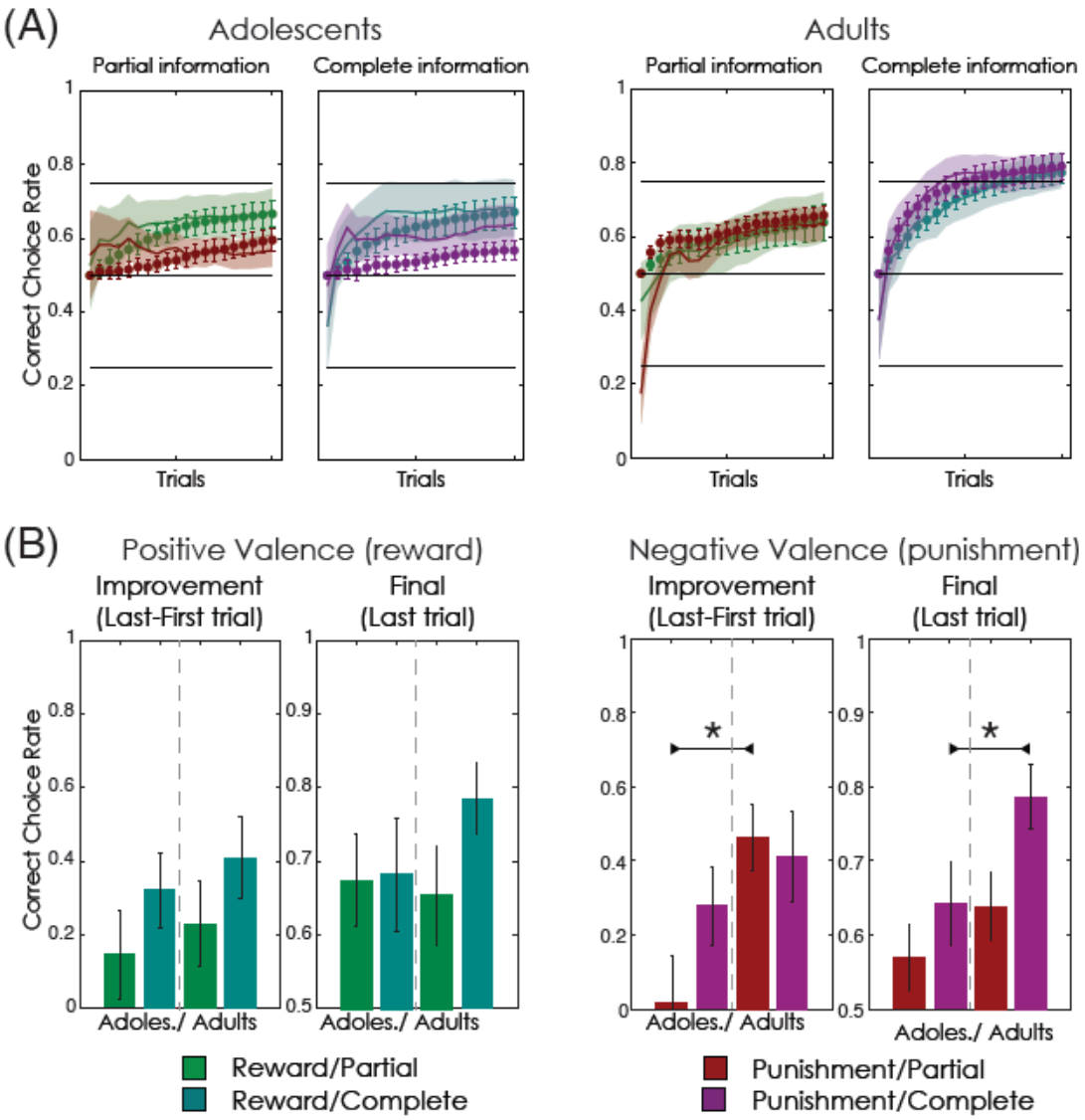

Figure 4.4. Correct choice rate. (A) Learning curves in adolescents and adults. Mean correct choice rate is plotted as bold lines set within shaded areas representing *SE*. The different colours represent different choice contexts. Ex-post model-simulated learning curves, estimated using parameters from each age group's best fitting model (Model 1 for adolescents; Model 3 for adults), are superimposed on the behavioural data, with the dots representing model-simulated correct choice probabilities (*M* ± *SE)*. (**B**) Bars represent the correct choice rate improvement (difference in correct choice rate between last and first trials) and the final correct choice rate (last trial) in Reward and Punishment contexts (*M* ± *SE*). Chance level (i.e. no learning) is 0.0 for correct choice rate improvement, and 0.5 for final correct choice rate. *$p < .05$; independent-samples *t*-test (2-sided).

Post hoc comparisons performed on the correct choice rate in the final trial (trial 20) indicated that, compared to adults, adolescents had lower rates of correct choice in the Punishment/Complete context ($t(36) = 2.1$, $p < .05$; **Figure 4.4B**). Finally, while there was no significant interaction between feedback information and group, exploratory analyses indicated that whereas adults performed better in Complete feedback contexts (final correct choice rate: $t(19) = 2.7$, $p < .05$), adolescents showed no such positive effect of counterfactual information on correct choice rate ($t(17) = 0.9$, $p > .4$). To summarise, adolescents displayed reduced punishment learning compared to adults. Also consistent with the computational analyses, adolescent performance did not benefit from counterfactual feedback, although the interaction with group did not reach statistical significance (see **Table 4.5**).

4.3.5 Ex-post model simulations: Learning task

The behavioural analyses support the model comparison analyses, suggesting that adolescents implement a simpler computational model than adults (**Figure 4A** and **4B**). To further verify the ability of the models to reproduce the observed behaviour, the optimised model parameter values were used to simulate correct choice rate (ex-post model simulations; see **Section 4.2.6**). Trial-by-trial model estimates of the probability of choosing the correct response in the learning task were generated for each participant using the best fitting model for their age group (i.e. Model 1 for adolescents; Model 3 for adults). Model-simulated data were submitted to the same analyses as the behavioural data, which indicated a significant 3-way interactions between group, valence and trial ($F(19,684) = 2.8$, $p < .001$), and between group, feedback information and trial ($F(19,684) = 8.7$, $p < .001$), consistent with the reduced capacity to learn from counterfactual information and to efficiently avoid punishments observed in adolescents (**Figure 4A**).

4.3.6 Behavioural analyses: RTs

RTs were analysed in the same way as correct choice rate, using a mixed-design ANOVA with group (Adolescents, Adults) as between-subjects factor and trial (1 : 20), valence (Reward,

Punishment) and feedback information (Partial, Complete) as within-subject factors (**Figure 4.5**). There was a significant main effect of trial on RT ($F(19,684) = 12.1$, $p < .001$), reflecting a learning-induced RT improvement. There was also a significant main effect of valence ($F(1,36) = 9.6$, $p < .01$), and a significant interaction between valence and trial ($F(19,684) = 5.9$, $p < .001$), which reflected shorter RTs in the Reward compared to the Punishment contexts.

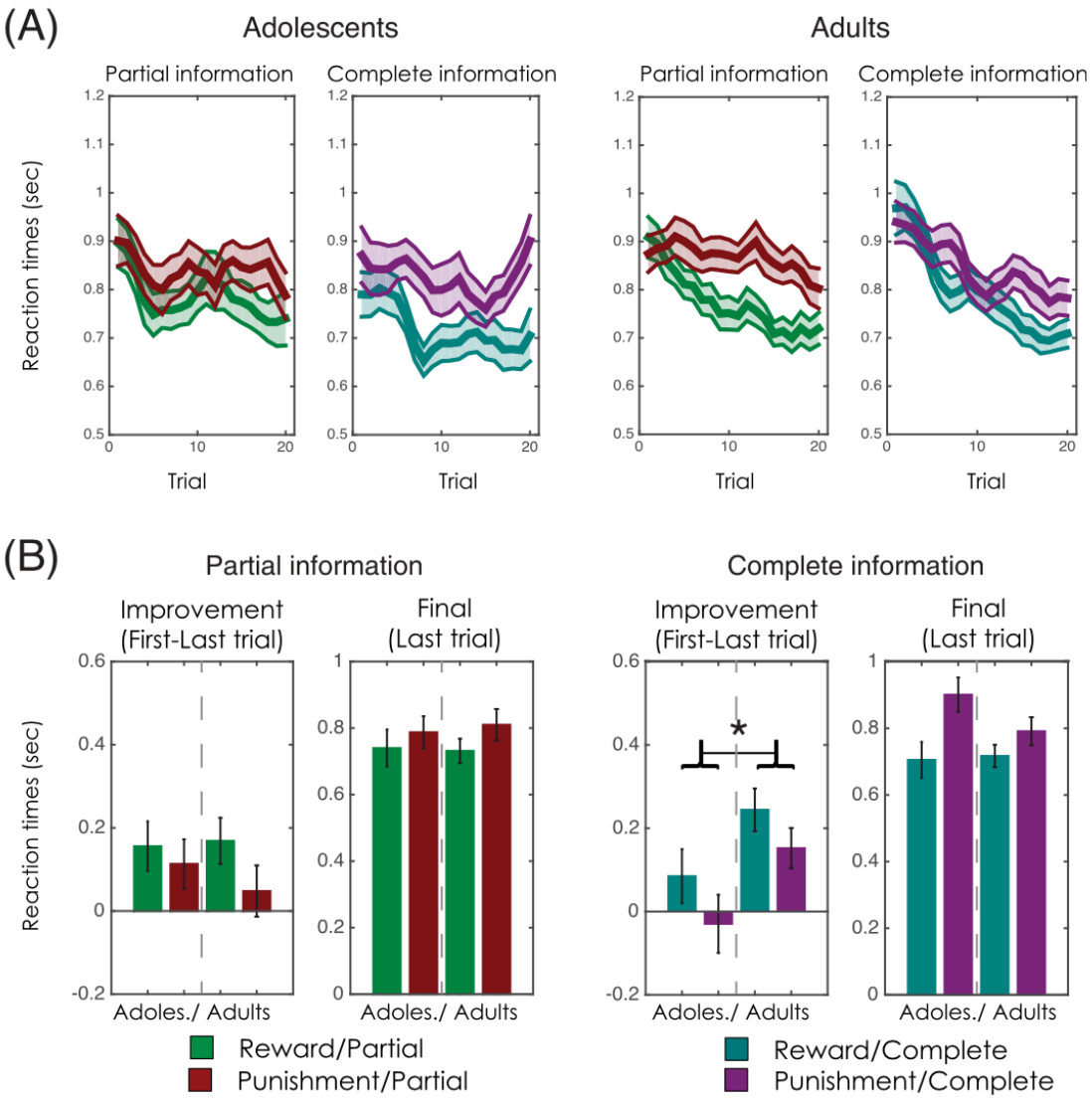

Figure 4.5. Analysis of RT effects. (A) RT curves in adolescents and adults. Mean RT is plotted as bold lines set within shaded areas representing *SE*. The different colours represent different choice contexts. (**B**) Bars represent the RT improvement (difference in RT between first and last trials) and the final RT (last trial) in the Partial and the Complete feedback contexts ($M \pm SE$). *$p < .05$; independent-samples *t*-test (2-sided).

Table 4.5. Behavioural data as function of choice context (*M* ± *SE*).

	Adolescents	Adults
Correct Choice Rate (% correct)		
Overall	64.1 ± 5.0 #	71.4 ± 2.9 ###
Reward/Partial	67.4 ± 6.2	65.3 ± 6.8
Punishment/Partial	56.8 ± 4.5	63.8 ± 4.6
Reward/Complete	68.2 ± 7.7	78.1 ± 4.9
Punishment/Complete	63.8 ± 5.6	78.6 ± 4.3
RT (s)		
Overall	.79 ± .03	.83 ± .03
Reward/Partial	.78 ± .03	.78 ± .03
Punishment/Partial	.84 ± .03	.87 ± .03
Reward/Complete	.71 ± .03	.81 ± .03
Punishment/Complete	.82 ± .03	.85 ± .03

Note: Overall refers to average performance collapsed across contexts. Neither overall correct choice rate ($t(36) = 1.3$, $p > .1$) nor overall RT ($t(36) = 1.3$, $p > .3$) differed between groups. $^{\#}p < .05$ and $^{\#\#\#}p < .001$ (2-sided, one-sample, t-test), when comparing to chance level (i.e. 50% correct responses; random performance).

Post hoc comparisons performed on the final RT (RTs at trial 20) indicated that both adults and adolescents showed higher RTs (i.e. slower responses) in the Punishment compared to the Reward contexts (adults: $t(19)= 2.1$, $p < .05$; adolescents: $t(17) = 2.9$, $p < .05$). There was also a significant interaction between feedback information and trial, indicating that RT improvement differed in Partial and Complete feedback contexts ($F(19,684) = 2.3$, $p < .001$). There was no main effect of group on RT ($F(1,36) = 1.6$, $p > .20$), however there was a significant interaction between group and feedback information ($F(1,36) = 12.2$, $p < .01$), which was further moderated by trial ($F(19,684) = 4.1$, $p < .001$), indicating that RT improvement in the two groups was differentially influenced by the presence of counterfactual information. Post hoc comparisons performed on the RT improvement (i.e. RTs at trial 1 minus RTs at trial 20) indicated that, compared to adults, adolescents showed less of a reduction in RT in the Reward/Complete context, which was not quite significant ($t(36) = 1.8$, $p < .06$), and the

Punishment/Complete context, which was significant ($t(36) = 2.2$, $p < .05$; $t(36) = 2.4$, $p < .05$; when collapsed across the two Complete contexts; **Figure 4.5B**). Accordingly, whereas adult RT was reduced in the Complete compared to the Partial context (–89.8ms: $t(19) = 2.4$, $p < .05$), adolescents increased their speed (+10.7ms; $t(17) = 1.8$, $p < .09$). To summarise, in both age groups RTs were slower in the Punishment compared to the Reward contexts, which is consistent with an implicit Pavlovian inhibition effect (Guitart-Masip et al., 2014). Consistent with the model comparison analyses and choice, the influence of counterfactual information on RT over the course of the learning task was reduced in adolescents compared to adults (see **Table 4.5**).

4.3.7 Behavioural analyses: Post-learning test

The post-learning test measured the ability to retrieve and transfer the value of the cues, as learnt by trial and error during the learning task. Post-learning choice rate was extracted for each of the eight cues and analysed using a mixed-design ANOVA with group (Adolescents vs. Adults) as a between-subjects factor, and cue valence (Reward vs. Punishment), feedback information (Partial vs. Complete), and cue correctness (Correct vs. Incorrect) as within-subject factors. There was a significant effect of valence ($F(1,36) = 92.2$, $p < .001$) on post-learning choice rate, indicating that cues associated with reward (G75 and G25) were preferred over those associated with punishment (L25 and L75). Similarly, Correct cues (G75 and L25) were preferred over Incorrect ones (G25 and L75; $F(1,36) = 38.1$, $p < .001$; **Figure 4.6**). These effects indicate that, overall, participants were able to retrieve the value of the cues during the post-learning test. Crucially, the analysis also revealed a significant interaction between feedback information and cue correctness ($F(1,36)= 11.6$, $p < .01$), which was further moderated by group ($F(1,36) = 6.0$, $p < .05$). Post hoc between-groups comparisons of these difference scores (**Figure 4.6** and **Table 4.6**) indicated that cue discrimination was significantly lower in the adolescents than in the adults in both the Complete contexts (Reward/Complete: $t(36) = 2.4$, $p < .05$; Punishment/Complete: $t(36) = 2.6$, $p < .05$). While adults showed improved cue

discrimination in Complete contexts compared to Partial contexts ($t(19) = 4.1$, $p < .001$), adolescents did not ($t(17) = 0.6$, $p > .5$). To summarise, in adults, cue value retrieval in the post-learning test was enhanced for cues associated with counterfactual feedback during the learning task. Adolescents did not show this effect.

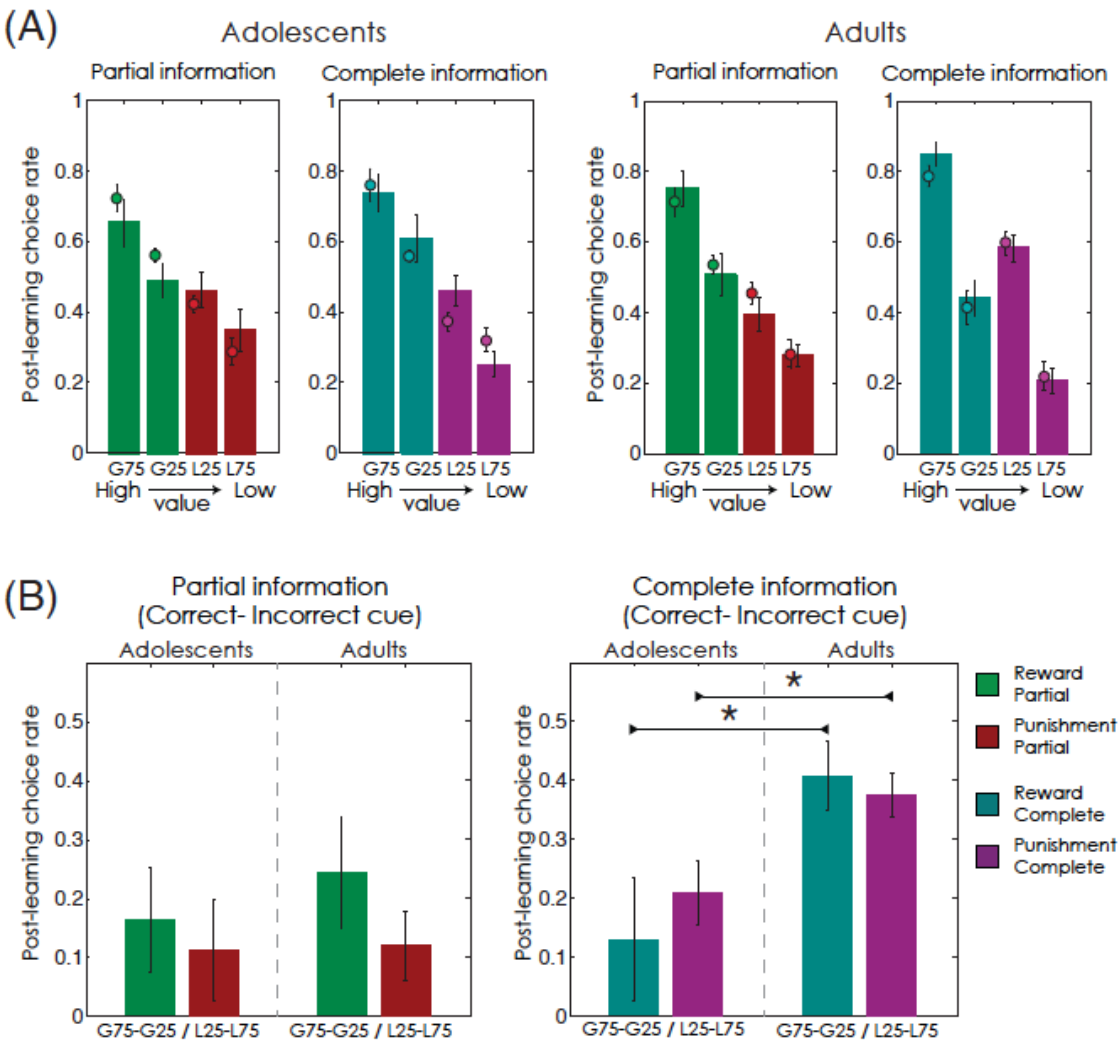

Figure 4.6. Post-learning test. (A) Post-learning test choice rates for adolescents and adults. The behavioural data are superimposed with coloured dots representing the model-simulated post-learning choices, estimated using parameters from each age group's best fitting model (Model 1 for adolescents; Model 3 for adults). **(B)** Bars represent cue discrimination, the difference between post-learning choice-rates for Correct vs. Incorrect cues (G75 minus G25 in Reward contexts; L25 minus L75 in Punishment contexts), in Partial and Complete contexts. Chance level (i.e. no cue discrimination) is 0.0. Error bars represent *SE*. * $p < .05$: independent samples *t*-test (2-sided).

Table 4.6. Post-learning test choice rates.

Post-Learning Test Choice Rate (%)	Adolescents	Adults
G_{75} Reward/Partial (Correct)	65.3 ± 6.8	75.0 ± 5.1
G_{25} Reward/Partial (Incorrect)	48.8 ± 5.0	50.7 ± 5.8
L_{25} Punishment/Partial (Correct)	46.0 ± 5.0	39.5 ± 4.7
L_{75} Punishment/Partial (Incorrect)	34.7 ± 6.1	27.7 ± 3.0
G_{75} Reward/Complete (Correct)	73.6 ± 5.2	84.6 ± 3.3
G_{25} Reward/Complete (Incorrect)	60.7 ± 6.7	43.9 ± 5.1
L_{25} Punishment/Complete (Correct)	45.8 ± 4.3	58.0 ± 3.8
L_{75} Punishment/Complete (Incorrect)	25.0 ± 3.6	20.5 ± 3.5

Note: Post-learning test choice rates (*M* ± *SE*) are summarised according to cue type (cue correctness is indicated In brackets)**.** G75 and G25: options associated with 75% and 25% chance of gaining a point, respectively; L75 and L25: options associated with 75% and 25% chance of losing a point, respectively.

4.3.8 Ex-post model simulations: Post-learning test

The model's ability to account for choices made in the post-learning test was also tested. Under the assumptions that choices in the post-learning test were dependent on the final option values in the learning task, and that there was no significant memory decay between the two tasks, the post-learning test, as in previous studies, can be used as an out-of-sample measure to compare the predictions of the different models (Frank, 2004; Wimmer & Shohamy, 2012). The probability of choice in the post-learning test was calculated using a softmax function, using the same individual choice inverse temperature optimised during the learning task (note that similar results have been obtained by optimising a beta specific to the post-learning test). Again, the model-simulated post-learning choice rates were submitted to the same statistical analyses as the behavioural data (**Figure 4.6**). Analysis of the model-simulated choices in the post-learning test also showed a significant interaction between group, feedback information and correctness ($F(1,36) = 13.0$, $p < .001$), consistent with the behavioural finding of enhanced cue value retrieval in adults for cues associated with

counterfactual information that was not observed in adolescents, and the model comparison analyses. As indicated by the ex-ante model-simulated option values, higher cue discrimination in both the Reward/Complete and Punishment/Complete contexts, and inverted preferences for intermediate value cues (i.e. small gains and small losses), requires both counterfactual learning and value contextualisation (**Figure 4.2B**).

4.4 Discussion

Adolescents and adults performed an instrumental probabilistic learning task that involved learning to seek rewards or to avoid punishments. Feedback information was also manipulated: in some contexts, participants could only learn from the outcome of their choice, whereas in other contexts they could learn from both the outcome of the chosen and the unchosen option (counterfactual learning). Bayesian model selection indicated that a sophisticated model, incorporating a counterfactual learning module (necessary to learn from the unchosen option outcome) and a value contextualisation module (necessary to learn equally well from rewards and punishments), best accounted for adult behaviour, replicating previous findings (Palminteri et al., 2015). Behavioural analyses showed that adults learnt equally well to seek rewards and avoid punishments and also efficiently integrated counterfactual information in instrumental learning. However, adolescent behaviour displayed a different pattern. In adolescents, Bayesian model selection significantly favoured the simplest action-value algorithm (Q-learning). This computational observation was supported by behavioural analyses of the learning task, in which the adolescents displayed reduced punishment avoidance learning, and in which RT improvement differed between adolescents and adults in the Reward/Complete context. Post-learning test analysis further corroborated the computational and behavioural findings of the learning task. The findings of this study support the hypothesis that adolescents and adults do not implement the same computational strategies.

4.4.1 Reward learning

Within the factorial design of the task, the Reward/Partial context represented a 'baseline' learning context. From a computational perspective, this context is the simplest as participants can efficiently maximise rewards by directly tracking outcome values using a basic model of RL. Neuroimaging and pharmacological studies have demonstrated the importance of subcortical structures, particularly the VS, in this basic reward-value learning (Daw, 2014; Dayan, 2012). The striatum shows earlier anatomical maturation compared with the more protracted development of the PFC (Casey, 2015; Shulman et al., 2015; Ernst & Fudge, 2009). Basic reward seeking has also been associated with the dopaminergic modulation of the striatum (Frank, 2004; Palminteri et al., 2009; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006) and animal studies show that striatal dopamine peaks during adolescence (Benes, Taylor, & Cunningham, 2000; Brenhouse, Sonntag, & Andersen, 2008). A previous task using a simple reward maximisation task, comparable to the Reward/Partial condition used here, showed stronger encoding of reward learning signals in the striatum in adolescents compared to adults, with no negative behavioural consequences (Cohen et al., 2010) Consistent with these data, there were no differences between age groups in basic reward learning in the Reward/Partial context. The similar performance between groups in the Reward/Partial context provides evidence that the group differences observed concerning punishment and reward learning cannot be explained by a generalised lack of motivation or attention, but rather are likely to be associated with specific computational differences.

4.4.2 Counterfactual learning

While less extensively studied than simple action-value learning, previous neuroimaging and computational studies of counterfactual learning suggest that learning from the outcome of the unchosen option recruits dorsolateral and polar prefrontal structures (Boorman et al., 2011; A. G. Fischer & Ullsperger, 2013; Koechlin, 2014). It was hypothesised that, since these regions are still developing in adolescence (reviewed in **Chapter 1**) adolescents would display a

reduced ability to learn from counterfactual feedback. Both the computational and behavioural analyses (specifically the RTs and post-learning test) supported this prediction. This reduced integration of counterfactual outcomes in adolescent behaviour is also consistent with a previous study showing limited feedback use as a possible source of higher risky decision-making during adolescence (Figner et al., 2009). Counterfactual learning can also be understood within the framework of 'model-based' (as opposed to 'model-free') RL (Doll, Simon, & Daw, 2012; O'Doherty, Lee, & McNamee, 2015). Algorithms that operate without using a representation (model) of the environment, such as basic Q-learning, are termed model-free. Conversely, algorithms that build option values by simulating different possible courses of action (i.e. planning), based on an explicit model of the environment (the task), are termed model-based. Counterfactual learning can be conceptualised as a model-based process, as it involves the updating of option values according to mental simulations of what the outcome could have been if we had chosen an alternative course of action (Koechlin, 2014). Like counterfactual learning, model-based learning has been theoretically and experimentally associated with prefrontal systems (Daw, Niv, & Dayan, 2005; Gläscher, Daw, Dayan, & O'Doherty, 2010; Smittenaar, FitzGerald, Romei, Wright, & Dolan, 2013). A key area for future research will be to examine whether or not the developmental changes in counterfactual learning observed here generalise to and interact with other forms of computation implicated in model-based learning, such as state transition learning.

4.4.3 Punishment learning

In the task used here, symmetrical performance in the reward seeking and punishment avoidance learning conditions depends on the ability to contextualise outcome values. Value contextualisation consists of updating option value as a function of the difference between the experienced outcome and an approximation of the average value of the two options (i.e. the context value). Thus, in Punishment contexts, where the overall context value is negative, an intrinsically neutral outcome (neither gaining nor losing points: 0 points; **Figure 2A** and **4**)

acquires a positive value and can therefore reinforce selection of the options that lead to successful avoidance of punishment. In the absence of value contextualisation, the neutral outcome, which represents the best possible outcome in the Punishment contexts will inevitably be considered as less attractive than a positive outcome (the best possible outcome in the Reward contexts: +1 point), and consequently the participant will perform less optimally in Punishment contexts.

Previous studies of punishment avoidance learning, using the same or similar tasks as this study, have implicated the dmPFC and dorsal ACC in the representation of negative values and negative prediction errors (Palminteri et al., 2012; Ullsperger et al., 2014). Similar to counterfactual learning, it was predicted that adolescents would show reduced punishment avoidance learning based on the continuing development of prefrontal regions associated with cognitive control (see **Section 1.3.1**). Indeed, the results of this study demonstrated that adolescents were less likely to engage in value contextualisation computation and thus showed less effective punishment avoidance learning and different cue evaluation in the post-learning test. These results could therefore be conceptualised as providing a computational substrate to neurobiological theories pointing to a reward/punishment imbalance as a driving force of adolescent risk- and novelty-seeking behaviour (Casey, 2015; Casey et al., 2016; Shulman et al., 2015; Ernst & Fudge, 2009).

Previous studies of punishment avoidance learning in adolescents have elicited somewhat inconsistent results. While some studies showed a reduction of punishment learning in adolescents (Christakou et al., 2013; Javadi, Schmidt, & Smolka, 2014; van Duijvenvoorde et al., 2008), others reported no effect of valence (van den Bos, Güroğlu, van den Bulk, Rombouts, & Crone, 2009), or even higher performance in Punishment than Reward contexts (Hämmerer, Li, Müller, & Lindenberger, 2011; van der Schaaf et al., 2011). One possible way to reconcile these discrepancies is to consider the modular nature of computational RL. In

addition to value contextualisation, at least one other learning process, the Pavlovian inhibitory system, has been implicated in punishment avoidance learning (Guitart-Masip et al., 2014). According to this theory, and supported by experimental findings, Pavlovian expectations may influence choice behaviour via Pavlovian-Instrumental Transfer (PIT; Guitart-Masip et al., 2012). In instrumental tasks, PIT is observed in the form of increased motor inertia for actions leading to potential harm (losses). Since Pavlovian learning has been shown to be underpinned by subcortical structures, such as the amygdala, which mature relatively early in adolescence (Mills, Goddings, et al., 2014; Olsson & Phelps, 2007), it is possible that PIT occurs similarly in adolescents and adults. It would be predicted that, for avoidance tasks that rely only on PIT, adolescents and adults would display similar performance, whereas in tasks that require value contextualisation (such as multi-armed bandit tasks with probabilistic outcomes), adolescents and adults would not behave similarly. As described in **Section 4.3.6**, both adolescents and adults had longer RT in Punishment than in Reward contexts. Interpreted within the framework of PIT learning, this effect may reflect an increase in motor inertia of actions associated with potential losses. In other words, compared to reward seeking actions, punishment avoidance actions require more time to be performed, because avoidance is more naturally linked to no-go responses. It is possible that in adolescents the Pavlovian inhibitory system is fully responsive and can mediate successful punishment avoidance in tasks that do not require value contextualisation (van der Schaaf et al., 2011). This 'multiple systems' account of avoidance learning is also consistent with the proposal that reward/punishment imbalances in pathology, development and aging, could be underpinned by different neurophysiological mechanisms (Hämmerer & Eppinger, 2012; Palminteri & Pessiglione, 2017).

4.5 Methodological implications

From a methodological perspective, this study underlines the importance of using computational approaches to study the development of learning and decision-making

(O'Doherty, Hampton, & Kim, 2007; Wang & Krystal, 2014). Few studies have used computational models to interpret adolescent behaviour (Cohen et al., 2010; Javadi et al., 2014; van den Bos, Cohen, et al., 2012), and fewer still have implemented model comparison techniques (Christakou et al., 2013; van den Bos et al., 2009). Behavioural measures provide a relatively rough measure of performance in learning tasks for the following reasons. First, in probabilistic learning tasks an incorrect response, as defined by the experimenter with knowledge of the task design, may locally be a 'correct' response, according to the actual history of choices and outcomes experienced by the participant, as a function of misleading outcomes. Second, the final estimation of learning performance may be affected by differences in initial choice rate. For example, a participant who starts choosing the correct option by chance is favoured compared to a participant who would need to 'explore' the options in order to find out the correct option. Third, aggregate model-free analyses are not able to formally tease apart the possible computational processes underlying performance differences, which could be characterised either by differences in free parameter values within the same model, or by differences in the computational architecture itself. By incorporating into the analysis the individual history of choices and outcomes, and formalising different learning mechanisms in discrete algorithmic modules, computational model-based analyses offer an elegant solution to these issues. As such, this study, together with others, has to be seen as part of a broader agenda aiming at moving from a 'heuristic' to a 'mechanistic' modelisation of human cognitive development (van den Bos & Eppinger, 2015).

This study suggested that adolescents show heightened reward seeking compared to punishment avoidance learning and a reduced ability to take into account the outcomes of alternative courses of action. Together, these processes may contribute to the adolescent propensity to engage in risky, value-based decision-making. Furthermore, the findings of this study may have implications for education and increasing our understanding of adolescent mental health (discussed in **Section 7.5**).

CHAPTER 5: Social Reward and Social Anxiety in Adolescence

Social interactions are a powerful source of reward. This study investigated: 1) developmental changes in the processing of social rewards, in the context of another salient reward, money; and 2) whether reward processing during adolescence was associated with individual differences in self-reported social anxiety. Eighty female adults and adolescents aged 13-34 years performed two versions of a probabilistic reward anticipation task, in which a speeded response could result in either social (Facebook 'Like' symbol) or monetary (pound symbol) rewarding feedback. Response speed on the social reward task was associated with self-reported value of being admired by others, suggesting that individuals who place a higher value on the admiration of others were more motivated to pursue the social rewards in the task. Performance on both reward tasks was best characterised by a quadratic effect of age, with the fastest responses at around 22 years. A similar quadratic effect was found for subjective liking ratings of both the reward stimuli, however these were not associated with task performance, highlighting the fact that although often correlated, liking of a stimuli, and its salience as a reinforcer represent two distinct components of motivational processing. Social anxiety was not associated with subjective liking of the reward stimuli, but did predict performance on both reward task. Although there were observed age-related changes in self-reported anxiety symptoms, these did not account for developmental changes in subjective liking or reward task performance, suggesting that both social anxiety and age were associated with variation in reward sensitivity, but their effects were largely independent from one and other.

5.1 Introduction

Social stimuli are typically pleasurable and rewarding, whether they are simple (e.g. viewing a static picture of a smiling face) or complex (e.g. sharing with a friend, or being liked by others). It has been proposed that the heightened effects of social influence in adolescence (reviewed in **Section 1.5.3**) might be due to an increase in the value of socially rewarding stimuli during this period (reviewed in Foulkes & Blakemore, 2016). Reward processing and sensitivity undergoes marked changes in adolescence, with the majority of evidence suggesting that reward sensitivity is heightened in this period of life (see **Section 1.3.4**; see van Duijvenvoorde, Peters, Braams, & Crone, 2016 for an in-depth review). However, reward processing is complex, and involves several overlapping, yet distinct psychological components, including pleasure, salience, and often learning and decision-making processes (Sescousse et al., 2013). While the existing behavioural and neuroimaging evidence is not inconsistent with the idea that social approval has a heightened reward value in adolescence, further research is needed before conclusions can be drawn.

Social reward processing has also been emphasized as an important factor in the development of social anxiety (Caouette & Guyer, 2014), a disorder which has a particularly high rate of onset during early adolescence (Beesdo, Pine, Lieb, & Wittchen, 2010; Stein, 2006; see **Section 1.6.2.3**). SAD is defined by the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV; American Psychiatric Assocation, 2000) as a persistent and impairing fear of one or more social or performance situations, in which the individual will be exposed to unfamiliar people and/or the possibly evaluation or scrutiny of others. Fears centre around the individual being embarrassed and humiliated by their behaviour, and/or their anxiety symptoms, with feared situations tending to elicit intense arousal, distress and anxiety or be avoided altogether. Thus, while adolescence is often thought of as a period of increased salience of social rewards, such as heightened motivation to approach peers to gain social

affiliation, individuals at increased risk for SAD may experience approach-avoidance conflict in these situations, due to being simultaneously highly invested in what their peers think of them and extremely fearful of humiliation or rejection (Caouette & Guyer, 2014; Lucock & Salkovskis, 1988). Experimental evidence suggests that individuals with, or at risk of, SAD show heightened neural sensitivity to aversive social outcomes such as social threat, rejection or negative evaluation (e.g. Guyer et al., 2008; McClure et al., 2007). However, there are also studies which suggest that adolescents with or at risk of SAD exhibit atypical activity and connectivity in reward-related brain circuits during the anticipation of both monetary (Guyer et al., 2006; 2012) and social rewards (Guyer et al., 2014). Thus it has been hypothesised that socially anxious individuals may show altered processing of social rewards (Caouette & Guyer, 2014).

One outstanding question for research into social reward processing in adolescence and/or socially anxious individuals is to what extent alterations in the salience of social information arise from domain-general alterations in sensitivity to motivational-affective stimuli, or are specific to the social domain (see Adolphs, 2010). To address this challenge, this study used a behavioural task that has been previously used with adults to provide an index of reward sensitivity to social rewards in the context of another type of salient reward, money (Foulkes et al., 2014). Previous studies comparing responses to monetary and social reward have tended to employ stimuli that typically differ substantially from each other both perceptually and conceptually, thus complicating interpretations of the findings from these studies (Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2012; Rademacher et al., 2010; Richey et al., 2014; Spreckelmeyer et al., 2009).

For example, Richey et al. (2014) represented monetary reward with a currency symbol (a dollar sign), a simple conceptual representation for which an association with reward has been learned over time (and thus may vary in strength according to experience), whereas social

reward was represented with an image of a smiling face. Studies in healthy adult samples that have used smiling faces as social rewards (Sprecklemeyer et al., 2009; Rademacher et al., 2010) have indicated that although response speeds were overall faster for monetary rewards, the anticipated intensity of social rewards modified reaction speed and activation of reward-related brain regions in a linear manner, comparable to that observed for monetary rewards. However, emotionally valenced faces are more complex and biologically salient than a dollar sign (Richey et al, 2014), and in addition to representing an immediate, primary reward, also directly elicit affective reactions in line with the valence of the stimuli (e.g. smiling compared with angry/fearful faces; Vuilleumier, Armony, Driver, & Dolan, 2001).

In addition to being a popular stimulus in experiments designed to assess social reward processing, emotional faces are also one of the most common stimuli used as affective distractors in the study of emotional regulation and the interplay between cognitive control and affective reactivity in adolescence (reviewed in **Section 1.3.3.2**). Behavioural and neural responses to emotional faces differ in adolescence not just according to the valence of the facial expression, but according to the extent to which an experimental paradigm taxes cognitive control processes, such as when facial stimuli serve as distractor stimuli to which responses need to be inhibited (Cohen-Gilbert & Thomas, 2013; Cromheeke & Mueller, 2015; Grose-Fifer et al., 2013). As a result, it can be difficult to disentangle whether behaviour is being influenced by the processing of the affective responses elicited by a stimulus, its value as a reward, or concurrent demands on cognitive control processes, all of which show pronounced changes during adolescent development (see **Section 1.3**). A similar limitation exists for many studies of reward processing in adolescence, which often involve either a cognitive control component, such as decision-making (reviewed in Blakemore & Robbins, 2012), learning (see **Section 1.3.4.1**) or response inhibition (Geier et al., 2010; Padmanabhan et al., 2011). For example, while monetary rewards have been shown to improve response inhibition in young people but not adults (13-17 vs. 18-30 years, Geier et al., 2010; 8-17 vs. 18-

25 years, Padmanabhan et al., 2011), it is difficult to disentangle the influence of developmental changes in reward sensitivity from developmental changes in inhibitory control.

Few studies have concurrently assessed the processing of both social and monetary reward in a healthy developmental sample (8-16 years, Demurie et al., 2012; 8-12 years, Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009) and these have not investigated the relationship between these factors and social anxiety (see Richey et al., 2014 for a study of monetary and social reward processing in adults with SAD). The study of Demurie et al. (2012) found that task performance improved in line with reward magnitude for both monetary and social reward stimuli (pictograms accompanied by written compliments and points) and that this was not moderated by age group (8-11 years vs. 12-16 years). However, while reward magnitude modified task performance comparably for both monetary and social rewards that consisted of pictograms accompanied by written compliments and points, in a second phase of the task in which smiling faces with spoken compliments were used as a social reward, despite being liked by the participants, there was no effect of reward magnitude on task performance. This suggests that social rewards are able to act as reinforcers in children as young as 8 years of age, however the specific representation of social reward may influence the extent to which behaviour is modified in line with reward intensity, regardless of the extent to which the stimuli is liked.

5.1.1 Current study and research questions

The current study assessed sensitivity to social and monetary rewards using a probabilistic reward task developed by Foulkes et al. (2014), in which social reward was represented by the 'Like' symbol from the social networking site Facebook (www.facebook.com), a thumbs-up icon used to express approval/admiration from one user to another in response to user-posted items, such as photos or comments. This symbol was selected in order to more closely match

the currency symbols (e.g. the pound sterling sign: '£') typically used to represent monetary reward in experimental paradigms, as both symbols are images that have a learnt association with reward (i.e. indicate conceptual representations of reward). They also both have similar, simple visual features, which therefore enables the comparison of the relative processing of monetary and social reward value as validly as possible. The task uses response speed to a simple shape target as an index of reward sensitivity, and thus, relative to reward tasks involving a learning and/or decision-making component, is less cognitively demanding. This behavioural task was used in combination with questionnaire assessments to address the following research questions in a sample of female adult and adolescent participants:

1. Is the probabilistic reward task developed by Foulkes et al. (2014) a sensitive measure of social and non-social reward sensitivity within a sample of female adolescents and adults?
2. Does reward processing change with age between adolescence and adulthood, and does this occur for both social and non-social rewards?
3. Is reward processing during adolescence associated with individual differences in social anxiety, and is this specific to social rewards?

5.2 Materials and Methods

5.2.1 Participants

For this study, 106 female participants aged between 11.45–34.53 years (M = 19.51, SD = 5.88) were recruited. Adult participants (≥ 18 years old; N = 54) were recruited from UCL volunteer databases and adolescents (< 18 years old; N = 52) were recruited from schools in the Greater London area. Of those recruited, only participants who were current Facebook users were selected for inclusion in the study, giving a final sample of size of 80 participants aged between 13.12–34.53 years (M = 21.46, SD = 5.39). The study was approved by the UCL Research Ethics

Committee, and all adult participants, or the parent or guardian of adolescent participants, gave written informed consent.

Only females were recruited due to the higher prevalence of SAD and symptoms in females (Caballo, Salazar, Jesús, Arias, & Hofmann, 2014) and to ensure power was not lost in the relatively small sample size by needing to control for gender. 57.5% of participants spoke English as their first language, and all participants who spoke English as a second language were studying at an English speaking school or university and did not report any difficulties understanding the task or questionnaire. 10% of participants reported a history of a developmental disorder (3 adults, 5 adolescents; auditory processing difficulties = 1; dyslexia = 4, dyspraxia = 1, language delay = 1, attention deficit hyperactivity disorder (ADHD) and dyscalculia = 1). Ethnicity of the sample was as follows: 58.8% Caucasian, 13.8% East Asian, 7.5% African/Caribbean, 7.5% Mixed, 8.8% Asian, 2.5% Latino, 1.3% not stated. For adult participants, 84.9% were currently students and the highest completed level of education was as follows: 32.1% 3+ A levels, 37.7% undergraduate degree, 26.4% postgraduate degree, 3.8% not stated.

5.2.2 Experimental Reward Task

As in Foulkes et al. (2014), two versions of a probabilistic reward anticipation task (monetary and social) were used, with task order counterbalanced. Social reward was represented by the Like symbol from the social networking site Facebook (www.facebook.com), a thumbs-up icon used to express approval/admiration, whereas monetary reward as represented by the pound sterling symbol. The monetary and social tasks were conducted separately (rather than as part of one task) for two reasons. Firstly, separating the two tasks by having participants perform another task in between reduced the possibility of boredom or fatigue effects. Secondly, conducting separate tasks removed the effect of shifting costs that could incur if participants had to change frequently between the two symbolic representations. Comparing two types of

reward by using two separate tasks has been done previously (e.g. Foulkes et al., 2014; Izuma et al., 2008).

In both task versions, the participant responded to an abstract shape target by pressing the space bar, and subsequently received feedback, which was either a reward (a monetary or social point gain) or no reward (no point gain; there is no loss condition). In each task there were three possible anticipatory cues (see **Figure 5.1**), which indicated to the participant that there was a P = 0, p = 0.5 or p = 1 probability of receiving a point in that trial, provided they pressed the space bar fast enough when the target appeared (within 400 ms). If the space bar was pressed within 400 ms on a rewarded trial (i.e. in 100% of the 1 probability trials and a randomised 50% of the 0.5 probability trials), '1' was displayed next to the reward symbol (either the Facebook Like or Pound sign) on the feedback screen to indicate a point gain (see **Figure 5.1**). If the space bar was not pressed, was pressed outside of the 400 ms window, or was pressed within the 400 ms window on a no-reward trial (i.e. in all 0 probability trials and 50% of 0.5 probability trials), '0' was presented alongside the reward symbol to indicate no point gain. On each feedback screen, cumulative winnings were shown underneath the trial winnings in order to maintain interest (see **Figure 5.1**). Each trial therefore consisted of six sequential components: (1) 1000 ms fixation cross/inter-trial interval, (2) 500 ms anticipatory cue, (3) 750–2250 ms (mean 1500ms) fixation cross, (4) 400 ms green triangle target, (5) 500 ms blank screen, (6) 1000 ms feedback, and lasted a total of 4.15–5.65 seconds (*M*= 4.9 seconds). Each task had 108 trials, and lasted approximately 9 min and within each task version the sequence of trials (0, 0.5 or 1) was randomised for each participant.

The original paradigm used by Foulkes et al. (2014) was adapted by shortening the duration of the individual task components, decreasing the total number of trials and varying the length of the interval between cue onset and target onset across trials to reduce the predictability of target onset. These adaptations were made after piloting the task with adolescent and adult

participants, in order to minimise boredom and fatigue effects and to shorten the task for use in school settings. All participants completed a practice session of 9 trials at the start of each condition.

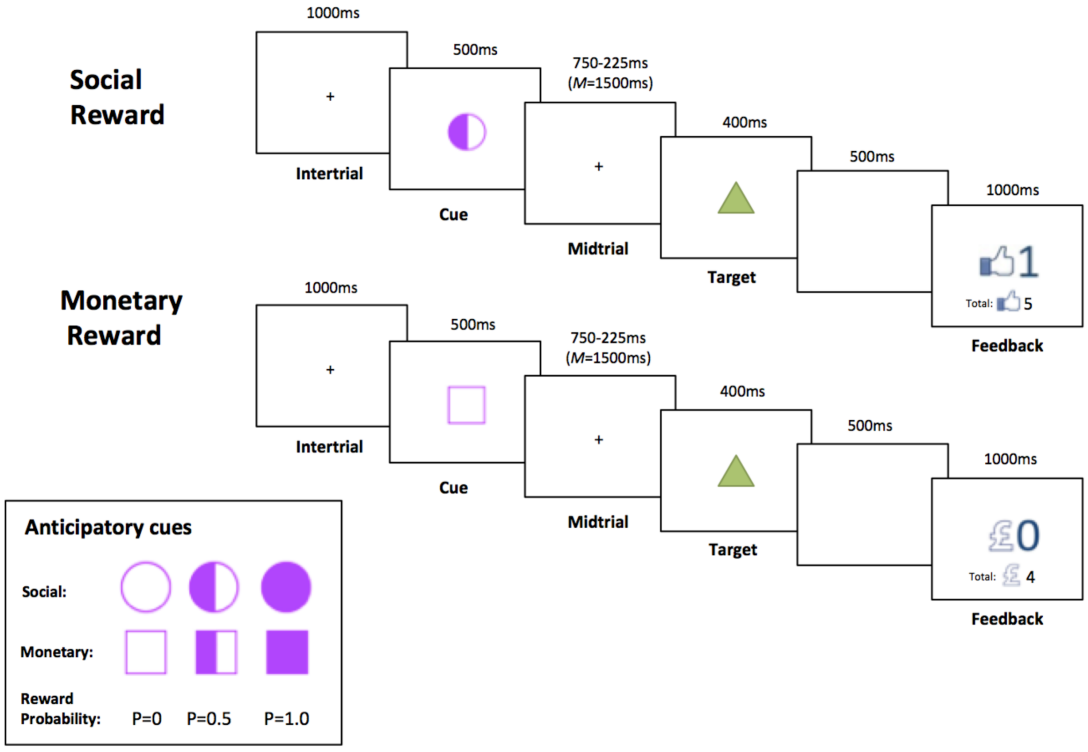

Figure 5.1. Social and monetary reward tasks. Trial sequence for the social and monetary reward tasks. In each task participants were required to respond to a triangular target with a button press as fast as possible. Before target presentation, participants saw one of three anticipatory cues (simple circles or square shapes) signalling the probability of receiving a reward, providing that the button was pressed fast enough (< 400ms). Trial outcome was then presented on the feedback screen. Trials could result in either a reward outcome in the form of a point gain presented next to the reward symbol (either the Facebook 'Like' or Pound Sterling symbol) or no-reward outcome (no point gain). Adapted from Foulkes et al. (2014).

It is worth noting that no actual reward was awarded on the basis of task performance. Participants were told that the objective of the reward tasks was simply to earn as many points as possible. This decision was made in order to keep the two tasks as equivalent as possible (i.e., translating the monetary points into winnings in the monetary condition could not be

matched in the social condition). Instead, the learned association between the two symbols (pound sign and Like symbol) and reward value was relied on. This is in line with other studies comparing the two types of reward, where winnings are not translated into actual monetary reward (Kohls et al., 2009; Rademacher et al., 2013; Foulkes et al., 2014).

5.2.3 Questionnaire Assessments

5.2.3.1 Social Reward

The Social Reward Questionnaire for Adolescents (SRQ-A; Foulkes, Neumann, Roberts, McCrory, & Viding, 2017) is a 20-item scale used to measure individual differences in the value of different aspects of social reward, which was adapted for suitability for use in adolescents from the Social Reward Questionnaire (SRQ; Foulkes, Viding, McCrory, & Neumann, 2014). The SRQ-A consists of five subscales, each representing a domain of social reward: *Admiration, Negative Social Potency, Passivity, Prosocial Interaction*s, and *Sociability* (see **Table 5.1;** note that the adult version also includes a sixth subscale assessing *Sexual Relationships*, which was not included in the current study). Although the adolescent version contains subtle wording differences to the original adult version (e.g. 'I enjoy feeling emotionally connected to someone' was simplified to 'I enjoy feeling emotionally close to someone'), the items are otherwise comparable.

Each item begins ''I enjoy'' and then describes a different type of social interaction. Participants are asked to consider the item in relation to all their social interactions, e.g. friends, colleagues/classmates or people they have just met. Responses are given on a 1 to 7 scale (1=Disagree strongly, 7=Agree strongly). Each subscale has good psychometric properties and has been shown as having a unique pattern of associations with external measures, providing support for the meaning of each subscale (Foulkes et al., 2014; 2017; see **Appendix A.4** for the full questionnaires).

5.2.3.2 Social Anxiety

The Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) is a 24-item scale used to measure the effects of social anxiety in everyday life, across a variety of situations. The items consist of two subscales assessing two distinct domains of social anxiety: fear/avoidance of social interactions (11 items, e.g. 'Meeting strangers'; *LSAS Social Interactions*) and fear/avoidance of performance situations (13 items, e.g. 'Taking a test'; *LSAS Performance*). For all items participants rate (i) the degree to which they fear the situations (0 = None; 1 = Mild, 2 = Moderate, 3 = Severe), and (ii) the degree to which they avoid the situations (0 = Never, 1 = Occasionally, 2 = Often, 3 = Usually). General trait anxiety was also assessed using the trait section of the STAI (Spielberger, 1983), to differentiate between effects of social anxiety, and general anxiety, i.e. anxiety that is not necessarily specific to the social domain, on performance.

Table 5.1. Detail of SRQ-A subscales.

SRQ-A subscale	Description	Example item
Admiration	Being flattered, liked and gaining positive attention	*'I enjoy getting praise from others'*
Negative Social Potency	Being cruel, antagonistic and using others for personal gains	*'I enjoy embarrassing others'*
Passivity	Giving others control and allowing them to make decisions	*'I enjoy following someone else's rules'*
Prosocial Interactions	Having kind, reciprocal relations	*'I enjoy treating others fairly'*
Sociability	Engaging in group interactions	*'I enjoy going to parties'*

5.2.3.3 Subjective Symbol Liking Ratings

In order to assess the subjective value of the reward stimuli used in both tasks, after completing the reward tasks, participants indicated how much they liked each reward symbol using a Visual Analogue Scale (anchored with '*Not at all*' and '*Very much*'). Participants were shown the two symbols and asked to place a mark to indicate their response to the question '*How much do you like the symbol above?*', which was then converted into a score of between 0 and 30). Participants also rated their familiarity with the reward symbols using the same scale, and the question '*How familiar are you with the symbol above?*'. Symbol familiarity was then entered as a covariate for analyses of subjective liking ratings, to ensure any effects of age reflected differences in the extent to which participants liked the rewards, and not merely how familiar they were with them.

5.2.4 Procedure

Participants were tested individually on behavioural tasks either at UCL or in their school. Participants performed the first session of the experimental reward task (either money or social; counterbalanced across participants) and then completed the matrix reasoning subscale of the WASI (Wechsler, 1999). They then performed the second session of the experimental reward task before rating their liking of the two task symbols (Facebook 'like' and pound sterling sign). Questionnaire assessments of Social Reward (*SRQ-A*; Foulkes et al., 2017) and Social Anxiety (*LSAS*; Liebowitz, 1987) were completed either in advance of the session (48.1%) or, where participants failed to complete them in advance, at the end of the session (51.8%).

5.2.5 Statistical Analyses and Hypotheses

In the experimental reward task, trials with RTs that were < 100 ms or > 900 ms (including any missing trials, i.e. those in which participants failed to respond at all) were considered invalid and excluded from analysis (2.12% of experimental trials: 1.08% social, 1.04% monetary). According to these criteria, no participant had > 20% invalid trials in either the monetary or social reward task and therefore no one was excluded from analysis. Mean RT for each

probability level (0, 0.5 and 1) were calculated in both conditions (monetary and social) for each participant, with faster RTs hypothesised to represent stimuli being more rewarding/salient.

5.2.5.1 Validation of experimental paradigm

The first aim of this study was to assess whether the reward tasks and stimuli used by Foulkes et al. (2014) in a sample of adult males would yield similar behavioural effects in a sample of female adolescents and adults, indicating that participants were sensitive to the reward stimuli used. To assess this, the same analysis procedure as in Foulkes et al. (2014) was used: a 2 (reward type: monetary, social) × 3 (reward probability: 0, 0.5, 1) ANOVA. As in Foulkes et al. (2014), RT was used as an indication of the reward value of the cued stimuli. It was predicted that RTs would increase as reward probability increased in step-wise function for both monetary and social conditions, which would indicate participants were sensitive to the differences in reward probability, and that both the monetary and reward symbols were serving as reward stimuli.

5.2.5.2 Relationship between experimental task and self-reported reward values

Before using the behavioural task to assess how age and social anxiety are associated with reward sensitivity, correlational analyses were used to assess whether task performance was sensitive to individual differences in the value of social rewards, as assessed by participants' self-reported enjoyment of certain types of social reward (*SRQ-A*). The rationale for this was to assess whether the nature of the reward symbol used (monetary vs. social) influenced performance specifically, as opposed to participants simply being influenced by the point gain in a domain general manner (see Demurie et al., 2012). Due to the fact that the Facebook Like symbol represents social admiration/approval it was specifically predicted that as enjoyment of admiration (*SRQ-A Admiration* score) increased, participants would show faster response times to the abstract social rewards used in the experimental task. To assess the degree to which any association between social reward task performance and *SRQ-A Admiration* scores

was specific to enjoyment of admiration, as opposed to a more general enjoyment of social rewards, scores on the other four *SRQ-A* subscales were included as exploratory variables. Benjamini and Hochberg False Discovery Rate (Benjamini & Hochberg, 1995) was used to control for the probability of making a Type 1 error on multiple comparisons, and only corrected *p* values are presented.

5.2.5.3 Developmental changes in reward processing

Two hierarchical (step-wise) linear regression models were used to investigate whether the value of different kinds of reward, as measured by (1) subjective liking ratings and (2) task performance, varied with age. The association between age and participants' subjective liking ratings of the social and monetary reward stimuli was assessed, first controlling for symbol familiarity (*Step 1*). Linear (*Step 2*) and quadratic (*Step 3*) age regressors were then added in turn and improvements in model fit at each step were assessed by examining the significance of the *F* change.

Regression models were also used to examine associations between age and mean RT at each probability level of the monetary and social reward tasks. As in Foulkes et al. (2014), RT was used as an indication of the reward value of the stimuli, however without assessing subjective value ratings it would be difficult to conclude that any developmental changes on task performance are as a result of developmental changes in reward value, as they could also be due to changes in the salience of the stimuli, or other developmental effects influencing response speed. Therefore, to assess the extent to which subjective liking accounted for age effects on reward task performance, subjective liking ratings were included as the first step in the regression model (*Step 1*). Linear (*Step 2*) and quadratic (*Step 3*) age regressors were then added in turn and improvements in model fit at each step were assessed by examining the significance of the *F* change.

Based on studies suggesting that behavioural and neural assessments of reward sensitivity peak in mid-late adolescence (Braams et al., 2015; Urošević, Collins, Muetzel, Lim, & Luciana, 2012), it was predicted that developmental changes in reward sensitivity (as assessed by subjective liking ratings and reward task performance) would be more likely to be characterised by a quadratic pattern. There were no strong predictions as to whether developmental changes in reward processing would differ according to reward type (monetary vs. social), as currently there are very few studies that have assessed behavioural responses to social reward in adolescence and young adults in the context of other domains of reward (reviewed in Foulkes & Blakemore, 2016).

The matrix reasoning subscale of the WASI (Wechsler, 1999) was originally intended to be used as an age-standardised assessment of non-verbal IQ (as in **Chapter 4**). However, subsequent to the completion of the study described **Chapter 4** it was observed that, contrary to evidence that relational reasoning continues to improve in late childhood and throughout adolescence (Crone, 2009; Dumontheil, 2014; Dumontheil, Houlton, Christoff, & Blakemore, 2010), T-score conversion of raw scores according to the WASI manual served to decrease the scores of younger participants and increase those of older participants. Although both age-standardised and raw scores on the matrix reasoning subscale were significantly correlated with participant age (T-scores: r (80) = .422, p > .001; raw scores: (r (80) = .265, p = .017), they were not significantly correlated with task performance, liking of the reward symbols, or social anxiety symptoms. Thus, due to concerns regarding the suitability of this measure as an assessment of non verbal IQ, it was not included as a predictor in developmental models, as there were no a priori hypotheses regarding the relationship between reward processing and relational reasoning.

5.2.5.4 Is reward processing in adolescence influenced by individual differences in social anxiety?

Hierarchical linear regression models were first used to assess the relationship between self-reported social anxiety symptoms (*LSAS* subscales), general trait anxiety (*STAI*) and age. For each anxiety measure, linear (*Step 1*) and quadratic (*Step 2*) age regressors were added in turn, and improvements in model fit at each step were assessed by examining the significance of the *F* change. Based on the fact that SAD onset rates increase markedly at age 10, with approximately 50% of SAD cases having their onset by age 13 (Beesdo et al., 2010; Stein, 2006), the youngest age included in the study sample, it was predicted that SAD symptoms would likely either decrease or remain stable with age.

To assess whether reward processing was influenced by individual differences in social anxiety, the two hierarchical linear regression analyses that were used to assess developmental changes in subjective liking ratings and task performance in reward sensitivity were repeated, including self-report measures of anxiety. In both models, *STAI* was controlled for (*Step 1*), and then the two *LSAS* subscales were included in the same block, to enable examination of the unique effects of each subscale (*Step 2*). Where social anxiety was a predictor of reward processing, as assessed by i) liking ratings and ii) task performance, linear and quadratic age effects were then added in turn (*Steps 3* and *4*), to examine the extent to which variation in social anxiety accounted for age effects in reward sensitivity. Improvements in model fit at each step were assessed by examining the significance of the *F* change.

No strong directional predictions were made regarding whether there would be effects of individual differences in social anxiety on reward processing, or whether this would differ according to reward type (monetary vs. social). There is evidence that individuals with or at risk of SAD show altered neural processing of both monetary and social rewards (Guyer et al.,

2006, 2012, 2014; Helfinstein et al., 2011; Richey et al., 2014), and that this may be specific to social anxiety, as opposed to general anxiety (Guyer et al., 2012). However, behavioural evidence is mixed, with some studies reporting effects of social anxiety on reward task performance (both monetary and social rewards) or subjective liking ratings (Cremers, Veer, Spinhoven, Rombouts, & Roelofs, 2015; Maresh, Allen, & Coan, 2014), whereas others do not (Guyer et al., 2006; Richey et al., 2014). Only one study to date has investigated the effects of social anxiety on both social and monetary reward processing (Richey et al., 2014), and this was in an adult patient sample.

5.3 Results

5.3.1 Validation of experimental paradigm

Mean RTs were analysed using a 2 (reward type: monetary, social) × 3 (reward probability: 0, 0.5, 1) ANOVA. As in Foulkes et al (2014) there was a significant main effect of reward probability ($F(1.867, 147.522) = 40.806$, $p < .001$, $\eta^2_p = .341$), but no main effect of reward type ($p = .472$) and no interaction between reward type and reward probability ($p = .995$). Participants responded more quickly as reward probability increased in both monetary and social tasks (**Figure 5.2;** see **Table 5.2** for descriptives). Pairwise comparisons (Bonferroni corrected) showed that the decrease in RT between both increases in reward probability (0 and 0.5; 0.5 and 1) were significant in both monetary and social conditions (all $p \leq .001$; **Table 5.2.**).

While there was no effect of reward type on RT, there was an effect on participants subjective liking ratings ($t(79) = 5.068$, $p < .000$), whereby participants tended to rate liking the monetary symbol ($M = 22.79$, $SD = 6.86$) more than the Facebook like symbol ($M = 18.12$, $SD = 7.99$). There was no effect of reward type on symbol familiarity ratings ($p = .263$).

Table 5.2. Mean RTs across experimental conditions.

			Pairwise Comparisons	
Reward	**Probability**	**Mean RT *(SE)***	**(*A-B*)**	***A* - *B* (SE)**
Social	0	299.80 (4.61)	0 – 0.5	**7.57 (2.65) ***
	0.5	292.23 (4.92)	0 – 1	**16.91 (2.53) *** **
	1	282.89 (4.05)	0.5 – 1	**9.34 (2.62) ** **
Monetary	0	297.93 (5.05)	0 – 0.5	**7.42 (2.47) ***
	0.5	290.51 (4.17)	0 – 1	**17.07 (2.82) *** **
	1	280.85 (3.68)	0.5 – 1	**9.66 (1.82) *** **

Note: Corrected *p* values are shown. *** $p < .001$, ** $p < .01$, * $p < .05$.

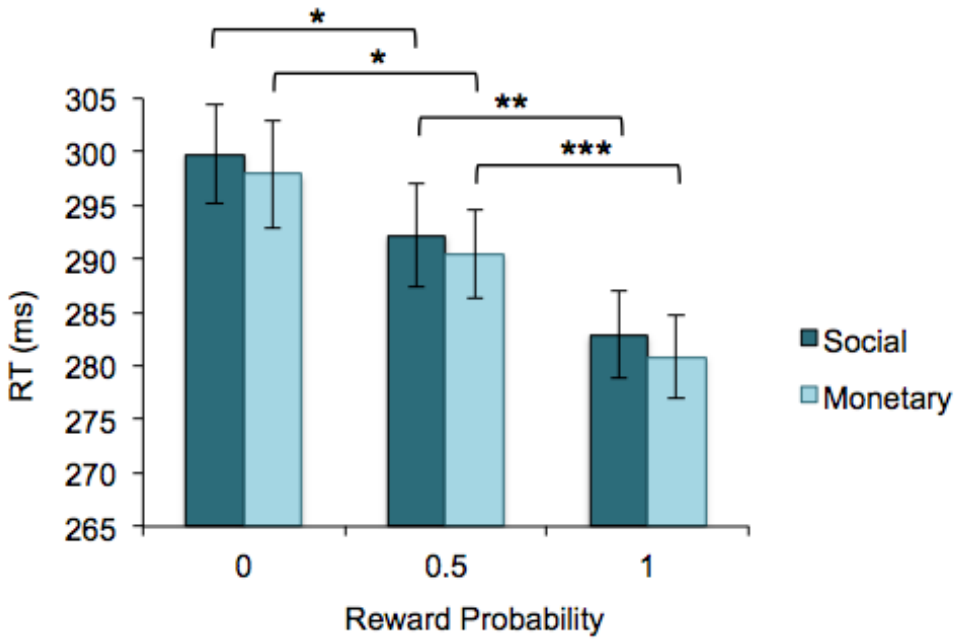

Figure 5.2. Mean RT for each probability level on the social and monetary reward tasks (*M*±*SE*). *** $p < .001$ ** $p < .01$, * $p < .05$.

5.3.2 Relationship between experimental task and self-reported reward values

The relationship between task performance and participants' self-reported enjoyment of different types of social rewards (*SRQ-A* subscales) was analysed using correlational analyses. Benjamini and Hochberg False Discovery Rate (Benjamin & Hochberg, 1995) was used to

control for the probability of making a Type 1 error on multiple comparisons. *SRQ-A Admiration* was significantly negatively associated with RTs to social rewards in all 3 probability conditions. Participants who reported greater enjoyment of being admired by others were faster to respond to targets in the social condition, and this was strongest when rewards were uncertain (0.5 probability condition; see **Table 5.3;** although it should be noted that despite the greater correlation co-efficient for this condition, statistical comparison using Fisher's Z transformation (Steiger, 1980) indicated that this difference was not significant; z = .545; p = .293; Steiger, 1980). *SRQ-A Admiration* was not associated with RTs to monetary rewards, and other SRQ-A subscales were not associated with task performance in either task condition.

Table 5.3. Correlations between reward task performance (mean RT) and *SRQ-A* subscales.

		SRQ-A				
Reward	**Probability**	***Admiration***	***NSP***	***Passivity***	***Prosocial***	***Sociability***
Social	0	**-.287****	.032	-.188	-.099	-.037
	0.5	**-.377****	.112	-.110	-.120	-.119
	1	**-.287***	.077	-.068	-.061	-.104
Monetary	0	-.117	.027	-.067	-.059	-.078
	0.5	-.196	-.022	-.049	.000	-.113
	1	-.208	-.035	-.056	.057	-.079

Note: Corrected p values are shown. N = 80. ** p < .01, * p < .05.

5.3.3 Developmental changes in social reward processing

Hierarchical linear regression models were used to assess the relationship between self-reported liking ratings of each of the task stimuli and age, entering symbol familiarity as a control variable (*Step 1*). Symbol familiarity was a significant predictor of subjective liking ratings for both symbols (p < .001, see **Table 5.4**), accounting for 17.2% and 18.5% of variance for the Facebook Like and Pound symbols, respectively. There was also a significant quadratic effect of age on subjective liking ratings of both symbols (*Step 3*), which in combination with symbol familiarity accounted for 24.5% of variance in ratings of the Facebook Like symbol (p =

.008) and 23.1% of variance in ratings of the Pound symbol (p = .042). There was no linear effect of age (see **Table 5.4** for all fitted models and **Figure 5.3**).

Hierarchical linear regression analyses were also used to investigate whether: 1) reward task performance varied according to participant age; and 2) whether this could be accounted for by age-related variance in participants' subjective liking ratings of the symbols (as described in **Section 5.3.5.3**). The extent to which age-related changes in social reward task performance could be accounted for by age-related changes in self-reported enjoyment of being admired was not assessed, as while SRQ-A *Admiration* was significantly correlated with reward task performance it was not associated with participant age (age^{linear}: p = .836; $age^{quadratic}$: p = .828).

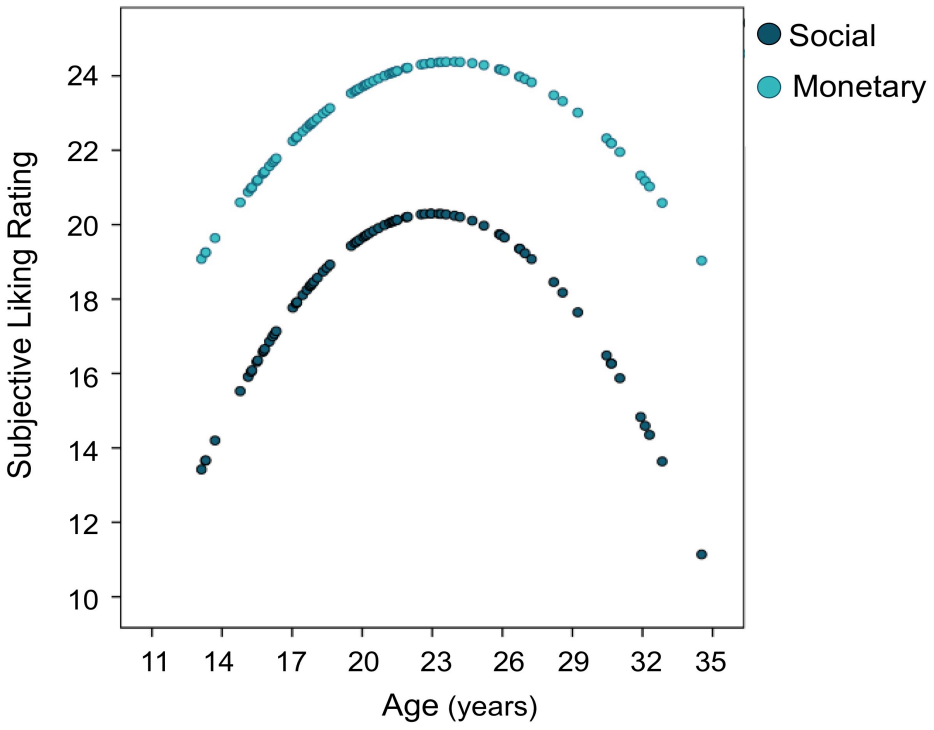

Figure 5.3. Age-related changes in subjective liking ratings of social and monetary rewards. Mean-standardised predicted values are plotted for subjective liking ratings of the reward symbols. Symbol familiarity ratings were first covaried, then the residuals were fitted by $age^{quadratic}$ and plotted as a function of age.

Table 5.4. Effects of age on subjective liking ratings of the reward symbols.

	Symbol Liking							
	Facebook Like				£ Symbol			
	R^2	FΔ	pFΔ	β	R^2	FΔ	pFΔ	β
Step 1	**.172**	**16.20**	**<.001**		**.185**	**17.67**	**<.001**	
Familiarity				**.415*** **				**.430*** **
Step 2	.172	0.00	.981		.188	.30	.586	
Familiarity				**.414*** **				**.431*** **
Age				.003				.056
Step 3	**.245**	**7.32**	**.008**		**.231**	**4.27**	**.042**	
Familiarity				**.377*** **				**.429*** **
Age				**2.214****				**1.738***
Age^2				**–2.219****				**–1.694***

Note: Summary of hierarchical regressions investigating linear (age) and quadratic (age^2) effects of age on subjective liking ratings of social (Facebook Like) and monetary (£) rewards. Symbol familiarity was controlled for as the first step of the model.
N = 80. ** $p < .01$, *** $p < .001$.

On both reward tasks, subjective liking of the respective symbols did not significantly account for variance in RT at any probability levels (*Step 1*; *p*'s > .556), nor was there a linear effect of age on task performance (*Step 2*; *p*'s > .413 ;see **Table 5.5**). On the social reward task, when P = 1, there was a significant quadratic effect of age on RT (*Step 3*), accounting for around 5.7% of the variance ($p = .037$; see **Table 5.5**). While there was a trend toward a significant improvement in model fit when a quadratic age regressor was included for P=0 trials, the improvement was not significant when P = 0.5 (**Table 5.5**). In contrast, performance on the monetary reward task at all reward probability levels was best described by a quadratic effect of age (*Step 3*), which accounted for 6.3% of variance in RTs when P = 0, 11.4% when P = 0.5 and 12.1% when P = 1 (see **Table 5.5**).

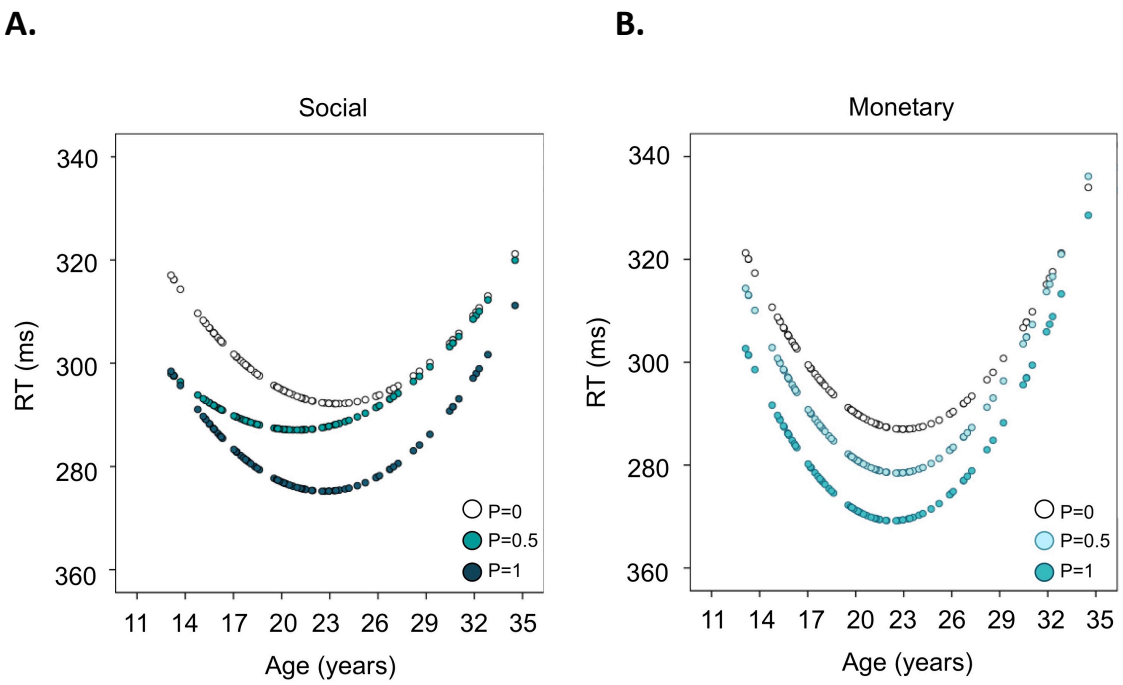

Figure 5.4. Age-related changes in social (A) and monetary (B) reward task performance at different reward probabilities. Mean-standardised predicted values for RT are plotted. Symbol liking ratings were first covaried, then the residuals were fitted by age^{quadratic} and plotted as a function of age.

Visual examination of the data plotted in **Figure 5.4A** suggested that when P = 0.5 on the social reward task, younger participants responded similarly to when P = 1, whereas older participants responded to the uncertain rewards in a similar way to trials with no chance of reward. Exploratory post hoc analyses were conducted to examine this possibility further. Separate repeated measures ANOVAs were conducted for each reward task, with reward probability (0, 0.5, 1) as a within subjects factor and subjective liking rating of the relevant reward symbol included as covariate. A median split was used to group participants by age (< 20.5 years, > 20.5 years), and this was included as a between subjects factor. Pairwise comparisons (Bonferroni corrected) were consistent with visual examination of the social reward task data (**Table 5.6**). Younger participants (< 20.5 years) showed significantly faster RTs when there was a possibility of a reward (P > 0), but RTs did not significantly differ

between uncertain and certain reward trials (RT 0 > RT 0.5 = RT 1; see **Table 5.6**). In contrast, older participants (> 20.5 years) did not differ between trials in which reward was either unobtainable or uncertain (P = 0), but responded significantly faster when successful performance was certain to result in a reward (P = 1; RT 0 = RT 0.5 < RT 1; see **Table 5.6**). This was not found for performance on the monetary reward task, where for all participants RTs were significantly faster than other trials only when reward was certain (P = 1; RT 0 = RT 0.5 < RT 1).

Table 5.5. Effects of age on social and monetary reward task performance (mean RT).

	Reward Probability											
	P = 0				**P = 0.5**				**P=1**			
	R²	***FΔ***	***pFΔ***	***β***	***R²***	***FΔ***	***pFΔ***	***β***	***R²***	***FΔ***	***pFΔ***	***β***
Social												
Step 1	.001	0.06	.809		.004	0.35	.556		.001	0.06	.815	
Liking				.027				.067				.027
Step 2	.001	0.05	.818		.012	0.56	.456		.001	0.05	.821	
Liking				.030				.058				.024
Age				-.026				.085				.026
Step 3	.039	3.00	.087		.034	1.80	.184		**.058**	**4.53**	**.037**	
Liking				.097				.110				**-2.008***
Age				-1.700^{+}				-1.211				**2.041***
Age^2				1.680^{+}				1.301				.105
Money												
Step 1	.001	0.07	.790		.000	0.00	.966		.003	0.24	.627	
Liking				.030				-.005				-.055
Step 2	.001	0.00	.979		.003	0.24	.629		.012	0.68	.413	
Liking				.030				-.007				-.059
Age				.003				.055				.093
Step 3	**.064**	**5.13**	**.026**		**.117**	**9.84**	**.002**		**.133**	**10.66**	**.002**	
Liking				.085				.066				.016
Age				**-2.081***				**-2.747****				**-2.797****
Age^2				**2.098***				**2.820****				**2.909****

Note: Summary of hierarchical regressions investigating linear (age) and quadratic (age^2) effects of age on social and monetary reward task performance (mean RT) at different reward probabilities. Subjective liking ratings of the reward symbols were controlled for in the first step of the model. *N* = 80. ** $p < .01$, * $p < .05$, $^{+}$ $p < .01$.

To summarise, participants showed quadratic effects of age on both subjective liking of the reward cues, and on their RTs to the reward cues on both the social and monetary reward tasks, with fastest response times and greatest liking ratings occurring at around 22–23 years of age. While this quadratic effect appeared to be relatively stable across reward likelihoods on the monetary reward task, there was only a clear quadratic effect on the social reward on performance on trials in which a fast response was certain to result in reward, with exploratory post hoc analyses suggesting that responses to uncertain social rewards may differ according to age. In contrast, the quadratic effect of age on subjective liking ratings was strongest for the social reward task. For both reward tasks, task performance was not associated with subjective liking ratings, at any reward probability level.

Table 5.6. Mean RTs across experimental conditions for younger and older participants.

		Pairwise Comparisons: *A* - *B* (SE)	
Reward Task	**Probability (*A* - *B*)**	**< 20.5 years**	**> 20.5 years**
Social	0 – 0.5	**11.28 (3.78) ***	3.86 (3.78)
	0 – 1	**16.91 (3.66) *****	**16.92 (3.66) *****
	0.5 – 1	5.62 (23.74)	**13.06 (3.74)****
Monetary	0 – 0.5	7.96 (3.53)	6.87 (3.53)
	0 – 1	**18.34 (4.00) *****	**15.81 (4.00)****
	0.5 – 1	**10.38 (2.59) *****	**8.94 (2.59)****

Note: Participants were split at the median age (20.5 years). Corrected *p* values are shown.

*** $p < .001$, ** $p < .01$, * $p < .05$.

5.3.4 Is reward processing during adolescence influenced by social anxiety?

Hierarchical linear regressions were used to examine whether there was a relationship between participant age, and their self-reported social and trait anxiety symptoms (see **5.3.5.4**

for regression models). Age was a significant negative linear predictor of *LSAS Social Interactions*, accounting for 5.9% of the variance in scores (β = -.244, p = .029), but did not significantly predict *LSAS Performance* (β = -.157, p = .165). Age was also a significant negative linear predictor of *STAI*, accounting for 5.5% of variance in scores (β = -.235, p = .036). Inclusion of a quadratic age regressor did not improve model fit for any measure (p's >.497).

Table 5.7. Effects of social anxiety on subjective liking ratings of the reward symbols.

	Symbol Liking							
	Facebook Like				**£ Symbol**			
	R^2	***FΔ***	***pFΔ***	***β***	***R^2***	***FΔ***	***pFΔ***	***β***
Step 1	**.172**	**16.20**	**< .001**		**.185**	**17.67**	**< .001**	
Familiarity				**.415*****				**.430*****
Step 2	.174	0.22	.640		.185	0.03	.862	
Familiarity				**.406*****				**.426*****
STAI				-.049				.056
Step 3	.188	0.65	.523		.193	0.39	.681	
Familiarity				**.392****				**.424*****
STAI				-.061				-.048
LSAS-S				-.196				-.088
LSAS-P				.234				.160

Note: Summary of hierarchical regressions investigating the relationship between social anxiety (LSAS *Social Interactions* and *Performance* subscales) on subjective liking ratings of the social and monetary reward symbols. Symbol familiarity was controlled for as the first step of the model, followed by trait anxiety (*STAI*). *N* = 80. LSAS-*S: LSAS Social Interactions;* LSAS-*P: LSAS Performance*; ** p < .01, *** p < .001.

Next, to assess whether reward processing was influenced by individual differences in social anxiety, the two hierarchical regression models used to assess developmental changes in i) subjective liking ratings, and ii) task performance, were modified to include the two *LSAS* subscales, and *STAI* as additional predictors (models described further in **Section 5.3.5.4**). Subjective liking ratings of each of the reward task stimuli (controlling for symbol familiarity; *Step 1*) were not significantly predicted by *STAI* (*Step 2; p'*s > .640) or *LSAS* subscales (*Step 3; p's* > .523; see **Table 5.7**). Since liking ratings were not predicted by social anxiety, it was not

necessary to investigate the role of social anxiety in developmental changes in reward value (assessed by subjective liking ratings), and thus the model was not extended to include age regressors.

Performance on both reward tasks was assessed using a modified version of the hierarchical linear regression used to assess age effects. In *Step 1* general trait anxiety was controlled for, which did not significantly predict performance on either task version, at any level of reward probability (see **Table 5.8**). *LSAS Social Interactions* and *Performance* subscales were then entered together as *Step 2* of the model. Across reward probabilities, on both tasks, *LSAS Social Interactions* was a significant negative predictor of RTs, while *LSAS Performance* was a significant positive predictor (see **Table 5.8**). In other words, after controlling for general anxiety symptoms, participants with higher levels of social anxiety symptoms regarding social interactions showed faster RTs on the reward tasks, and participants with higher levels of social anxiety symptoms regarding performance situations showed slowed RTs on the reward tasks (see **Figure 5.5**).

5.4 Discussion

5.4.1 Validation of experimental paradigm

A probabilistic reward paradigm, originally developed for use in a sample of adult males (Foulkes et al., 2014), was used to assess social and monetary reward sensitivity in a sample of female adolescents and adults. As in Foulkes et al. (2014), participants showed faster RTs as reward probability level increased in both the social and monetary conditions, and there were no significant differences between mean RTs in the monetary and social reward conditions, suggesting that the Facebook Like symbol was serving as a reward stimulus in a manner similar to the Pound sterling symbol. These findings are also consistent with previous studies showing effects of reward magnitude/intensity on response speeds for both social and monetary rewards (Demurie et al., 2012; Sprecklemeyer et al., 2009; Rademacher et al., 2010).

Table 5.8. Effects of social anxiety and age on social and monetary reward task performance.

	Reward Probability											
	P = 0				P = 0.5				P = 1			
	R^2	FΔ	pFΔ	β	R^2	FΔ	pFΔ	β	R^2	FΔ	pFΔ	β
Social												
Step 1	.012	0.94	.355		.036	2.93	.091		.004	0.31	.582	
STAI				-.109				**.190**$^{+}$				-.063
Step 2	**.146**	**5.97**	**.004**		**.154**	**5.26**	**.007**		**.114**	**4.73**	**.012**	
STAI				-.121				**-.207**$^{+}$				-.114
LSAS-S				**-.629****				**-.580****				**-.487***
LSAS-P				**.716****				**.670****				**.644****
Step 3	.156	0.84	.361		.154	0.00	.950		.115	0.02	.877	
STAI				-.138				-.205				-.116
LSAS-S				**-.655****				**-.577***				**-.494***
LSAS-P				**.738****				**.668****				**.648****
Age				-.102				.007				-.018
Step 4	**.199**	**3.90**	**.050**		.178	2.19	.143		**.172**	**5.09**	**.027**	
STAI				-.142				-**.209**$^{+}$				-.122
LSAS-S				**-.702***				**-.605****				**-.536***
LSAS-P				**.764*****				**.688****				**.678****
Age				**-1.798***				-1.459				**-2.258***
Age^2				**1.703***				1.479				**2.256***
Money												
Step 1	.011	0.88	.354		.018	1.44	.233		.025	1.89	.424	
STAI				-.105				-.135				-.158
Step 2	**.125**	**4.93**	**.010**		**.127**	**4.72**	**.012**		**.109**	**3.59**	**.001**	
STAI				**-.171**				-.182				-.159
LSAS-S				**-.460***				**-.491***				**-.513***
LSAS-P				**.645****				**.640****				**.565***
Step 3	.127	0.21	.651		.127	0.01	.943		.109	0.03	.881	
STAI				**-.179**				-.184				-.156
LSAS-S				**-.478***				**-.494***				**-.507***
LSAS-P				**.656****				**.642****				**.561***
Age				-.051				-.008				.018
Step 4	**.196**	**6.37**	**.014**		**.255**	**12.73**	**.001**		**.255**	**14.50**	**<.001**	
STAI				-.185				-.192				**-.165**
LSAS-S				**-.525***				**-.558****				**-.575****
LSAS-P				**.689****				**.687****				**.609****
Age				**-2.200***				**-2.931****				**-3.100*****
Age^2				**2.157***				**2.935****				**3.131*****

Note: Summary of hierarchical regressions investigating the relationship between social anxiety and age on social and monetary reward task performance (mean RT) at different

reward probabilities. After controlling for trait anxiety (*STAI*; *Step 1*), social anxiety symptoms (*LSAS Social Interactions* and *Performance* subscales) were entered into the model (*Step 2*). In *Steps 3* and *4* linear (age) and quadratic (age^2) regressors were added to the model in turn. *N* = 80. LSAS-*S: LSAS Social Interactions;* LSAS-*P: LSAS Performance*; *** $p < .001$, ** $p < .01$, ** $p < .05$, + $p < .1$.

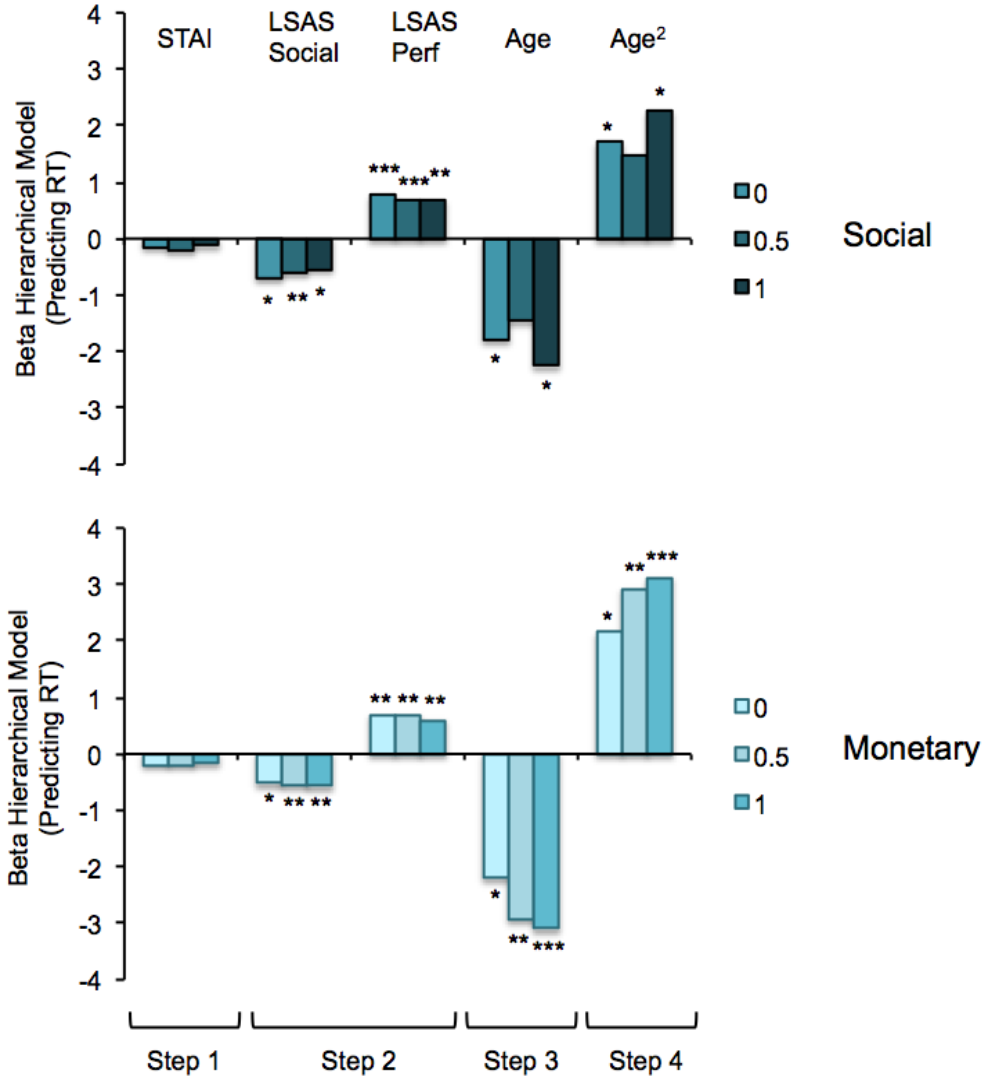

Figure 5.5. Effects of social anxiety and age on social and monetary reward task performance. Visual summary of hierarchical regression analyses presented in **Table 5.7.** General anxiety (*STAI*), social anxiety symptoms (*LSAS Social Interactions* and *Performance* subscales) and linear (age) and quadratic (age^2) effects of age on social and monetary reward task performance across different reward probabilities were entered into a hierarchical regression model. The four steps correspond to the order in which the variables were entered. Betas from *Step 4* of the hierarchical regression models depicted in **Table 5.7** are plotted. *** $p < .001$, ** $p < .01$, * $p < .05$.

5.4.2 Relationship between experimental task and self-reported reward values

The experimental paradigm developed by Foulkes et al. (2014) aims to assess sensitivity to social and monetary rewards, using simple symbols which have learnt associations with rewards, to match the two reward stimuli as closely as possible. However, as noted by Demurie et al. (2012), when both reward tasks feature quantifiable, cumulative rewards (points), it is difficult to say whether participants differentiate between the reward domains, or simply are motivated to obtain as many points as possible irrespective of reward domain. To address this issue, associations between RTs on the experimental tasks and individual differences in participants' subjective value ratings of different kinds of social rewards were examined.

The Facebook Like symbol, used in the social reward condition, represents social admiration and/or approval, and therefore it was hypothesised that RTs in the social reward condition would be associated with participants' self-reported enjoyment of receiving the approval of others, as measured by the SRQ-A *Admiration* subscale. Consistent with this hypothesis, self-reported enjoyment of admiration was associated with faster responses in the social reward condition for all reward probabilities, and was greatest when reward contingencies were uncertain, suggesting that individuals who place a higher value on the admiration and approval of others were more motivated to pursue the social rewards. Other domains of social reward were not associated with social reward task performance, suggesting that faster performance in the social reward condition specifically reflected an increased value of social admiration, rather than of social rewards more generally. Furthermore, enjoyment of admiration was not associated with performance on the monetary reward task, suggesting that the social reward task was sensitive to individual differences in the value of receiving approval/admiration from others, rather than simply reflecting more domain-general variation in reward sensitivity. The fact that individual differences in the value of admiration of others had the strongest

association with trials on the social reward task in the likelihood of reward was uncertain (P = 0.5), is of interest given findings that VS activation during the anticipation of rewards is greatest for rewards of maximal uncertainty (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009). Future studies of social reward may benefit from assessing both reward likelihood *and* magnitude, as these factors may have dissociable effects on behaviour.

5.4.3 Developmental changes in reward processing

Hierarchical regression analyses were used to investigate whether the processing of different kinds of rewards varied with age, as measured by both participants' subjective liking ratings and RTs to obtain social and monetary rewards. After controlling for symbol familiarity, there was a quadratic effect of age on liking of both reward symbols with liking ratings peaking at around 23 years of age for both symbols. A quadratic effect of age was also observed for reward task performance, defined as RT to the cued target, while controlling for subjective liking of the reward symbols. Monetary reward task performance was characterised by a quadratic effect of age, with fastest RTs observed at around 22 years across all probability levels, although the effect was stronger when there was a possibility of obtaining a reward (i.e. reward probability was not zero). For the social reward task, when a fast response was certain to result in reward performance also followed a quadratic effect (fastest performance at around 22 years), and there was a trend toward a similar effect when there was no chance of reward. However, when reward likelihood was uncertain, age effects did not follow a quadratic effect.

The experimental paradigm developed by Foulkes et al. (2014) assesses reward sensitivity to different kinds of rewards by equating faster RTs with a higher stimulus reward value. To evaluate this assumption, the extent to which age-related effects on reward task performance could be accounted for by age-related changes in subjective liking of the reward stimuli was investigated. While both subjective liking ratings and task performance showed quadratic

effects of age, contrary to the assumption that RTs to reward stimuli would reflect reward value, subjective liking ratings did not predict performance on either reward task, at any probability level. This could suggest that RTs on the reward task more closed reflect motivational salience, rather than reward value *per se.* While reward value indicates the degree of pleasure anticipated by an individual from obtaining an outcome, motivational salience refers to the extent to which a stimulus captures an individual's attention (regardless of valence) and drives their goal-directed behaviour (Puglisi-Allegra & Ventura, 2012). The fact that, particularly for the monetary task, age effects were observed on RT across probability levels may therefore reflect developmental changes in reward salience, as while reward value would be expected to be modified by the explicit reward probabilities present in the task, salience would be similar across probability levels.

The pattern of developmental effects observed on the social and monetary reward tasks showed both similarities and differences. While quadratic effects of age, peaking in the early 20's, were observed for liking and RT on both tasks, age effects were stronger for the subjective ratings of the social rewards, whereas effects of age on task performance were stronger on the monetary task, and no quadratic effect of age was observed on the social reward task when the probability of obtaining a reward was uncertain. Exploratory post-hoc analyses based on visual examination of the RT data (see **Figure 5.4A**) suggested that the way in which participants behaved when the chance of receiving a social reward was uncertain may vary with age. While older participants only showed faster RTs when fast performance was certain to result in social reward, relative to non-rewarded trials younger participants (< 20.5 years) showed faster RTs to both certain and uncertain social rewards, and did not differentiate between the two. This was not found for the monetary reward task, in that RTs were only significantly faster when reward probabilities were certain, for participants of all ages.

The study of Demurie et al. (2012) varied reward value by manipulating reward intensity, as opposed to reward probability, and thus unlike the present study was unable to assess the impact of uncertainty on the processing of different kinds of rewards (Demurie et al., 2012). In everyday life, social rewards are often more unpredictable than monetary rewards (e.g. we often know how much money we will earn in advance of engaging in a task, whereas the extent to which our behaviour is likely to receive a social reward such as approval or admiration is much harder to predict both between social interactions and over time). Thus, while this was an exploratory finding, it yields interesting questions for future studies examining developmental changes in the processing of different kinds of rewards. For example, does the influence of outcome uncertainty on reward processing differ between social and non-social rewards, and if so does this change during development?

5.4.4 Is reward processing during adolescence influenced by social anxiety?

While self-reported social anxiety symptoms were not associated with subjective liking ratings of either the monetary or social reward stimuli, they were associated with RTs on both reward tasks, over and above variation in trait anxiety, which was not a significant predictor of performance. On both tasks, anxiety specifically relating to social interactions (*LSAS Social*) was associated with faster responses to reward stimuli at all reward probabilities, whereas anxiety specifically relating to performing/being observed was associated with slower responses (*LSAS Performance*).

There were not strong *a priori* hypotheses as to whether individual differences in social anxiety would influence reward sensitivity, in part due to mixed behavioural findings in the existing literature examining reward processing in SAD. The finding that social anxiety symptoms predicted performance on both reward tasks, and across probability levels, but were not associated with subjective liking ratings of the reward stimuli is consistent with a performance

monitoring hypothesis of reward processing in SAD (Caouette & Guyer 2014). This hypothesis argues that rather than reflecting differences in reward sensitivity *per se*, the pattern of elevated striatal reactivity seen in socially anxious individuals (Bar-haim et al., 2009; Guyer et al., 2006, 2012) instead reflects an increase in the salience of performance-contingent outcomes, resulting from a strong motivation to avoid failure. Furthermore, the fact that different domains of social anxiety symptoms had opposing influences on task performance suggests that there may be some utility in examining associations between specific symptoms of social anxiety and behaviour.

Self-reported *LSAS Social* and *STAI* scores decreased linearly with age (*LSAS Performance* did not show a significant decrease). This suggests that, relative to adults, adolescents experienced a greater degree of anxiety regarding social situations, as well as generally elevated feelings of anxiety, which is reasonably consistent with the fact that the median age of onset for anxiety disorder is 11 years (Kessler et al., 2005), and that the risk for developing SAD increases dramatically in late childhood/early adolescence before decreasing considerably by age 25 (Wittchen, Stein, & Kessler, 1999).

Although age-related changes in self-reported anxiety symptoms were observed, these did not account for the developmental changes observed in subjective liking ratings or task performance. Rather than diminishing the effects of age observed on reward task performance, inclusion of social anxiety symptoms as predictors in the model increased the strength of these effects. This suggests that social anxiety and age both influence performance on the reward tasks, but that that these influences are largely independent from one another. The fact that effects of age became stronger when individual variation in anxiety was included in the model highlights the potential importance of considering developmental effects within the context of other individual differences, which may also influence the behaviour or cognitive process of interest (see **Section 1.6**).

CHAPTER 6: Affective bias and current, past and future adolescent depression: a familial high risk study

Affective bias is a common feature of depressive disorder. However, a lack of longitudinal studies means that the temporal relationship between affective bias and depression is not well understood. One group where studies of affective bias may be particularly warranted is the adolescent offspring of depressed parents, given observations of high rates of depression and a severe and impairing course of disorder in this group. A two wave panel design was used in which adolescent offspring of parents with recurrent depression completed a behavioural task assessing affective bias and a psychiatric interview. The affective processing of adolescents with current, prior and future depressive disorder was compared to that of adolescents free from disorder. Adolescents with current depression and those who developed depression at follow-up made more commission errors for sad than happy targets compared to adolescents free from disorder. There was no effect of prior depression on later affective processing. Small cell sizes meant it was not possible to separately compare those with new onset and recurrent depressive disorder. Valence-specific errors in behavioural inhibition index future vulnerability to depression in adolescents already at increased risk and may represent a measure of affective control. Currently depressed adolescents show a similar pattern of affective bias or deficits in affective control.

The study presented in this chapter has been previously published as:

Kilford, E.J., Foulkes, L., Potter, R. Collishaw, S. Thapar, A., Rice, F. (2015). Affective bias and current, past and future adolescent depression: a familial high risk study. *Journal of Affective Disorders, 174*, 265-271. doi: 10.1016/j.jad.2014.11.046.

6.1 Introduction

Adolescence is associated with a marked increase in the prevalence of depressive symptoms and disorder (Kim-Cohen et al., 2003; Lewinsohn et al., 1998; Thapar et al., 2012). Depression in young people is not benign and is associated with a range of poor outcomes including deliberate self-harm, academic failure and poor mental health in adulthood. Cognitive theories of depression propose that affective bias and negative styles of thinking play a crucial role in the development and maintenance of depression (Beck, 2008; Roiser et al., 2012). More recent models emphasise the role of 'low level' affective information processing biases in the development of 'higher level' negative schemata and depression (Roiser et al., 2012). Whilst it is clear that depressive symptoms and affective biases *co-occur*, the precise role of affective biases in the *onset* of depression and the role of prior depression on later affective processing is unclear (Jacobs et al., 2008; Roiser et al., 2012). Longitudinal studies are required in order to determine whether affective biases are state markers associated with current depression, or ''trait' markers of risk that precede depression onset or persist after remission.

One group where the investigation of affective processing and depression is particularly warranted is the offspring of depressed parents. Parental depression is a robust risk factor for depression in adolescence, with approximately 40% of the offspring of depressed parents developing depressive disorder themselves by early adulthood (Rice, Harold, & Thapar, 2002). Although there is heterogeneity in outcome for the children of depressed parents, when depression does develop, evidence suggests a severe and impairing course (Lieb, Isensee, Höfler, Pfister, & Wittchen, 2002). The potential importance of affective processing in explaining outcome in this high-risk group is illustrated by the efficacy of a preventive form of Cognitive Behavioural Therapy (CBT) that seeks to challenge negative thinking in selected high-risk groups (Garber et al., 2009), and reports of more negative explanatory styles (schemata) in high-risk compared to low-risk offspring when self-report measures are used (Garber &

Robinson, 1997). However, existing studies of affective bias in adolescent depression are often cross-sectional making it difficult to draw conclusions about the direction of influence over time. Moreover, very few studies to date have used behavioural measures of affective processing which are thought to provide a more objective assessment of affective bias than self-report questionnaires, which rely on introspection and awareness of affective bias.

The Affective Go/No Go task (AGN; Murphy et al., 1999) is an inhibitory control paradigm that has been used to investigate affective biases in depressed adults and adolescents. The task requires participants to make a motor response ('go') to words of a target valence (happy or sad), while simultaneously inhibiting motor responses ('no-go') to words of the competing valence. It also involves affective set-shifting of attention and responses, as the target category changes across experimental blocks. Depressed adults have been shown to respond faster to sad targets than happy targets, and miss more happy than sad targets (Erickson et al 2005; Murphy et al, 1999), suggesting the presence of affective biases in currently depressed adults.

Two cross-sectional studies have examined affective processing in adolescent depressive disorder using the AGN. Although these studies have found evidence of affective bias, they do not precisely mirror those reported in adult studies. Kyte et al. (2005) compared the performance of healthy controls to that of adolescents with a first onset of depression in the past year. Recently depressed adolescents made more commission errors during blocks with happy targets, suggesting they were less able to inhibit responses to sad distractors. Maalouf et al. (2012) included current and remitted depression groups as well as healthy adolescent controls. They found evidence of state-dependent affective biases; currently depressed adolescents responded more quickly when shifting to sad targets than when shifting to happy targets compared to remitted and control adolescents. To date, there is no longitudinal study of affective bias measured with the AGN and adolescent depression, and no such study in adolescents at high familial risk of developing depression.

6.1.1 Current study and research questions

This study examined affective bias in a 1-year longitudinal study of adolescents at risk of depression due to parental history of depression. The aim was to assess relationships between adolescent depressive disorder and affective bias by making use of a two-wave panel design where psychopathology and affective bias had been assessed on two occasions using well-validated methods. The following question was examined: What is the cross-sectional and longitudinal relationship between measures of affective bias and depression in a high-risk sample? Specifically, this study examined: 1) the association of affective bias with current depression; 2) the relationship between earlier depression and later affective bias, in order to assess whether experience of depression alters affective processing; and 3) whether individuals with depression at follow-up (new onset or recurrence) differed in their affective processing at baseline from those who did not.

6.2 Method

6.2.1 Participants

Participants came from a three-wave longitudinal study of the offspring of parents with recurrent unipolar depression: the Early Prediction of Adolescent Depression (EPAD) study (Mars et al., 2012). Parents were recruited predominantly from primary care (general practice surgeries) in South Wales, UK on the basis of treatment for at least two episodes of DSM-IV (American Psychiatric Assocation, 2000) major depressive disorder (confirmed at interview). The mother was the affected parent in 93% of the eligible sample at baseline. This paper reports on data collected at the second (hereafter referred to as baseline) and third assessments (carried out on average 12.5 months later; hereafter referred to as follow-up) of this cohort, when adolescents completed a test battery including the AGN. Assessments were conducted in families' homes. Parents and adolescents aged 16 years and over provided

written informed consent, younger participants provided written assent. Ethical review and approval were provided by the Multi-Centre Research Ethics Committee for Wales.

Analyses included participants with no disorder or with depressive disorder (see **6.2.2. Assessments**). **Figure 6.1** describes participation rates, reasons for non-completion of assessments and the groups that were compared. Technical issues at baseline meant that the AGN completion rate was lower than at follow-up. Nevertheless, there was no evidence of systematic differences in participation between study phases: there were no differences between adolescents who completed the AGN and those who did not in terms of gender (baseline: χ^2 (1) = .099, p = .753; follow-up: χ^2 (1) = .874, p = .350) or depressive symptoms (baseline: t(282) = .07, p = .948; follow-up: t(282) = .73, p = .474), although participants completing the AGN had higher IQ scores (baseline: t(328) = 2.83, p = .005; follow-up: t(328) = 4.32, p < .001).

6.2.2 Assessments

6.2.2.1 Emotional processing task

Participants completed the AGN task (www.camcog.com; Murphy et al., 1999), which takes approximately 10 minutes to administer. Sad and happy words are rapidly presented one at a time in the centre of a screen and participants are required to respond to words matching a target valence by pressing a button, while ignoring words of the other valence (distractor stimuli). The task consists of 10 blocks (2 practice and 8 experimental) of 18 words (nine happy and nine sad), each of which is presented for 300ms, with an inter-stimulus interval of 900ms. 45 happy words (e.g. joyful, confident) and 45 sad words (e.g. mistake, gloomy) matched for word length and frequency are presented randomly. In each block either happy (H) or sad (S) words are specified as the target valence, in one of the following randomly assigned presentation orders: HHSSHHSSHH, SSHHSSHHSS. The first two blocks are practice blocks. Of the eight experimental blocks, in four the target valence stays the same between blocks (non-

shift condition), and in four the target valence changes between blocks (shift condition). In shift blocks participants are required to inhibit their previous response and respond to a new target valence, enabling assessment of set shifting and cognitive/inhibitory control. The task gives three outcome measures of interest: 1) mean RT to respond to target words in trials where the correct response is given (latency); 2) total number of button presses to distractor stimuli (commissions) and 3) the total number of missed responses to targets (omissions). A 500ms/450 Hz tone sounded for commissions, however no feedback was given for omissions.

6.2.2.2 Psychopathology and derivation of groups

Adolescent psychiatric disorders and symptoms were assessed using the Child and Adolescent Psychiatric Assessment (CAPA; Angold & Costello, 2000), which is a semi-structured interview that provides a detailed assessment of psychopathology over the previous 3 months. Interviews were conducted separately with the parent and adolescent, and a disorder was considered present if a diagnosis was made based on either interview. All cases meeting DSM-IV (American Psychiatric Assocation, 2000) criteria and sub-threshold cases were reviewed by two child psychiatrists and diagnoses agreed by clinical consensus. Group comparisons in the present analyses focused on those with depressive disorder and those free from psychopathology. Participants were classified as having depressive disorder if they received a diagnosis of major depressive disorder, dysthymia, depression not otherwise specified or minor depression (2 weeks of low mood plus 1 symptom with associated incapacity). Minor depression was included in the depressed group on the basis that symptoms below the diagnostic threshold are impairing and associated with future depressive episodes (Angold, Costello, Farmer, Burns, & Erkanli, 1999). Participants were classified as having no disorder if they were free from psychopathology.

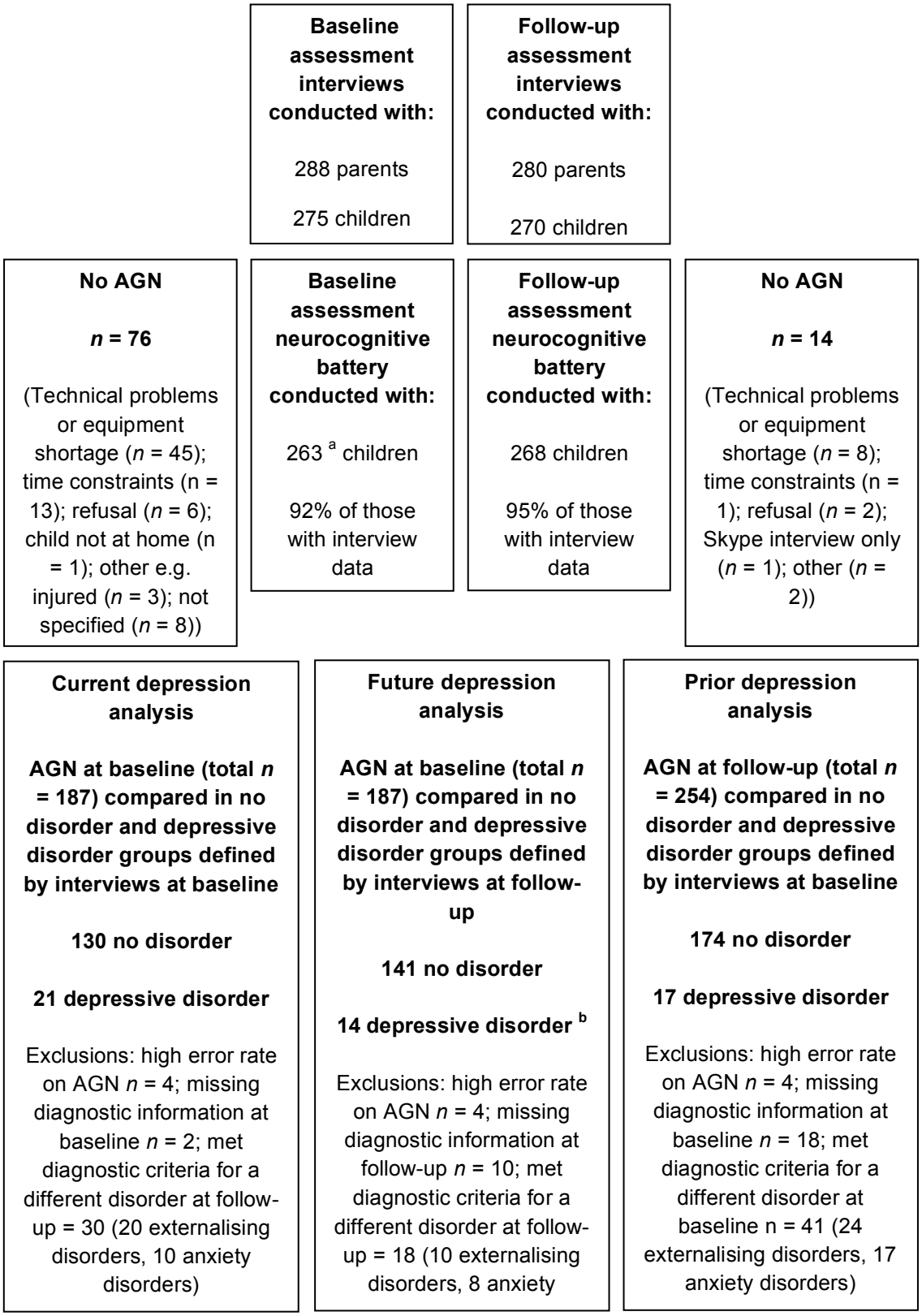

Figure 6.1. Participation details. Externalising disorders included diagnoses of oppositional defiant disorder, conduct disorder, disruptive disorder or ADHD (but no diagnosis of depression). Anxiety disorders included diagnoses of generalised anxiety disorder, separation anxiety, social phobia, panic disorder, agoraphobia, or obsessive–compulsive disorder (but no

diagnosis of depression). Adolescents were assigned to the 'no disorder' group if they were free from psychopathology. [a] Assessments were completed on 265 children but this included 2 children who were later excluded due to parental bipolar disorder. [b] 5 cases were new onset episodes of depressive disorder, 6 were recurrences from the baseline assessment and 3 individuals had different disorders at baseline (one individual had diagnoses of generalised anxiety disorder and disruptive behaviour disorder not otherwise specified at baseline, one had a diagnosis of obsessive compulsive disorder and one had a diagnosis of oppositional defiant disorder).

Symptom counts of depression (possible range 0-9) and generalised anxiety (possible range 0-14) from the CAPA were also calculated. Full scale IQ was assessed using 10 subscales of the Wechsler Intelligence Scale for Children – Fourth Edition (Wechsler, 2004).

In order to address the primary research question, three groups of depressed participants were formed (current, prior and future) and the affective processing of these groups was compared to that of participants with no disorder. The *current depression* analysis compared affective processing at baseline in individuals depressed or free from disorder at baseline. The *prior depression* analysis compared affective processing at follow-up in individuals depressed or free from disorder at baseline. Finally, the *future depression* analysis compared affective processing at baseline in those depressed or free from psychopathology at follow-up. **Figure 6.1** outlines the numbers of participants with AGN data for each of these three comparisons. Basic demographics of the groups are illustrated in **Table 6.1**. As expected, the depressed groups tended to be older and include a greater proportion of females than the no disorder groups but there were no differences between the three depression groups. AGN data were excluded where the number of missed responses was high (omissions > 70%; **Figure 6.1**). The final samples were: *Current depression* (21 depressed, 130 no disorder); *Prior depression* (17 depressed, 174 no disorder); *Future depression* (14 depressed, 141 no disorder). Of the 14 *future depression* cases, 5 were new onset depressive disorders, 6 were persistently depressed at baseline and follow-up and 3 cases had different disorders at baseline (**Figure 6.1**). Group

sample sizes were discrepant as would be expected in a naturalistic cohort study of this kind. However, there were no substantial group variance differences (Tabachnick & Fidell, 2001).

Table 6.1. Basic demographics of the diagnostic groups.

Analysis:	**Current Depression**		**Prior Depression**		**Future Depression**	
Compares:	Baseline diagnostic groups on baseline AGN performance		Baseline diagnostic groups on follow-up AGN performance		Follow-up diagnostic groups on baseline AGN performance	
	No Disorder	**Depressed**	**No Disorder**	**Depressed**	**No Disorder**	**Depressed**
n	130	21	174	17	141	14[a]
% Female	58	81	59	88	59	71
Baseline Age						
Mean (*SD*)	13.5 (2.1)	14.5 (2.3)	13.5 (2.0)	14.7 (2.1)	13.6 (2.0)	14.8 (1.6)
Range	10–18	10–17	10–18	11–18	10–18	12–17
Depressive Symptoms						
Mean (*SD*)	1.09 (1.05)	5.24 (1.82)	1.13 (1.04)	4.82 (1.67)	1.25 (1.24)	5.21 (2.15)
Gen. Anxiety Symptoms						
Mean (*SD*)	1.02 (1.39)	5.05 (2.96)	1.07 (1.49)	5.29 (3.04)	1.05 (1.48)	4.69 (2.63)

Note: Symptom counts of depressive (possible range 0-9) and generalised anxiety symptoms (possible range 0-14) were calculated from the CAPA and pertain to the assessment phase when participants in the depression groups met DSM-IV (American Psychiatric Assocation, 2000) diagnostic criteria for depressive disorder (i.e. baseline for current and prior groups; follow-up for future group). A larger number of participants completed the AGN at follow-up, hence the larger number of participants included in the prior depression analysis (which compared AGN data at follow-up in those without disorder and with depressive disorder at baseline). [a] 5 cases were new onset episodes of depressive disorder, 6 were recurrences from the baseline assessment and 3 individuals had different disorders at baseline.

6.3 Results

6.3.1 Data Analysis

Total commissions, omissions, and depressive and anxiety symptom counts were square root transformed prior to analysis to approximate normality, however presented means are untransformed. To assess the effect of current, prior and future depression on affective bias, mixed repeated ANOVAs were performed on each of the three AGN measures (mean correct latency, total commissions and total omissions). Diagnostic group (no disorder vs. depressive disorder) was a between-subjects factor. Within subjects factors were valence (happy vs. sad targets) and shift condition (shift vs. non-shift blocks). All analyses included gender, IQ, age and generalized anxiety symptom counts from the CAPA as covariates. Anxiety was included in order to control for potential influences of co-occurring anxiety on affective bias (e.g. Ladouceur et al., 2006). Depressive symptom counts from the CAPA were included as a covariate in the 'future depression' analysis in order to rule out the possibility that any observed effects stemmed from continuity of depression over time. Three-way interactions were followed up by conducting separate repeated measures ANOVAs for each diagnostic group. Two-way interactions were followed up using simple effects analysis (Howell, 1997). AGN data collected at the *baseline assessment* was used to assess the effects of *current and future depression* on affective processing. AGN data collected at the *follow-up assessment* was used to assess the effects of *prior depression* on affective bias (**Figure 6.1**).

6.3.2 Current Depression and Affective Bias

There was a main effect of group on response latency ($F(1,136) = 4.44$, $p = .037$, $\eta^2 = .032$; **Table 6.2**), with the depressed group responding more quickly than the no disorder group (see **Table 6.3** for descriptives)**.** There were no significant interaction effects with group (see **Table 6.2**).

Table 6.2. Association of AGN measures of affective bias with current, prior and future depression.

	Current Depression	Prior Depression	Future Depression
Latency			
Group	***F*(1,136) = 4.44, *p* = .037**	*F*(1,171) = .008, *p* = .929	***F*(1,141) = 5.16, *p* = .025**
Group x Valence	*F*(1,136) = .946, *p* = .332	*F*(1,171) = .806, *p* = .371	*F*(1,141) = 2.42, *p* = .122
Group x Shift	*F*(1,136) = .004, *p* = .948	*F*(1,171) = .792, *p* = .375	*F*(1,141) = .678, *p* = .412
Group x Valence x Shift	*F*(1,136) = 2.56, *p* = .112	*F*(1,171) = .392, *p* = .532	*F*(1,141) = .024, *p* = .878
Commissions			
Group	*F*(1,136) = .732, *p* = .394	*F*(1,171) = .258, *p* = .612	*F*(1,141) = .056, *p* = .813
Group x Valence	*F*(1,136) = .067, *p* = .796	*F*(1,171) = .042, *p* = .837	***F*(1,141) = 6.09, *p* = .015**
Group x Shift	*F*(1,136) = .022, *p* = .884	*F*(1,171) = .014, *p* = .906	*F*(1,141) = 2.87, *p* = .092
Group x Valence x Shift	***F*(1,136) = 5.46, *p* = .021**	*F*(1,171) = 1.70, *p* = .194	*F*(1,141) = .000, *p* = .985
Omissions			
Group	*F*(1,136) = .209, *p* = .648	*F*(1,171) = 2.64, *p* = .106	***F*(1,141) = 4.02, *p* = .047**
Group x Shift	*F*(1,136) = 1.85, *p* = .176	*F*(1,171) = .007, *p* = .932	*F*(1,141) = .762, *p* = .384
Group x Shift	*F*(1,136) = .330, *p* = .566	*F*(1,171) = .319, *p* = .572	*F*(1,141) = .382, *p* = .537
Group x Valence x Shift	*F*(1,136) = 1.04, *p* = .309	*F*(1,171) = .623, *p* = .431	*F*(1,141) = .290, *p* = .591

*Note: R*esults of ANOVAs assessing association of AGN measures of affective bias with diagnostic group (No disorder, Depressive disorder). Current Depression: Effect of baseline diagnostic group on baseline AGN performance. Prior Depression: Effect of baseline diagnostic group on follow-up AGN performance. Future Depression: Effect of follow-up diagnostic group on baseline AGN performance. Note that *n*'s varies slightly from those in **Figure 6.1** due to some participants missing scores on model covariates (IQ or symptom scores).

For commission errors, there was a 3-way interaction between diagnostic group, valence and shift ($F(1,136) = 5.46$, $p = .021$, $\eta^2 = .039$). Analysis of each group separately revealed an interaction between valence and shift in no disorder participants ($F(1,117) = 4.46$, $p = .037$, $\eta^2 = .037$) but not depressive disorder participants ($F = .011$). Simple effects analysis showed that for the no disorder group, there was an influence of shift only when target valence was happy (Happy: $F(1,117) = 4.81$, $p = .030$, $\eta^2 = .039$; Sad: $F(1,117) = .248$, $p = .620$, $\eta^2 = .002$), with more

commissions made on shift trials. In contrast, set-shifting had a greater effect on commission rates in depressive disorder participants when target valence was sad (Sad: $F(1,15) = 4.05$, $p = .062$, $\eta^2 = .213$; Happy: $F(1,15) = .105$, $p = .751$, $\eta^2 = .007$), with more commissions made on shift trials (see **Table 6.3** for descriptives). There was no significant main effect of group, or 2-way interactions with group on commission errors (**Table 6.2**).

There were no significant main or interaction effects of group on omission errors (**Table 6.2**).

6.3.3 Previous Depression and Affective Bias

There were no significant main or interaction effects of group at baseline on AGN measures at follow-up for any of the three AGN measures (**Table 6.2**).

6.3.4 Future Depression and Affective Bias

When examining depressive disorder at follow-up, controlling for baseline depressive symptoms, there were main effects of group on both latency ($F(1,141) = 5.16$, $p = .025$, $\eta^2 = .035$) and omission errors ($F(1,141) = 4.02$, $p = .047$, $\eta^2 = .028$). Those meeting diagnostic criteria for depression at the follow-up assessment were faster and made more omission errors than the no disorder control group (see **Table 6.3**). There were no significant interaction effects with group on latency or omission errors (**Table 6.2**). However, there was an interaction between valence and group for commission errors ($F(1,141) = 6.09$, $p = .0156$, $\eta^2 = .041$). Follow-up simple effects showed this was due to individuals with future depressive disorder making a greater number of commission errors for sad compared to happy stimuli ($F(1,141) = 8.85$, $p = .003$, $\eta^2 = .059$). There was a similar though much less pronounced effect of valence in individuals without a disorder ($F(1,141) = 1.68$, $p = .197$, $\eta^2 = .012$; see **Table 6.3** for descriptives). There was no significant main effect of group, or 2-way interactions with group on commission errors (**Table 6.2**).

Table 6.3. Descriptive statistics for mean AGN measures of affective bias, assessing effects of current, prior and future depression.

	Current Depression		Prior Depression		Future Depression	
	No Disorder	**Depressed**	**No Disorder**	**Depressed**	**No Disorder**	**Depressed**
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Latency						
Total	**495 (93)**	**469 (91)**	497 (89)	508 (68)	**497 (91)**	**454 (96)**
Happy	492 (95)	474 (86)	494 (90)	504 (68)	494 (94)	459 (89)
Sad	499 (95)	464 (98)	500 (94)	512 (75)	500 (93)	447 (104)
Shift to Happy	485 (101)	463 (92)	489 (93)	493 (66)	489 (100)	444 (91)
Shift to Sad	493 (98)	474 (112)	498 (98)	509 (80)	494 (97)	441 (111)
Non-Shift Happy	497 (98)	484 (85)	498 (95)	516 (79)	499 (97)	472 (99)
Non-Shift Sad	503 (104)	455 (102)	502 (99)	517 (75)	505 (103)	449 (113)
Commissions						
Total	19.11 (12.59)	20.00 (12.86)	15.92 (11.77)	12.47 (8.69)	19.32 (12.57)	18.08 (11.89)
Happy	9.12 (6.44)	9.45 (6.44)	7.66 (5.82)	5.81 (4.50)	**9.30 (6.34)**	**7.92 (5.95)**
Sad	9.98 (6.63)	10.55 (6.89)	8.26 (6.54)	6.65 (4.72)	**10.01 (6.70)**	**10.15 (6.15)**
Shift to Happy	**4.85 (3.48)**	**4.65 (3.38)**	4.09 (3.24)	3.35 (2.64)	4.95 (3.35)	3.77 (2.83)
Shift to Sad	**5.00 (3.45)**	**5.95 (3.87)**	4.31 (3.57)	3.65 (2.83)	5.12 (3.46)	4.92 (3.23)
Non-Shift Happy	**4.27 (3.40)**	**4.80 (3.41)**	3.57 (2.97)	2.47 (2.24)	4.36 (3.40)	4.15 (3.44)
Non-Shift Sad	**4.98 (3.65)**	**4.60 (3.36)**	3.94 (3.37)	3.00 (2.21)	4.90 (3.69)	5.23 (3.42)
Omissions						
Total	15.34 (11.77)	17.05 (11.28)	12.70 (10.16)	11.18 (8.88)	**15.13 (11.64)**	**21.23 (12.23)**
Happy	8.16 (6.19)	7.90 (5.29)	6.49 (5.34)	6.35 (5.72)	8.01 (6.24)	11.08 (6.37)
Sad	7.19 (6.14)	9.15 (6.85)	6.21 (5.94)	4.82 (4.05)	7.13 (6.06)	10.15 (6.47)
Shift to Happy	4.17 (3.40)	3.90 (3.14)	3.22 (2.99)	3.00 (2.78)	4.06 (3.53)	5.85 (3.65)
Shift to Sad	3.53 (3.24)	4.60 (4.10)	3.13 (3.23)	2.35 (2.62)	3.58 (3.27)	5.15 (3.89)
Non-Shift Happy	4.20 (3.50)	3.40 (2.39)	3.26 (2.82)	2.47 (2.48)	4.07 (3.42)	5.85 (3.16)
Non-Shift Sad	3.66 (3.32)	4.55 (3.53)	3.08 (3.12)	2.47 (2.35)	3.55 (3.27)	5.00 (3.44)

Note: Descriptives of effects from the ANOVAs presented in **Table 6.2.** Significant effects are shown in bold.

6.4 Discussion

Our aim was to use a naturalistic longitudinal high-risk design to assess the temporal relationship between affective bias and adolescent depression. Results indicated a mood-congruent effect of current depressive disorder on affective processing and no influence of prior depression on later affective processing, which is consistent with a previous study comparing adolescents with remitted and current depressive disorder (Maalouf et al., 2012). In addition, when controlling for baseline depressive symptoms and co-occurring symptoms of generalized anxiety, adolescents who later developed depressive disorder showed baseline

affective processing that was more negatively biased than those who were later free of psychopathology. This indicates that negative biases in affective processing may pre-date depressive symptoms, making this a potentially useful target for detection and prevention of future depressive disorder.

The present results suggest valence-specific effects on cognitive control that differ for adolescents who are currently depressed or free from disorder and also predict the development of depressive disorder over time. Group-dependent effects of valence were observed for commission errors (on shift trials) whereby currently depressed individuals showed a greater number of errors for sad targets and healthy individuals showed a greater number of errors for happy targets. This perhaps indicates that sad stimuli interfere with cognitive control (i.e. result in a greater number of errors in behavioural inhibition) in depressed individuals while happy stimuli are interfering in adolescents with no disorder. Findings consistent with this interpretation are evidence of a bias for positive (happy faces) compared to negative targets (sad faces) shown by quicker RTs and greater commission errors in healthy individuals (Schulz et al., 2007), and a pattern of neural activation consistent with greater arousal for happy compared to sad targets in healthy controls (Elliott, Dolan, & Frith, 2000). Furthermore, greater activation in dlPFC has been reported for sad targets in depressed adults and for neutral targets in healthy controls (Elliott, Rubinsztein, Sahakian, & Dolan, 2002), which is consistent with the suggestion that there may be depression dependent valence-specific effects on behavioural action and inhibition. The present study indicated that the observed valence-specific effect on commission errors also appeared to index vulnerability to *later* depression. Thus, a greater number of commission errors to sad than happy targets differentiated adolescents with depressive disorder at follow-up from those free from disorder at follow-up indicating that this may be a cognitive risk marker for future depressive disorder.

It is worth noting some differences in the present pattern of results to those reported in previous cross-sectional studies of adolescent depression. In particular, the two previous studies that have used this task to assess affective bias in adolescent depression reported results consistent with a difficulty in disengaging from sad stimuli as opposed to an interference effect of sad stimuli as reported in the present study (Kyte et al., 2005; Maalouf et al., 2012). In contrast, the results of this study suggest that sad targets may result in an interruption in cognitive control, leading to greater commission errors for sad compared to happy targets in those who are currently depressed or become depressed at the 1-year follow-up. It is possible that differences between the samples may partly explain differences in findings. In particular, the age range in the current sample was wide and the mean age was lower than that of the two previous studies, thus it seems likely that the participants in this study found the task more difficult. This is reflected in the higher error rates seen in the present sample.

This study only included adolescents at familial risk of developing depression due to recurrent parental unipolar depression, which may limit the generalizability of findings to other samples. Indeed, this may have made this study more conservative as all participants were at increased risk of developing depression compared to the general population. Small cell sizes meant it was not possible to separately examine the influence of recurrent and new onset depressive disorders in the analysis of 'future depression'. However, the inclusion of prior symptoms as a covariate will have partially addressed this limitation. Minor depression was included in the depressed group, however results were similar when these cases were excluded. As lifetime diagnoses were not assessed (instead current psychopathology was assessed on two occasions), depressive episodes may have been missed in some individuals classified as unaffected. However, this would serve to make analyses more conservative. The choice to assess current rather than lifetime psychopathology is warranted given the superior reliability of the former approach (Hardt & Rutter, 2004; Moffitt et al., 2010). Taken together, results are

consistent with valence-specific effects on cognitive control in adolescents with current depressive disorder and those who later develop depressive disorder. This is the first demonstration that a measure of affective bias derived from a behavioural task indexes future vulnerability to adolescent depression.

CHAPTER 7: GENERAL DISCUSSION

The studies in this thesis aimed to investigate how interactions between social cognition, motivational-affective processing, and cognitive control change over development, and how this is influenced by individual differences in affective reactivity and genetics. This thesis takes an interdisciplinary approach to studying adolescent neurocognitive development, and how this may vary between individuals, using a combination of genetic, cognitive and computational techniques, in both healthy and clinical populations. The main findings of each chapter are summarised in the context of three broader research themes: 1) developmental changes in the influence of dopaminergic variance on cognition; 2) reward processing and learning in adolescence; and 3) individual differences in mood and anxiety during adolescence. Methodological considerations and outstanding issues are discussed, and possible directions for future research are considered.

7.1 Developmental changes in genetic effects on cognition

Chapters 2 and **3** used a common genetic polymorphism that affects the function of the COMT enzyme to investigate the development the dopamine neurotransmitter system, and how dopaminergic genetic variance is associated with different aspects of cognition during development. As described in **Chapter 1,** according to a developmental hypothesis of *COMT* effects on cognition (**1.6.1.3**), greater extracellular prefrontal dopamine levels in childhood and adolescence are proposed to shift the relative position of each *COMT* genotype rightwards along the dopamine-performance curve, resulting in altered pattern of genetic associations with cognition compared to those observed in adulthood (see **Figure 1.9**).

The influence of *COMT* Val^{158}Met genotype was previously investigated in a sample of healthy adult participants on a range of cognitive processes, including social and non-social WM (Dumontheil et al., 2014), and the flexible modulation of the balance between processing self-generated and processing stimulus-oriented information, in the presence or absence of affective distractors (Kilford et al., 2015). Consistent with findings in adults that the Met allele is associated with higher levels of prefrontal dopamine and superior executive cognition (for reviews see Tunbridge et al., 2006; Dickinson and Elvevåg, 2009; Witte and Flöel, 2012), this study showed evidence of a Met allele benefit for both social and non-social WM (Dumontheil et al., 2014) and the ability to select and manipulate self-generated information (Kilford et al., 2015). Here, I compared data from this adult sample with data collected from a sample of children and adolescents, in order to investigate: 1) age-related changes in these cognitive processes; 2) whether the genetic observations observed between *COMT* genotype and cognition during adulthood were stable across the lifespan or were instead moderated by developmental stage. Based on previous findings suggesting that relationships between dopaminergic genetic variation and neurocognitive function may be best understood from a developmental perspective (see **Section 1.6.3**), it was hypothesised that genetic associations with cognition would vary with age. In line with a developmental hypothesis of *COMT* effects on cognition, it was predicted that, in contrast to the typically observed adult pattern of superior performance in Met homozygotes relative to Val carriers (**Figure 1.9A**), adolescent Met homozygotes would show relatively poor cognitive performance (**Figure 1.9B**). It was also predicted that developmental improvements in prefrontal cognition (see **Section 1.3.1**) may be greater in Met homozygotes relative to Val carriers, due to their respective shifts toward and away from the peak of the dopamine performance curve (**Figure 1.9B**).

Chapter 2 investigated developmental changes in verbal, visuospatial and social WM, and how this varied according to *COMT* Val^{158}Met genotype. In line with predictions, the association between *COMT* genotype and visuospatial and social WM was moderated by developmental

stage. While the Val allele was associated with relatively poorer WM performance in adulthood, this was not the case in childhood and adolescence, and while WM performance was significantly better in Met/Met adults than Met/Met adolescents, the performance of Val carriers did not differ between age groups. Although a similar pattern was observed for verbal WM, the interaction between *COMT* and age was not significant (**Figure 2.2A**), which may suggest that the verbal WM task used was less sensitive to dopaminergic genetic variation than the other WM assessments.

Chapter 2 also investigated developmental changes in social, relative to non-social WM, as well as the extent to which associations between *COMT* genotype and social WM performance could be accounted for by *COMT*'s association with non-social WM skills. Social WM was assessed using a novel social WM paradigm, which requires participants to maintain and manipulate information about the traits of their family and friends over a delay. As discussed in **Chapter 1**, prolonged developmental changes occur during adolescence in both WM and social cognition, and the structure and function of the brain networks supporting these cognitive processes. Consistent with these developmental improvements, adults performed significantly better than adolescents on all three measures of WM assessed in **Chapter 2**. However, and of particular interest, the effect of age group on social WM performance was not accounted for by variation in non-social measures of WM (see **Section 2.3.3**). While these results are behavioural in nature, they are consistent with neuroimaging evidence suggesting that, in adults, the effortful processing of social information is supported by regions of the social brain network, as well as traditional WM networks (Meyer et al. 2012; 2015). The findings of **Chapter 2** are also consistent with evidence suggesting that social and non-social higher cognitive brain systems tend to be recruited in parallel (e.g. Dumontheil et al., 2012; Magis-Weinberg et al., 2017), with developmental improvements in effortful social processing, such as perspective-taking (**Sections 1.4.3.2**) and social decision-making (**1.4.3.3**), proposed to reflect parallel developmental changes in these systems and their improved integration. The

findings of **Chapter 2** therefore raise interesting questions for future research, such as how developmental changes in the social brain and cognitive control regions are associated with the development of social WM processing (see **Section 7.5.1**).

Chapter 3 investigated whether a developmental model of *COMT* effects on WM would extend to a novel aspect of executive function, specifically, the flexible processing of self-generated and perceptually-derived information, an aspect of executive function that can be measured using the Alphabet task (Gilbert et al., 2005). As reviewed in **Chapter 1**, the PFC shows protracted developmental changes during adolescence (reviewed in **Section 1.2**), and is associated with developmental improvements in cognitive control - the ability to actively guide behaviour in a goal-directed manner. Consistent with evidence of developmental improvements in executive function during adolescence (**Section 1.3.1**), independent of genotype, adolescents were less accurate and slower at the task, particularly when they were required to process self-generated information (**Section 3.4.1**). Furthermore, there was an interaction between age and *COMT* genotype on Alphabet task performance, with adolescents showing the opposite pattern of association to that observed in adults (see also Kilford et al., 2015). In line with the predictions of a developmental model of *COMT*, the executive function benefits associated with the Met allele in adulthood appeared to emerge during adolescence, and Met homozygotes showed steeper age-related improvements in task performance. Adult Met homozygotes showed significantly better task performance than their adolescent counterparts, particularly when they were required to process self-generated information, an effect which was not observed in Val carriers (**Section 3.4.2**).

As described in **Chapter 2**, a significant interaction was observed between age group and *COMT* on visuospatial WM (which was also significant in the slightly smaller sample analysed in **Chapter 3**). A previous study of only the adult sample (Kilford et al., 2015) suggested that the association of *COMT* genotype with Alphabet task performance was partly accounted for by

associations of *COMT* with visuospatial WM ability. Therefore, the extent to which age-moderated effects of *COMT* genotype on the Alphabet task were accounted for by visuospatial WM task performance was also evaluated. While the effects of age, and the interaction between age and genotype, remained significant when visuospatial WM performance was controlled for, these effects were no longer moderated by whether or not the information to be processed was perceptually derived or self-generated (see **Section 3.4.3**). This suggests that variation in visuospatial WM ability, whether due to developmental improvements in cognitive control (see **Section 1.3.1**), genetic variance or other factors not assessed here, may to some extent account for variation in the ability to select and manipulate self-generated information.

In adults, in addition to being associated with superior executive function and WM (Tunbridge et al., 2006; Dickinson and Elvevåg, 2009; Witte and Flöel, 2012), the Met allele has shown associations with increased anxious temperament and affective reactivity (Goldman et al., 2005; Mier et al., 2010; Montag et al., 2012). This pattern of reciprocal variation has been hypothesised to represent a trade-off between cognitive efficiency and emotional resilience (Dickinson & Elvevåg, 2009; Goldman et al., 2005; Mier et al., 2010; Montag et al., 2012; Papaleo et al., 2008). Therefore, in addition to examining the developmental changes in the influence of *COMT* genotype on executive functioning, **Chapter 3** also detailed an exploratory examination of whether developmentally moderated effects of *COMT* Val1^{58}Met extended to reciprocal variation in trait anxiety (discussed further in **Section 7.3**). This revealed the existence of a similar interaction between age group and genotype on anxiety to those observed for Alphabet task (**Chapter 3**), visuospatial (**Chapters 2** and **3**) and social WM performance (**Chapter 2**)

To summarise, the findings presented in **Chapters 2** and **3** replicate and extend previous cross-sectional and longitudinal findings (Dumontheil et al., 2011; Wahlstrom et al., 2007; Wahlstrom, Collins, et al., 2010; Wahlstrom, White, et al., 2010) that the pattern of superior

cognitive control in Met homozygotes typically observed in adulthood emerges during development. For example, a longitudinal study by Dumontheil et al. (2011) demonstrated that Met homozygotes showed steeper age-related performance improvements than Val carriers, and furthermore that child and adolescent Val carriers did not show performance deficits relative to their Met/Met counterparts, consistent with a decrease in prefrontal basal dopamine levels during adolescence (Dumontheil et al., 2014; Wahlstrom et al., 2007; Wahlstrom, Collins, et al., 2010; Wahlstrom, White, et al., 2010; see **Figure 1.9**). **Chapter 2** replicated these findings, and suggested the existence of a similar developmentally moderated association of *COMT* genotype with social WM, over and above the association of *COMT* with domain-general WM abilities.

Chapter 3 demonstrated that a developmental hypothesis of *COMT* effects also accounted for variation in the flexible processing of self-generated and perceptually-derived information, a novel aspect of executive function, which shows extended development late into adolescence (Dumontheil et al., 2010). While the ability to select and manipulate self-generated information appeared to show a degree of shared variance with visuospatial WM, this was not the case for overall task performance. Therefore, the hypothesised interaction of age and genotype on prefrontal dopamine function may also impact other aspects of executive function required for successful task performance, such as maintaining and updating current task goals, or ignoring distracting information. **Chapter 3** also provided preliminary evidence for a reciprocal age-moderated association of *COMT* genotype with trait anxiety, an aspect of cognition which has not previously been studied within the framework of a developmental mode of *COMT*.

Taken together, the findings presented in **Chapters 2** and **3** provide indirect evidence in support of the hypothesis that prefrontal dopamine levels decrease during human adolescence (Dumontheil et al., 2011; Jucaite et al., 2010; Wahlstrom et al., 2007), and highlight the utility

of genetic association studies as a non-invasive research tool to further our understanding of the association between prefrontal dopaminergic variance and cognition during development. Relationships between *COMT* genotype and cognition have not always been replicated and meta-analyses indicate that effect sizes are relatively low, similar to the effect of other polymorphisms on cognitive variables (Barnett et al., 2008; Dickinson & Elvevåg, 2009; Montag et al., 2012; Witte & Flöel, 2012). One factor contributing to this may be a failure to consider the impact of individual differences such as developmental stage, sex or stress on an individual's position on the dopamine performance curve, and how this may moderate associations between genotype and cognition both between and within individuals. Had adolescents and adults been studied as a single population, no effects of *COMT* genotype would have been observed as the opposing patterns of associations for the different age groups would have cancelled each other out. The findings presented in **Chapters 2** and **3** therefore highlight the principle that effects of genetic variation on neurocognitive function may not necessarily be stable across development and suggest that a developmental perspective may be a crucial step in furthering our understanding of genetic effects on neurocognitive function.

7.2 Reward processing and learning in adolescence

Reward processing and sensitivity undergo marked changes in adolescence, and significant changes are observed in value-based decision-making during this period (reviewed in **Section 1.3.4**). Thus, **Chapters 4** and **5** investigated developmental changes in different components of reward processing during adolescence, using questionnaire assessments, behavioural tasks and computational modelling.

Chapter 4 employed a novel learning task to investigate how adolescents and adults learn from reward versus punishment, and counterfactual feedback about decisions. During the

learning task, participants made choices between two options, presented within different choice contexts, each of which was associated with different probabilities of an advantageous outcome. In reward contexts an advantageous outcome was gaining a point relative to an outcome of no points, whereas in punishment contexts an advantageous outcome was not losing a point, relative to losing a point. Feedback availability was also manipulated, whereby in some contexts participants only received feedback about the outcome of their choice, whereas in others they were provided with the outcome of both their chosen option and the hypothetical outcome of the alternative option. Participants' choices on the learning task were submitted to computational analyses, based on an algorithm that has been shown to provide a good account for both behavioural and neural data within the same task in adults (Palminteri et al., 2015; see **Figure 4.2**). Computational analyses revealed that adults and adolescents did not implement the same algorithm to perform the learning task. In contrast to adults, adolescents' performance did not take into account counterfactual information; adolescents also learned preferentially to seek rewards rather than to avoid punishments, whereas adults learned to seek and avoid both equally. Analysis of the behavioural data supported the findings of the computational analyses.

In reward contexts in which no additional feedback information was available, adults and adolescents did not differ in their performance, suggesting that both age groups were both motivated and able to successfully learn from rewarding feedback associated with their choices, in order to maximise reward in future outcomes. This context was computationally the simplest within the task, as future rewards could be successfully maximised by directly tracking outcome values as modelled by a basic, or Q-learning, RL algorithm (Rescorla & Wagner, 1972; Watkins & Dayan, 1992). Indeed, this RL model (our Model 1) best described adolescent performance across all task contexts. This finding is consistent with studies suggesting that the ability to learn from positive feedback is present in children as young as 8

years (Cohen et al., 2010), and that adolescent value-based decision-making is characterised by behavioural and neural increases in reward sensitivity (see **Section 1.3.4**).

In contrast, similar to a previous study in adults (Palminteri et al., 2015), adult task performance was best characterised by a more complex RL model, in which in addition to standard Q-learning, unchosen outcome values are also tracked and therefore counterfactual information provides increased information from which to learn. The model also updates outcome values within the overall value of the context they are presented in, so that in contexts in which the best outcome is no reward (as opposed to a punishment), the absence of a negative outcome acts as a reinforcer in a similar way to a rewarding outcome. Behavioural analyses again supported the model comparison analyses. Where adults showed improved learning rates, and faster decision times when they were provided with feedback about the outcome of the unchosen option, adolescents did not benefit from this information either during the learning task, or on a subsequent test of their ability to discriminate between the cues according to their values, as learnt from the task. Adolescents, relative to adults, also showed a lower rate of learning in punishment contexts.

Both learning from counterfactual information and value contextualisation are more computationally demanding than reward maximisation, involving the representation, transformation and integration of information. While reward learning is robustly associated with striatal activation, these more complex computations are associated with the dlPFC, an area associated with the flexible co-ordination of a range of executive functions (see **Section 1.3.1**). The results of **Chapter 4** are largely consistent with a dual systems hypothesis of adolescent neurocognitive development, in that they suggest a relatively early emergence of striatal reward-maximisation learning strategies, with more complex computational strategies emerging later as prefrontal regions mature and become increasingly integrated with sub-cortical motivational processing systems.

Studies investigating the relationship between cognitive control and motivational processing in adolescence indicate that the presence of incentives can lead to both impairments and improvements in performance, indicative of the complexity of these systems. For example, while the presence of rewards has been associated with enhanced response inhibition in adolescence, it has also been associated with increases in sub-optimal or risky-decision making (reviewed in **Section 1.3.4**). Furthermore, findings from a longitudinal study suggest that the effect of incentives (both rewards and punishments) on cognitive performance shows a large degree of individual variation, for some individuals incentives enhanced performance on an inhibitory control task, whereas others showed impairments (Paulsen et al., 2015). One potential explanation for these seemingly paradoxical effects is that the influence of rewards on performance follows an inverted U-shape pattern, whereby the increased salience of a potential reward enhances motivation up until a certain point, at which incentives begin to hinder performance, a phenomenon sometimes referred to as 'choking under pressure' (Baumeister & Showers, 1986; Mobbs et al., 2009). Such a proposal would be consistent with the inverted U-shape pattern of dopamine effects on cognitive function (see **Figure 1.9**), which is perhaps not surprising given the crucial role of dopamine signalling in the coding of incentives, and evidence suggesting that dopaminergic prediction error responsivity may be heightened in adolescence (Cohen et al., 2010).

In contrast to **Chapter 4**, **Chapter 5** assessed developmental changes in reward sensitivity in the absence of a learning or decision-making component. As reviewed in **Section 1.3.4**, experimental evidence largely supports the hypothesis that reward sensitivity is heightened during adolescence (see also van Duijvenvoorde, Peters, Braams, & Crone, 2016 for more in-depth review), and it has also been proposed that increases in the susceptibility to peer influence during this period may, at least in part, be due to an increase in sensitivity to social rewards in adolescence (see Foulkes & Blakemore, 2016 for detailed review). Thus, **Chapter 5**

assessed developmental changes in sensitivity to social and non-social rewards, using a combination of a reward processing task and subjective value ratings of reward stimuli.

Despite the relatively large body of research assessing developmental changes in reward processing, there are few developmental studies assessing sensitivity to social rewards in the context of a non-social reward. A study by Kohls et al. (2009) assessed the effects of social and monetary rewards on inhibitory control performance in 8 to 12 year old boys, a younger age group than assessed in **Chapter 5**. Demurie et al. (2012) recruited a wider age range of participants (8-16 years), but the upper age limit of 16 used in their study is still a relatively young age in the context of current definitions of adolescence (see **Section 7.4.1**), and thus little is known about sensitivity to social rewards in adolescence (reviewed in Foulkes & Blakemore, 2016). As a result, the cognitive demands of the task used in **Chapter 5** were kept as simple as possible in an attempt disentangle developmental changes in the sensitivity to different types of reward from parallel changes occurring in cognitive control, and the way in which it is integrated with motivational processing (as examined in **Chapter 4**).

The findings of Demurie et al. (2012) suggested that, while social rewards are able to reinforce behaviour in children and adolescents, this may not be the case for all types of social reward, including rewards that have previously been shown to reinforce behaviour in adults (i.e. smiling faces; Rademacher et al., 2010; Spreckelmeyer et al., 2009). In **Chapter 5** participants performed two versions of a reward anticipation task, in which a speeded response to a target could result in either a social (Facebook 'Like' symbol) or monetary (pound symbol) reward outcome, and subsequently rated the extent to which they liked each reward. In each task version, a cue indicated the likelihood participants would be rewarded, providing they made a sufficiently fast response. Unlike in **Chapter 4**, participants did not receive actual monetary rewards as a result of their performance on the monetary reward task. The rationale for this was that there would not have been an equivalent translation of winnings into real-life

rewards in the social task, which would have reduced the comparability of the two tasks as closely as possible. Thus, the paradigm instead relied on participants' learned associations between the symbolic representations of reward (pound sign and Like symbol) and reward value, an approach which has been employed in previous studies of monetary and social reward in adults (Kohls et al., 2009; Rademacher et al., 2013; Foulkes et al., 2014). An inherent difficulty when studying monetary reward across different ages is the fact that the subjective value of money almost certainly differs between children, adolescents and adults. Thus, participants' familiarity with both the reward stimuli, as well as their ratings of the subjective value of each reward were also assessed.

This paradigm has only previously been used with an adult sample (Foulkes et al., 2014), and thus the first aim of **Chapter 5** was to assess whether the task would be a sensitive measure of reward processing within a sample of female participants aged between 13 and 34 years. In line with other studies of reward processing (Demurie et al., 2012; Spreckelmeyer et al., 2009; Rademacher et al., 2010), response speed was used as an index of reward sensitivity, with faster speeds hypothesised to represent a greater motivation to obtain the stimuli. Analyses indicated that, for both tasks, as reward probability increased, participants showed a stepwise increase in response speeds, indicating that both reward stimuli were capable of reinforcing behaviour in line with the expected likelihood of obtaining the reward. As in the social reward task of Demurie et al. (2012) that was a successful reinforcer in 8-16 year olds, the social (and monetary) task used in **Chapter 5** both featured a quantifiable, cumulative aspect (i.e. points). To examine whether the two task versions were sensitive to different domains of reward, and were not simply assessing an individual's motivation to acquire points regardless of the reward type, associations between reward task performance and the self-reported value of a range of social rewards was also assessed. While performance on the monetary reward task was not associated with self-reported value of social rewards, response speed on the social reward task was associated specifically with the self-reported enjoyment of being admired by others,

suggesting that individuals who place a higher value on the admiration and approval of others were more motivated to pursue the social rewards in the task.

The next aim of **Chapter 5** was to assess whether sensitivity to the two rewards varied with age, as assessed by both response speeds and subjective liking ratings of the stimuli. There was a quadratic effect of age for participants' liking of both reward symbols, which peaked at approximately 23 years of age, suggesting that the reward value of the stimuli was highest in young adults. Performance on both reward tasks was also best characterised by a quadratic effect of age, whereby the fastest responses were observed at around 22 years. However, task performance was not predicted by subjective liking ratings. Age effects were stronger and more consistent across reward probability levels for the monetary reward task than the social reward task, on which there was not a quadratic effect of age when the probability that a fast response would be rewarded was uncertain. Exploratory post-hoc analyses suggested that response to uncertain rewards may change with age. While younger participants showed similarly enhanced response speeds to both certain and uncertain social rewards relative to the non-rewarded trials, older participants only showed faster responses when performance was certain to result in reward. Despite being exploratory in nature, this finding yields interesting questions for future research. Uncertainty is an inherent property of real-world social rewards and thus it would be interesting to examine the development of the influence of outcome uncertainty on social relative to non-social rewards. Indeed, adult studies indicate that VS activation is greatest for rewards of maximal uncertainty (Dreher et al., 2009), and future studies would benefit from manipulating both magnitude and likelihood of social rewards, and examining the effect of these factors on decision-making and learning.

The findings of **Chapter 5** differ to those of Demurie et al. (2012), who found no effect of age on social or monetary reward task performance (no data were available regarding age effects on likeability ratings of the stimuli), as here, both task performance and subjective liking

ratings were associated with age. However, in addition to the fact that Demurie et al. (2012) used a categorical rather than continuous approach to analyse age effects, there was also only a 4 year overlap between their sample and that of **Chapter 5** (8–16 years vs. 13–34 years). The finding of a relatively late peak in reward sensitivity is consistent with previous behavioural and neuroimaging studies of reward sensitivity that have found a quadratic pattern of developmental effects, with sensitivity increasing during adolescence, peaking in late adolescence (around 17 years, Braams et al., 2015) or early adulthood (around 21 years, Urosevic et al., 2012), before subsequently declining. The results of **Chapter 5** suggests that late adolescence and young adulthood may be a stage at which reward processing is continuing to develop, however individuals in this age range are often classed as adults, or excluded altogether in categorical assessments of developmental effects (van Duijvenvoorde et al., 2016; see **Section 7.4.1**).

The finding that both subjective liking ratings and task performance showed quadratic effects of age, but that liking did not predict behavioural responses highlights the fact that, despite often being correlated, the hedonic value of a reward and its salience as a reinforcer represent two distinct components of motivational processing. The fact that subjective reward value changed with age also highlights the fact that rewards (both monetary and other types of rewards) may not be equivalent in value, and that studies of the development of reward processing should include this as an additional assessment. With regards to the hypothesis of elevated social reward value in adolescence, while the findings of **Chapter 5** did indicate an increase in sensitivity to rewards of a social nature in late adolescence/early adulthood, they did not suggest that this was specific to social rewards, as similar increases were observed for monetary rewards. Social reward is a complex and multi-dimensional construct, the specific social reward used in this study appeared to most closely reflect the enjoyment of being admired. Thus it may be that paradigms focussing on other dimensions of social reward may find different developmental effects. Furthermore, compared with other investigations of

social reward in adolescence, the paradigm used in **Chapter 5** had relatively low cognitive and affective demands. Many studies have used socio-affective stimuli such as faces as social rewards (e.g. Cromheeke & Mueller, 2015), and have indeed found that such stimuli are more distracting in adolescents compared to adults However, with such paradigms it is difficult to disentangle developmental changes in (social) reward sensitivity from concurrent developmental changes in affective reactivity and cognitive control (see **Section 1.3.3**).

7.3 Individual differences in mood and anxiety during adolescence

Many of the neurocognitive changes associated with adolescence assist the transition to an independent adult role in society. However, as reviewed in **Section 1.7**, adolescence is also a period of elevated risk for the onset of mood and anxiety disorders, and increased affective reactivity (Kim-Cohen et al., 2003; Lewinsohn et al., 1998; Thapar et al., 2012). Thus, the studies presented in **Chapters 3**, **5** and **6** examined how individual differences in genetics (**Chapter 3**), reward sensitivity (**Chapter 5**) and the regulation of affective information (**Chapter 6**) were associated with the symptoms and/or diagnosis of mood and anxiety disorders in adolescence.

Chapter 3 aimed to investigate age-related changes in the association of *COMT* genotype with variation in executive function and affective reactivity, based on studies in adult samples suggesting that *COMT* genotype is associated with reciprocal variation in these two aspects of cognition (see **Section 1.6.1.2**; Mier et al., 2010; Montag et al., 2012). As discussed in **Section 7.2**, there was an interaction between age group and *COMT* genotype on both task performance and trait anxiety. Met/Met adults had significantly better executive function *and* higher trait anxiety scores than Met/Met adolescents, an effect which was not found in Val carriers (**Figure 3.3**), suggesting greater age-related changes in associations between *COMT* and cognitive phenotypes in Met homozygotes than Val carriers. Furthermore, the opposite

pattern of genetic associations was found in adolescents to adults, whereby adolescent Met homozygotes showed poorer executive function *and* lower trait anxiety. Due to practical constraints of adolescent data collection, anxiety data was only available for a subsample of participants, and thus this finding should be treated as exploratory. However, it does provide preliminary evidence that the trade-off pattern of reciprocal *COMT* genotype effects on executive function and affective reactivity may also be moderated by developmental stage, a hypothesis that warrants further investigation. Another limitation of the study presented in **Chapter 3** was its cross-sectional, categorical design (discussed further in **7.4.1**), and while the findings regarding executive function are consistent with studies employing longitudinal methods (Dumontheil et al., 2012), there are no equivalent studies examining developmental changes in the association of *COMT* genotype with affective reactivity. Longitudinal evidence supporting the hypothesis that *COMT* is associated with reciprocal variation in cognitive efficiency and affective reactivity, and that the pattern of associations changes over development would have important implications for the study of risk factors for mood and anxiety disorders, and the mechanisms underlying such risk.

COMT exerts a greater influence on dopaminergic function in the PFC than it does in subcortical regions, due to the relatively limited expression of other regulatory proteins that degrade dopamine in the PFC compared to elsewhere in the brain (see **Section 1.6.1.2**). Thus it has been proposed that variance in affective reactivity may result from *COMT*-associated imbalances in the prefrontal-subcortical networks implicated in emotional regulation (Witte & Flöel, 2012). For example, the higher dopamine levels associated with the Met allele may lead to increased limbic system reactivity to emotional stimuli due to higher dopamine-mediated gating of inputs, and therefore require greater prefrontal regulation (Drabant et al., 2006; Smolka et al., 2005). Another hypothesis is that higher prefrontal dopamine levels result in heightened stability of neural representations (see Bilder, Volavka, Lachman, & Grace, 2004), which while beneficial for executive functions and WM, may also result in cognitive inflexibility

and difficulty disengaging from negative emotions or stimuli. Furthermore, the impact of stressful situations and environments on dopamine release may be particularly disadvantageous for Met homozygotes, as stress-related increases in dopamine may result in performance impairments similar to those induced pharmacologically (see **Figure 1.9**). A developmental model of *COMT* effects on cognition suggests that during adolescence Met homozygotes may be vulnerable to particularly high levels of extracellular dopamine in prefrontal networks. Thus, examining how this may be associated with changes in affective reactivity is an important area for future enquiry. For example, what are the effects of elevated prefrontal dopamine during adolescence on the integration of prefrontal and subcortical systems implicated in emotional regulation (see **Section 1.3.3**), and how might this relate to the development of mood or anxiety disorders? Furthermore, how might state changes in dopaminergic function as a result of a stressful environment interact with *COMT* genotype, and are such effects exacerbated during adolescence?

Chapter 5 also examined individual differences in anxiety using self-report questionnaire assessments, with a particular focus on social anxiety, a disorder which has a particularly high rate of onset during early adolescence (Beesdo et al., 2010; Stein, 2006; see **Section 1.6.2.3**). Social reward processing has been emphasized as an important factor in the development of SAD. Neuroimaging studies suggest that adolescents with, or at risk of, SAD show altered neural processing of both monetary and social rewards (Helfinstein et al., 2011; Guyer et al., 2006; 2012; 2014; Richey et al., 2014), and that this may be specific to social anxiety, as opposed to general anxiety (Guyer et al., 2012). However, behavioural evidence is mixed, with some studies reporting effects of social anxiety on reward task performance (both monetary and social rewards) or subjective liking ratings (Maresh et al. 2014, Cremers et al., 2015), whereas others do not (Guyer et al., 2006; Guyer et al., 2012; Richey et al., 2014). Furthermore, only one study to date has investigated the effects of social anxiety on both social and monetary reward processing (Richey et al., 2014), and this was in an adult patient

sample. **Chapter 5** aimed to examined whether reward processing during adolescence was influenced by individual differences in social anxiety, and whether this differed between social and non-social rewards.

Chapter 5 assessed self-reported social anxiety symptoms in the general population using the LSAS (Liebowitz, 1987), a self-report scale used to measure the effects of social anxiety across a variety of everyday life situations relating to SAD's two core symptom domains: fear and avoidance of social interactions and fear and avoidance of performance situations. Since anxiety-related disorders show a degree of overlap in their symptoms, diagnoses and risk factors, trait anxiety was also assessed, to disentangle symptoms specifically related to social anxiety, from those relating from broader anxiety symptoms. While it would be expected that an individual with high social anxiety would also show elevated trait anxiety, those with high trait anxiety would not necessarily show elevated social anxiety, enabling the differentiation between effects of anxiety specific to social situations and more general effects of anxiety on reward sensitivity.

As detailed in **Section 5.3.4**, self-reported social anxiety symptoms were not associated with subjective liking of either the monetary or social reward stimuli. This finding is not inconsistent with that of Cremers et al. (2015), who found that adults with SAD did not differ from non-anxious adults in their subjective liking of social rewards (smiling faces), only on their ratings of neutral outcomes and social punishments (angry faces). Similarly, a study by Maresh et al. (2014) found that although socially anxious individuals showed heightened striatal activity during the anticipation of monetary rewards, they did not differ in subjective liking of the rewards. In contrast to subjective ratings, the study detailed in **Chapter 5** showed that social anxiety symptoms were associated with RTs on both reward tasks, over and above variation in trait anxiety, which did not predict performance. On both tasks, anxiety specifically relating to social interactions was associated with faster responses to reward stimuli at all reward

probabilities, whereas anxiety specifically relating to performing/being observed was associated with slower responses. Although age-related changes in self-reported anxiety symptoms were observed, these did not account for developmental changes in subjective liking or reward task performance, suggesting that effects of social anxiety on reward sensitivity were largely independent from those of age. The finding of opposing directions of effects for these two facets of social anxiety could speculatively be understood within the framework of a performance monitoring hypothesis of reward processing in socially anxious individuals (Caouette & Guyer 2014).

Our finding that social anxiety symptoms predicted performance on both reward tasks, and across probability levels, but were not associated with subjective liking ratings of the reward stimuli is consistent with a performance monitoring hypothesis of reward processing in SAD (Caouette & Guyer 2014). This hypothesis argues that rather than reflecting differences in reward sensitivity *per se*, the pattern of elevated striatal reactivity seen in socially anxious individuals in response to social or monetary gains and losses (e.g. Guyer et al., 2006; 2012; 2014; Bar-Haim et al., 2009) instead reflects an increase in the salience of performance-contingent outcomes, resulting from a strong motivation to avoid failure or making errors (Lago et al., 2017). This proposal is supported by evidence that socially anxious individuals show greater reactivity to negative, relative to positive, feedback (Helfinstein et al., 2011). It has been suggested that similar to extrinsic rewards (e.g. money), intrinsic rewards (e.g. the inner drive to perform well) may have an inverted U-shaped influence on task performance (van Duijvenvoorde et al., 2016), whereby as the salience of a performance-contingent outcome increases, performance improves up until a given point, at which the focus on the outcome becomes too great and hinders performance. Notably, while it was not a deliberate experimental manipulation, all participants performed the reward tasks in the presence of the experimenter. The presence of an unfamiliar other may therefore have increased the salience of performance-contingent rewards to the extent to which performance improved in

individuals with social anxiety not specifically characterised by performance anxiety, whereas for individuals with high anxiety regarding performance situations the drive to perform well heightened outcome salience to the extent to which it also impaired performance.

Our finding that social anxiety was associated with behavioural responses, but not subjective liking of the stimuli, suggests that performance may be more closely influenced by heightened effects of salience, as opposed to increased sensitivity to rewards *per se*. A performance monitoring hypothesis would predict that social anxiety would have exerted similar effects on performance had a punishment or loss condition been included, a proposal that could be examined using a modified version of the paradigm used in **Chapter 5** in future research. The fact that there were effects of social anxiety on performance of both reward tasks in **Chapter 5** suggests that alterations in reward processing in SAD may not be specific to social rewards, consistent with findings of neural altered processing of monetary rewards in adolescents with, or at risk of, SAD (Guyer et al., 2006; 2012). It is possible that the presence of an unfamiliar other may have had a greater influence on performance than the nature of the experimental reward stimuli, and therefore while the findings of **Chapter 5** do not rule out the existence of specific alterations in the processing of social rewards, in addition to domain-general ones, this question cannot be adequately addressed by the paradigm used here. Future research examining the effects of social anxiety on cognitive tasks should take into account the fact that the presence of an experimenter may have a greater effect on performance in socially anxious individuals than non-anxious participants, a hypothesis that warrants systematic investigation.

A socially relevant context may be particularly salient in adolescence (Blakemore and Mills, 2014). Consistent with this hypothesis, younger adolescents (10-14 years) and older adolescents (14-18 years) showed poorer relational reasoning performance when their performance was observed by a friend, whereas adult performance (21-34 years) was not affected by evaluative observation (Wolf et al., 2015). In contrast, when observed by an

experimenter, the older adolescent group demonstrated faster RTs. There are several potential, and not mutually exclusive, mechanisms for effects of evaluative observation on performance in both typically developing and socially anxious adolescents, and furthering our understanding of the contributions of these mechanisms in both adolescents and socially anxious individuals forms an interesting area for future research. First, the elevated fear of social evaluation seen in both adolescents (see **Section 1.5.2**) and individuals with SAD could lead to individuals spending more time mentalising how others will judge them on the basis of their performance, distracting them from the task itself and resulting in impaired performance. Second, the presence of others could increase participants' self-awareness of potential discrepancies between their current and the ideal performance (Duval & Wicklund, 1972), an effect which may be exacerbated in adolescents and socially anxious individuals. This explanation is consistent with a study which demonstrated that, with increasing age, adolescents become increasingly aware of their own performance in a perceptual judgement task (Weil et al., 2013), the 'imaginary audience' phenomenon (detailed in **Section 1.5.3**), and the performance monitoring hypothesis of SAD (Caouette & Guyer, 2014)**.** Finally, both socially anxious individuals and typically developing adolescents show heightened arousal when in a socially-evaluative context (Somerville et al., 2013), which could result in changes in performance (Zajonc, 1965). Enhanced striatal dopamine signalling, resulting from being in a state of elevated arousal, individual differences in anxiety, and/or normative developmental changes to motivational processing systems (see **Section 1.3.4**), would be expected to influence cognitive performance in line with the inverted U-shape dopamine performance curve (**Figure 1.9**).

While **Chapters 3** and **5** examined individual variation in anxiety symptoms in the general population using self-report questionnaire assessments, **Chapter 6** used a combination of psychiatric interviews and questionnaire measures in a high-risk population, a proportion of whom had clinical diagnoses of mood and anxiety disorders (see **Section 7.4.2** for further

discussion of issues of sample generalizability). Negative affective processing biases are a hallmark symptom of depressive disorder (Beck, 2008). Affective processing biases can result from both heightened 'bottom-up' reactivity to affectively salient stimuli and reduced 'top-down' cognitive control processes. These include those implicated in the resistance of distracting affective information, for example the ability to attend selectively according to current goals and disengage from irrelevant affective stimuli (Clark et al, 2009; Phillips et al, 2003). Thus, affective processing biases may reflect variation in affective processing and cognitive control systems, and their integration, all of which show pronounced development during adolescence (see **Section 1.3.3**).

Adolescence is associated with a marked increase in the prevalence of depressive symptoms and disorder (Kim-Cohen et al, 2003; Lewinsohn et al., 1998; Thapar et al., 2012), which is associated with a range of poor outcomes including deliberate self-harm, academic failure and poor mental health in adulthood. Whilst it is clear that depressive symptoms and affective biases *co-occur*, the precise role of affective biases in the *onset* of depression and the role of prior depression on later affective processing is unclear (Jacobs et al., 2008; Roiser et al., 2012). Thus, **Chapter 6** used a naturalistic longitudinal approach to examine temporal associations between affective processing biases and depression, in a sample of adolescents at high risk or depression due to parental history of depressive disorder. On two occasions, one year apart, adolescents and their families completed well-validated self-report, parent-report and clinical interview assessments of psychopathology, in addition to an inhibitory control paradigm which examines affective biases (AGN; Murphy et al., 1999). In order to examine whether affective biases are state markers associated with current experience of depression, or 'trait' markers of risk that precede depression onset or persist after remission this study assessed: 1) the association of affective bias with current depression; 2) the relationship between earlier depression and later affective bias; and 3) whether individuals with depression

at follow-up (new onset or recurrent) differed in their affective processing at baseline from those who did not.

The results of **Chapter 6** indicated an effect of current depressive disorder on affective processing, whereby currently depressed adolescents made more errors when responding to a negatively valenced target, whereas individuals without a diagnosis of psychopathology made more errors in response to positively valenced targets. This finding may indicate that sad stimuli resulted in greater bottom-up disruption to cognitive control processes in currently depressed adolescents, whereas in non-depressed adolescents happy stimuli may be more interfering, an explanation that is consistent with findings that healthy adolescents (aged 13-17 years) make more commission errors in response to positively valenced facial stimuli (Somerville et al., 2011). On the other hand, there was no influence of prior depression on later affective processing, a finding similar to a previous study comparing adolescents with remitted and current depressive disorder (Maalouf et al., 2012), which suggests that currently depressed adolescents may display mood-congruent effects on cognition.

Studies of negative affective biases in adults with remitted depression are relatively mixed (Leppänen, 2006; reviewed in Roiser et al., 2012), which may highlight the methodological benefits of studying adolescents at risk of, or in their first onset, of depression. Individuals who have previously suffered from a major depressive episode and subsequently recovered are at considerably increased risk for developing further episodes (Kendler, Neale, Kessler, Heath, & Eaves, 1993), and previous incidents of depression are proposed to have a potential 'scarring effect'. This term describes enduring neurocognitive changes resulting from a period of depression, for example elevated negative affective processing biases, which may act in a cumulative manner to increase vulnerability to relapse or recurrence (Post, 2007). It was not possible to separately examine the associations between recurrent and new onset depressive disorder, an inherent difficulty of a prospective sampling approach. Within the high risk sample

of 275 children with parents who had a history of recurrent depression that took part in the study presented in **Chapter 6**, of the 155 participants that provided data at follow-up only 14 participants had a diagnoses of depressive disorder (5 cases were new onset, 6 were recurrent, and 3 had other diagnoses at baseline). However, after controlling for baseline depressive and anxiety symptoms, adolescents with a diagnosis of depressive disorder at follow-up showed more negatively biased affective processing at baseline than those who did not have any form of clinical diagnosis at follow-up. This finding suggests that negative biases in affective processing may precede depressive symptoms, making this a potentially useful target for detection and preventative interventions (see **Section 7.6.2**).

7.4 Methodological considerations

In addition to specific limitations detailed in each of the sections above, the studies presented in this thesis are subject to a number of more general limitations, which are discussed in the following sections.

7.4.1 Age groups

One of the challenges in studying adolescent neurocognitive development related to how age is studied. Within the study of adolescent neurocognitive development there is substantial variation in age groups used to represent childhood, adolescence and adulthood, and the groups often show significant overlap (see van Duijvenvoorde et al., 2016 for a more extensive review of the heterogeneity of age groups used in studies of the development of reward processing during adolescence). In **Chapters 2**, **3**, and **4** of this thesis adolescents are defined as individuals aged 18 years and younger, and adults as those over the age of 18 years. This decision was based on the fact that this is consistent with legal definitions of adulthood (see **Section 7.6.1**), the way in which the two groups were recruited and that for the genetic studies, sample sizes were not large enough to be sufficiently powered to detect effects using a continuous analysis of age. However, it should be acknowledged that this is an arbitrary cut-

off, and that the age range of both groups is large, and there were likely developmental differences both between and within groups. Another limitation of using such arbitrary cut-offs is that it while they may be consistent with societal definitions of adulthood, they are not consistent with more recent conceptualisations of adolescence, which recommend extending the definition to include individuals aged between 10 and 24 years of age (Sawyer et al., 2018). As highlighted by the findings of **Chapter 5**, which used a continuous approach to analyse effects of age, and found that reward sensitivity showed a peak in the early twenties, it is likely that there might have been developmental changes during early adulthood, which the studies presented in **Chapters 2**, **3** and **5** were unable to examine. Similarly, in order to fully examine the nature (e.g. linear or non-linear) of developmental trajectories, studies should ideally include children, as well as adolescents and adults within the same design, enabling the comparison of adolescents to both adults and children. Another limitation of using a categorical approach is that it is unable to inform our understanding of the precise trajectories of the observed developmental effects. As outlined in **Section 7.5**, it would be of interest to compare the precise developmental trajectories of social, relative to non-social WM, in a continuous manner (**7.5.1**), and similarly to investigate the way in which different components of learning and decision-making change developmentally within the same individuals over time (**7.5.2**).

7.4.2 Sample Generalizability

With the exception of the high-risk sample studied in **Chapter 6**, a large majority of adolescent participants in the samples described in this thesis were recruited from academically selective schools. In an attempt to broadly match adult and adolescent participants in terms of educational background, socioeconomic status, and IQ, adult participants were predominantly university graduates. This recruitment strategy, combined with the inherent self-selection biases associated with relying on volunteers, and in the case of adolescents the support of their parents, almost certainly limits the extent to which findings can be applied to the general

population. Where possible, the studies presented in this thesis attempted to either match or control for differences in IQ. However, due to concerns emerging about the suitability of using performance on the matrix reasoning subscale of the WASI (Wechsler, 1999) as an age-standardised assessment of non-verbal IQ (discussed in **Section 5.2.5.3**), IQ assessments were not included in **Chapter 5**. The study presented in **Chapter 4**, was conducted before the emergence of these concerns and in this study matrix reasoning was used to match adults and adolescents on non-verbal ability. However, this approach is likely limited by the way in which scores on this subscale are standardised, and therefore there may have been differences in ability between the two age groups.

The study reported in **Chapter 5** only included female participants, in order to ensure power was not lost in a relatively small sample by needing to control for gender. Although few domains of cognition show reliable gender differences two areas that do are the processing of social information such as faces (Fuhrmann et al., 2016; Hyde, 2016; Sommer, Hildebrandt, Kunina-Habenicht, Schacht, & Wilhelm, 2013) and prevalence of mood and anxiety disorders (Steel et al., 2014). Due to the higher prevalence of SAD and symptoms in females (Caballo et al., 2013), only females were recruited. A recent study of healthy adults suggested there may be gender differences in electrocortical responses to monetary and social rewards (Distefano et al., 2018), thus findings from **Chapter 5** may only be generalizable to female samples. Future studies of social and monetary reward processing with larger samples could include gender as an additional between subjects factor.

Another reason for controlling for sex and gender differences in studies of adolescents is the existence of variation in pubertal onset between males and females (Sisk & Foster, 2004). While pubertal status and chronological age are correlated with each other, puberty onset can vary by 4-5 years in healthy individuals (Blakemore, Burnett, & Dahl, 2010), and thus using only age as an assessment of maturity fails to account for the effects of pubertal variation on

neurocognitive development (Goddings et al., 2014; Goddings, Burnett Heyes, Bird, Viner, & Blakemore, 2012). Although investigating the influence of pubertal development on cognition was beyond the scope of this thesis, it should be noted that the studies presented are unable to differentiate between effects of age and effects of puberty. There is also evidence that oestrogens down-regulate COMT activity (Gogos et al., 1998; Harrison & Tunbridge, 2008), which may be a factor contributing to sex differences in associations of *COMT* genotype with neural activity, cognition and mental health. Sex was included as a factor in **Chapters 2** and **3**, to try and control for the existence of possible sex effects on *COMT* associations. However, studies with larger sample sizes and measures of pubertal hormones would be needed to understand the possible role of sex differences in the dopaminergic system during adolescence.

While **Chapters 3** and **4** assessed relationships between cognition and self-reported anxiety symptoms in non-clinical samples, **Chapter 6** examined differences in cognition between individuals with and without a clinical diagnosis of an affective disorder in a high-risk sample. The difference between samples and assessment approaches should be taken into account when considering the generalizability of findings from these studies. For example, the fact that all participants in **Chapter 6** were at familial risk of developing depression due to recurrent parental unipolar depression, may limit the generalizability of findings to other samples. This factor may also have led to smaller effect sizes since all participants were at increased risk of developing depression compared to the general population. The use of self-report assessments of individual variation in mood and anxiety symptoms within the general population can be advantageous, as these methods are less costly than clinical assessments and recruitment is not limited to individuals within a clinical setting making it easier to recruit adequately powered samples. Indeed, the issue of sample size is particularly relevant when assessing associations between genetic variants and cognition (as in **Chapters 2** and **3**), due to the relatively small size of such effects (Barnett et al., 2008; Dickinson & Elvevåg, 2009;

Montag et al., 2012; Witte & Flöel, 2012). Affective disorders can be considered from a continuous perspective, whereby behaviour varies across a continuum ranging from healthy to psychopathogical, and it is likely that individuals with higher anxious traits are more vulnerable to developing anxiety disorders. However, there is also evidence that young people with clinical anxiety (Monk et al., 2006) show differential neural responses to socio-affective stimuli than those observed in young people with elevated, non-clinical trait anxiety (Telzer et al., 2008). Categorical comparisons of individuals with and without clinical diagnoses undoubtedly have greater clinical application and generalizability than continuous assessments of individual differences mood or anxiety. However, the use of discrete diagnostic categorisations, with arbitrary and evolving cut-offs, may also be limited in the extent to which they can be used to inform understanding of different aspects of heterogenous disorders, such as how they change during development or are associated with cognition and behaviour. For example, **Chapter 5** demonstrated that different domains of social anxiety symptoms had opposing influences on task performance suggesting that there may be some utility in examining associations between specific symptoms of social anxiety and behaviour.

7.5 Future directions

Several directions in which further research is warranted have been proposed throughout the discussion of the studies in this thesis presented in **Sections 7.1** to **7.4**. Here, two of these directions are described in further detail.

7.5.1 Neurodevelopmental changes in social WM

The ability to keep up to date with information of a social cognitive nature, for example peoples behavioural traits or internal states, is a fundamental aspect of successfully navigating our social environment. Thus, the behavioural findings of **Chapter 2** give rise to several pertinent questions for future research. Studies of perspective-taking, another aspect of cognition involving the effortful processing of social information, indicate that the ability to

use another's perspective to guide decisions continues to develop in late adolescence (17 years and older), over and above developmental improvements in domain-general cognitive control processes (see **Section 1.4.3.2**). As discussed in the previous section, a limitation of the findings presented in **Chapter 2** was that age was assessed categorically. However, it would be of interest to compare the precise developmental trajectories of social, relative to non-social WM, in a continuous manner, in order to examine whether the ability to maintain and manipulate social information shows a more protracted developmental trajectory than non-social information.

Neuroimaging studies of the development of other types of effortful social processing, such as perspective-taking (**Sections 1.4.3.2**), social decision-making (**1.4.3.3**), and the relational integration of social information (Magis-Weinberg et al. 2017) suggest that social and non-social higher cognitive brain systems are recruited in parallel, with developmental improvements in performance proposed to reflect both parallel developmental changes within these systems and their improved integration. As discussed in **Section 7.1**, the behavioural findings of **Chapter 2** were consistent with neuroimaging findings suggesting that in adults the effortful processing of social information is supported by both the social brain network and traditional WM networks (Meyer et al. 2012; 2015). Therefore it would be of interest to investigate whether there are also developmental changes in the relative contributions of social and non-social higher cognitive systems during social WM processing, and, if so, how this relates to behavioural improvements in this complex social cognitive ability.

7.5.2 Computational modelling of individual differences

From a methodological perspective, the study presented in **Chapter 4** demonstrates the utility of using computational approaches to increase our understanding of developmental changes in the different component processes involved in learning and value-based decision-making

during adolescence (O'Doherty, Hampton, & Kim, 2007; Wang & Krystal, 2014). Few studies have used computational models to interpret adolescent behaviour (Cohen et al., 2010; Javadi et al., 2014; van den Bos, Cohen, et al., 2012), and fewer still have implemented model comparison techniques (Christakou et al., 2013; van den Bos et al., 2009). Taking a 'mechanistic' rather than a 'heuristic' approach to the study of human cognition, in which individual choices and outcomes are considered within the framework of computational models, enables an increasingly nuanced assessment of the mechanisms underlying learning and decision-making behaviours (van den Bos & Eppinger, 2015), and how these may vary both within and between individuals. Learning and decision-making do not rely on a unitary system, but instead require the coordination of different cognitive processes that might show different rates of maturation, a suggestion supported by the findings of **Chapter 4.** Investigating the precise developmental trajectories of the components of motivational processing during adolescence may therefore inform and refine existing models of mature learning and decision-making, as the processes are likely to be less integrated in adolescence, making it easier to disentangle the effects of different components from one another.

Like many studies of adolescent development, the study described in **Chapter 4** aimed to characterise differences between adult and adolescent decision-making at the level of group averages. However, as discussed in **Section 1.6**, adolescence varies greatly between individuals. At the normative level, the computational and behavioural findings were consistent with the dual systems hypothesis of adolescent neurocognitive development (see **Section 1.3.1**). However, a key area of future research will be to use computational methods to investigate: 1) how different components of learning and decision-making change developmentally within the same individuals over time; and 2) how individual variation in learning and decision-making is associated with dopaminergic genetic variation, affective reactivity and mental health outcomes, or the maturational trajectories of brain regions implicated in motivational-processing.

The emerging field of developmental computational psychiatry offers a promising approach to advancing our knowledge of how changes at the brain level, such as the development and integration of neural systems, or maturational changes in the dopamine system map onto cognition and behaviour. In characterising developmental changes in the mechanisms underlying learning and motivation, it may then be possible to investigating how motivational processing differs in individuals with mental illness, and at what stage in development these differences emerge (Hauser, Will, Dubois, & Dolan, 2018). The ability to model the different component processes of learning and decision-making on an individual level may be particularly useful in furthering our understanding of cognitive and neural mechanisms that may contribute to the increased risk of social anxiety symptoms and SAD in adolescence. It has been proposed that the striatum, a region of the brain implicated in both motivation and avoidance, and critical for RL, may be implicated in social anxiety (Helfinstein, Fox, & Pine, 2012; Lago, Davis, Grillon, & Ernst, 2017). For example, Helfinstein et al. (2012) hypothesised that heightened striatal activity in socially anxious individuals may manifest as a heightened ability to learn from negative information, resulting in individuals learning rapidly to avoid situations or people associated with negative outcomes even after relatively minimal exposure. This theory is consistent with the fact that negative prediction error signals are heightened in healthy individuals under stressful conditions (O. J. Robinson, Overstreet, Charney, Vytal, & Grillon, 2013), a factor which may perpetuate a heightened sensitivity to negative outcomes, since socially anxious individuals are more likely to be in a state of stress, even in relatively non-aversive situations (Richards et al., 2015). There is also evidence suggesting that adolescents may show enhanced learning from negative prediction errors relative to adults (Hauser et al., 2015; Van den Bos et al., 2012), which could represent a mechanism through which adolescents show heightened reactivity to negative feedback.

Computational paradigms can be used to model the way in which participants process and learn from different types of feedback, including both monetary gains and losses (**Chapter 4**) and social approval and disapproval (Will, Rutledge, Moutoussis, & Dolan, 2017). They can also provide insights into how decision-making and learning are influenced by feedback valence, outcome uncertainty, and biases in information processing. A recent study demonstrated that healthy adults display valence-induced learning biases when learning from both factual and counterfactual information (Palminteri, Lefebvre, Kilford, & Blakemore, 2017), whereby participants learned preferentially from positive, relative to negative, prediction errors regarding their chosen outcomes. In contrast, for counterfactual learning, the opposite valence induced bias was found: negative prediction errors were preferentially taken into account, relative to positive ones, suggesting that adults tend to preferentially take into account information that confirms their current choice in the context of both factual and counterfactual learning. One potential explanation for the existence of such choice-supportive biases, which result in individuals tending to ascribe success to their own abilities and efforts, but relatively tending to neglect their own failures, is that they may help promote self-esteem and confidence. Such information processing biases are in stark contrast to those that characterise SAD (reviewed in Haller, Cohen Kadosh, Scerif, & Lau, 2015), and thus it would be of interest to examine whether similar confirmation biases exist during adolescence, and whether they are moderated by social anxiety.

7.6 Wider implications

Successful transition into an independent adult role requires the refinement and integration of a range of higher-level cognitive processes. The work in this thesis highlights the fact that these processes show development throughout adolescence. Variation in these processes and their integration, as a result of developmental changes and individual difference factors, may impact upon an individual's behavior, decision-making and mental health, which could have

wider implications for health and the legal systems.

7.6.1 Legal implications

From a legal perspective, laws determining an individual's rights and responsibilities often rely on categorical definitions of age, typically derived from historical precedents specific to the right or responsibility in question, that have arisen within a specific society. Viewed from a developmental neurocognitive perspective the arbitrary nature of these age cut-offs can be difficult to reconcile with existing laws affecting adolescents, such as the discrepancy between the age of criminal responsibility (10 years the UK) relative to the legal age at which one can drive (17 years in the UK), consume alcohol, serve on a jury or vote (all 18 years in the UK). Indeed, in the USA, findings from the field of adolescent neuroscience have been used to challenge sentences of death or life imprisonment in individuals under 18 years of age (Steinberg, 2013).

The findings of the studies in this thesis, considered within the context of existing studies of adolescent neurocognitive development, might have implications for the legal treatment of adolescents. The majority of legal systems emphasise the ability to think about and understand the potential consequence of one's actions, and this is often used as an indication of the liability of an individual. However, such thought processes are highly complex and rely on the maturation and integration of a range of cognitive processes that facilitate the ability to reason abstractly about alternative outcomes and their consequences. In addition to mentalising and the ability to experience counterfactually-mediated emotions (Burnett et al., 2010), processes which show continued development during adolescence (see **1.4.3.1**), the ability to generate alternative outcomes and use this information to guide behaviour also relies on counterfactual reasoning (see Baird & Fugelsang, 2004) and self-generated information processing. The findings of **Chapters 4** and **3** highlight the fact that both of these processes show significant changes between adolescence and adulthood. Furthermore, the majority of Western legal

systems take a highly punitive stance on young offenders (reviewed in Muncie, 2008). Based on the findings of **Chapter 4** that, relative to adults, adolescents were less able to use counterfactual information and punishing outcomes to guide behaviour, current legal definitions of criminal responsibility and approaches to sentencing and behavioural reform appear to overlook developmental changes in processes directly relevant to assessments of criminal responsibility and the assignment of appropriate sentences.

7.6.2 Health Implications

As discussed in **Chapter 1**, rates of accidents, unsafe sexual behaviour and substance abuse show a marked increase during adolescence (Patton & Viner, 2007; Viner et al., 2011; Willoughby et al., 2013). Increasing our understanding of adolescent reward processing and decision-making may therefore have implications for understanding how best to reduce the incidence of behaviours that have potentially adverse health consequences. The findings of **Chapter 4** suggest that the ability to use information about alternative outcomes to guide decisions, and to consider neutral outcomes within the context of potential negative outcomes is still developing in adolescence. Thus, interventions designed to reduce adverse health behaviours (e.g. unsafe sex, substance abuse or risky driving) are likely to have limited success if they are solely based on educating adolescents about the potential for negative outcomes of their choices. In contrast, interventions which provide adolescents with alternative, rewarding options that are less likely have harmful consequences (e.g., socially rewarding activities such as sports, volunteering, and hobbies) may be particularly effective.

Even brief and relatively mild mental illness can cause significant disruptions to a young person's development, and is often associated with impairments in social functioning, educational attainment, substance misuse and negative outcomes in adulthood (Gibb, Fergusson, & Horwood, 2010). Thus, an increased focus on adolescence, a developmental

period characterized by both elevated risk but also a potentially enhanced ability to benefit from interventions, has the potential to greatly impact upon health, productivity and social outcomes in society (reviewed in detail in McGorry, Goldstone, Parker, Rickwood, & Hickie, 2014). Instead, the UK mental health system is arguably weakest at this point, in part due to the fact that it is structured around legal categorizations of adulthood. There are substantial differences between child and adolescent, and adult mental health services, such as treatment approaches and the extent to which mental health is considered from a developmental perspective, in which mental illness is more likely to be characterized by co-morbidity and changing patterns of symptoms (McGorry et al., 2014). However, many adolescents requiring continuation of mental health care after reaching 18 years do not successfully transition to adult mental health services. This may be particularly detrimental at a period in life at which the individual is still developing and often making important developmental transitions such as leaving home, or going to university.

The majority of mental illnesses have their onset in before the age of 24 years (Kessler et al., 2007; **Figure 1.10**), Many of the processes, and their associated neural systems, that undergo pronounced development during adolescence (reviewed in **Chapter 1**) are implicated in mental illnesses, for example, motivational processing and learning (Maia & Frank, 2011; see **Section 1.6.2.2**), compromised cognitive control (Luna & Sweeney, 2004; Sweeney et al., 2004) and difficulty regulating affective responses (**Section 1.6.2.1**). Therefore, increasing our understanding of developmental changes in these processes, and how they vary between individuals over time may thus provide insight into why adolescence is a period of elevated mental health vulnerability, who may be most at risk, and how best to design interventions (Kadosh, Linden, & Lau, 2013). A better understanding of individual differences in the developmental trajectories of emotional regulation processes, and their associated neural systems, could be useful for determining when such interventions may be most effective.

7.7 Concluding remarks

Adolescence is a period of life during which social cognition, motivational-affective processing, cognitive control, and the neural systems supporting these processes, become increasingly refined and integrated. This thesis uses a combination of genetic, cognitive and computational research techniques, in both healthy and clinical populations to investigate how interactions between these cognitive processes change over development, and how this is influenced by individual differences in affective reactivity and genetics. The studies in this thesis demonstrate that effects of genetic variation on social cognition, affective processing, executive functions and their integration are best understood from a developmental perspective (**Chapters 2** and **3**). Furthermore, taking the effects of genetic dopaminergic variation on cognition into account can increase our understanding of developmental changes occurring to these processes, and the neural systems that support them. **Chapters 4** and **5** of this thesis provide evidence of developmental changes in the processing of both monetary and social rewards, at the level of hedonic reward value, motivational salience, reward and punishment learning, and the use of counterfactual information to guide decision-making. These findings underline the complexity of motivational processing and the neural systems that facilitate it, and highlight the utility of computational modelling methods for the future study of developmental changes in the different components implicated in learning and decision-making, and how individual differences in these processes and their integration may contribute to the development of affective disorders. **Chapters 2**, **3**, **5**, and **6** indicate the importance of taking individual differences in affective reactivity or genetic variation into account when investigating the development and integration of social cognitive, motivational-affective, and cognitive control systems during in adolescence. Increasing our understanding of the way in which these systems and their interactions vary both between individuals and across development has the potential to increase our understanding of both normative

changes in adolescent neurocognitive development, and how variation in these systems may be associated with the development of affective disorders.

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APPENDICES

A1. Supplementary Model Simulation (1): Different learning rates for positive and negative prediction errors

In principle, differences in performance between reward seeking and punishment avoidance domains could arise from the presence of different learning rates for positive prediction errors (frequently associated with rewards: α+) and negative prediction errors (frequently associated with punishments: α-; Niv, Edlund, Dayan, O'Doherty & O'Doherty, 2012). Thus, it could be argued that asymmetrical performance in reward seeking and punishment avoidance learning conditions, as predicted by Model 1 (reward > punishment learning), results from differential learning rates, whereby the negative learning rate is higher than the positive learning rate.

However, in the task used in **Chapter 4**, in which the outcomes are probabilistic and the Reward and Punishment contexts are separated (i.e. a reward, +1 point, never occurs in the Punishment context and a punishment, -1 point, never occurs in the reward context), positive and negative prediction errors can occur in both the reward and punishment contexts. Instead, symmetrical performance in the reward seeking and punishment avoidance learning conditions (as predicted by Model 3) depends on the ability to contextualise outcome values (as a function of the difference between the experienced outcome and the context value; an approximation of the average value of the two options), whereby in a negative value context, an intrinsically neutral outcome (0 points) can acquire a positive value and reinforce selection of the options that lead to successful avoidance of punishment. In the absence of value contextualisation, whereas the optimal outcome in the Reward contexts, 1 point results in a positive prediction error, the optimal outcome in the Punishment contexts, 0 points remains intrinsically neutral in value and consequently the participant will perform less optimally in

punishment contexts, independently of whether learning rates differ between positive and negative prediction errors.

To demonstrate this, additional simulations were run for a model with higher learning rates for positive compared to negative prediction errors ($\alpha+ = 2 * \alpha-$), another with higher learning rates for negative compared to positive prediction errors ($\alpha- = 2 * \alpha+$) and compared the simulated variables with those from a model with symmetrical learning rates (our Model 1: $\alpha+ = \alpha-$; **Figure A.1**). Learning parameters ranges comparable to those observed in previous studies were used for these simulations. (Lefebvre, Lebreton, Meyniel, Bourgeois-Gironde & Palminteri, 2017). Model simulations showed that (at least in the range of parameters tested) the model with ($\alpha- > \alpha+$) is still not capable of explaining symmetrical performance in the reward and punishment domain. Furthermore, neither model is structurally capable of explaining option value inversion (as observed in the post-learning test).

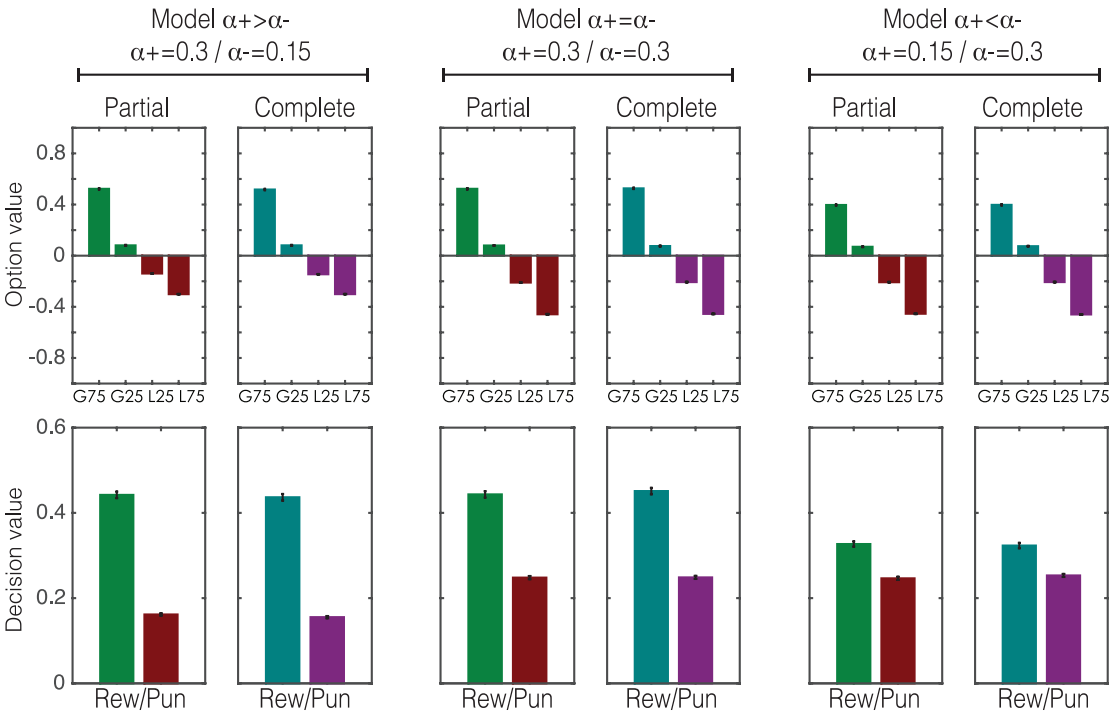

Figure A.1. Model simulation involving different learning rates for positive and negative prediction errors. The value of the β was 5.0 as in the other ex-ante model simulations. The number of virtual participants was N = 1000.

A.2. Supplementary model comparison: Value contextualisation without counterfactual learning

The model space did not include a model in which standard Q-learning (Model 1) was augmented with value contextualisation ($\alpha_3 > 0$) but not counterfactual learning $\alpha_2 = 0$), the rationale for which is detailed in **Section 4.2.4**). However, for the sake of completeness, an additional model comparison analysis including such a model was run (Model 4; value contextualisation without counterfactual learning). The addition of this model to the model space did not affect the main results and conclusions: adolescent behaviour was still best explained by Model 1 (Model 1: PP = .49 ± .04; XP = .6; Model 4: PP = .08 ± .02; XP = 0) and adult behaviour was best explained by Model 3 (Model 3: PP = .49 ± .04; XP = .6; Model 4 PP = .08 ± .02; XP = 0; **Table A.1**).

Table A.1. Supplementary model comparison.

	Model 1 (2 *df*)		**Model 2 (3 *df*)**		**Model 3 (4 *df*)**		**Model 4 (3 *df*)**	
	PP	**XP**	**PP**	**XP**	**PP**	**XP**	**PP**	**XP**
Adolescents	.43 ± .05	.73	.19 ± .03	.07	.12 ± .02	0.03	.26 ± .05	.17
Adults	.03 ± .01	.00	.39 ± .04	.31	.49 ± .04	0.69	.08 ± .02	.00

Note: Model 1: $\alpha_2 = \alpha_3 = 0$; Model 2: $\alpha_3 = 0$; Model 4: $\alpha_2 = 0$. PPs are reported as *M* ± *SE*. *df,* degrees of freedom.

A.3. Supplementary model simulations (2): Validation of the model comparison procedure

Bayesian model comparison methods are highly debated in cognitive neuroscience (Pitt & Myung, 2002; Corrado, Sugrue, Brown & Newsome, 2009). Different model comparison criteria have been proposed, which approximate model evidence while representing a trade-off between model accuracy and complexity. Critically, based on the same data, different criteria might provide different answers, since sample size, number of observation, the size of the effect to be detected and the presence of outliers differentially affects model comparison

results (Stephan, Penny, Daunizeau, Moran & Friston, 2009). A priori model simulations can be used to assess the adequacy of model comparison criterion for a given dataset a priori. A model comparison criterion can be considered 'adequate' when 1) it correctly rejects a more complex model, when the true generative model is the simpler one (i.e. it avoids 'overfitting') and 2) it correctly rejects a simpler model, when the true generative model is a more complex one (i.e. it avoids 'underfitting'). We applied these principles to the study presented in **Chapter 4**, by testing the adequacy of the frequently used BIC and the more recently introduced LPP, from which model PP and XP can be computed (see **Section 4.2.5**; Daunizeau et al., 2014).

Data were simulated from two groups of virtual participants (N = 200; **Figure A4.2**). Group 1 implemented Model 1 (standard Q-learning, with only two free-parameters ($\boldsymbol{\beta}$, α_1), whereas Group 2 implemented Model 3 (the more sophisticated model: standard Q-learning with two additional free-parameters accounting for counterfactual learning (α_2) and value contextualisation (α_3)). The parameter values in both groups were similar to those used in the model simulations presented in the main text (**Section 4.2.6: Model simulations**). Both groups of participants performed the learning task and produced very different behavioural results: Group 1 displayed preferential reward seeking compared to punishment avoidance learning and no performance enhancement in presence of counterfactual information, as expected from Model 1-estimates of behaviour (see **Figure A.2B**); Group 2 displayed similar learning from rewards and punishments and a performance enhancement in presence of counterfactual information, as expected from a Model 3-estimates of behaviour. For each virtual participant, model parameters were optimised by minimising the negative log-likelihood of the data, to calculate the BIC, and minimising the LPP, to calculate the PP. The BIC criterion correctly rejected Model 3 in Group 1, however failed to identify Model 3 as the correct model in Group 2 (Model 2 was selected as the best fitting model). In contrast, the LPP-based PP criterion correctly rejected Model 3 in Group 1 and correctly selected Model 3 in Group 2 (**Figure A.2B**). These results clearly indicate that for the task design and model space

employed in **Chapter 4** the LPP-based calculation of the PP is an 'adequate' model comparison criterion, while the BIC is not.

This result differs to a previous study in adults (Palminteri et al., 2015), in which both the BIC and LPP analyses detected Model 3 as the wining model. This may be due to several reasons. **Chapter 4** used a modified version of the task used in the previous study, with a reduced number of trials and sessions (due to practical constraints of working with developmental populations), resulting in a smaller and potentially noisier dataset. Furthermore, while Model 2 and 3 produce crucial differences in behavioural patterns, the likelihood gain when moving from Model 2 to Model 3 is smaller than that between Model 1 to Model 2 (shown in **Table A.2**; see also **Figure 4.2**, **Tables 4.2** and **4.3**).

Table A.2 Log-likelihood differences.

	M1 vs. M0	M2 vs. M1	M3 vs. M2
Subject-Level			
Adolescents	362.0	88.9	2.8
Adults	487.5	225.8	38.6
% Adolescents/Adults	82.5%	43.7%	8.0%
Group-Level			
Adolescents	150.4	0	0
Adults	293.7	130.0	2.4
% Adolescents/Adults	56.9%	0%	0%

Note: For each pair of models the log likelihood difference multiplied by 2 was calculated, which is a log-scale analogue of the likelihood ratio. M1-M3: Models 1-3; M0: Random model; Subject-level: Parameter optimisation assumed a set of free parameters per subject; Group-level: Parameter optimisation assume a single set of free parameters per age group; % Adolescents/Adults: percentage of likelihood difference improvement observed in the adolescent group compared to the adults (accounting for the different number of subjects).

It was therefore conclude that the LPP-based criterion is the most appropriate model selection criteria for this dataset and model set and is capable of providing reliable results that are in

line with the quantitative and qualitative behavioural differences observed in both the simulated and previous data (Palminteri et al., 2015).

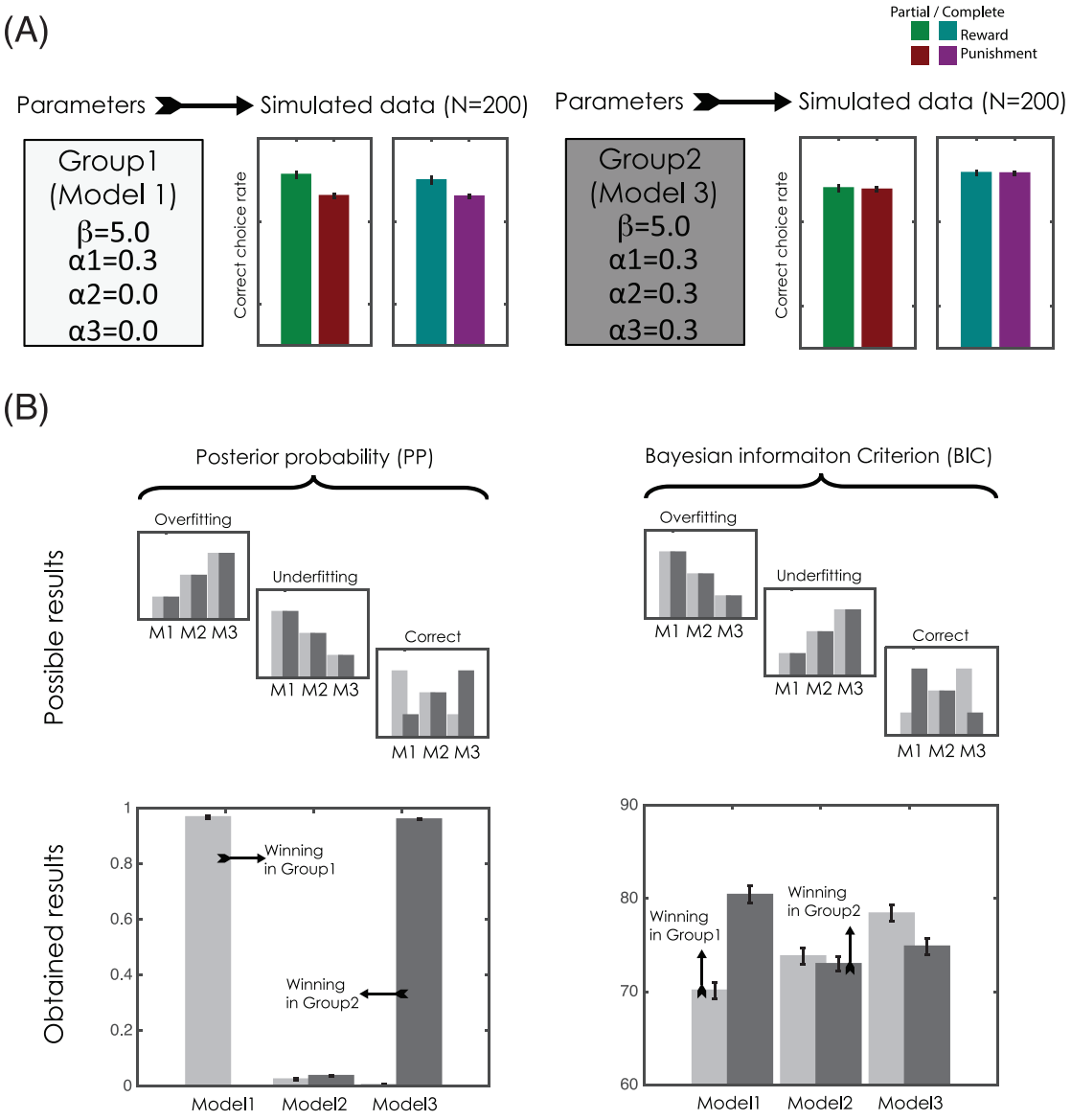

Figure A.2. Validation of the model comparison procedure. (A) Virtual groups' parameters and simulated data, plotted as a function of task context. **(B)** Possible and obtained model comparison results for Group 1 (light grey) and Group 2 (dark grey): better fit is indicated by a higher PP and lower BIC, respectively

A.4. Social Reward Questionnaires

Social Reward Questionnaire for Adolescents (SRQ-A; Foulkes et al., 2017)

Instructions: Here is a list of statements about what you enjoy when you spend time with other people. The statements refer to all people in your life, e.g. friends, classmates or people you have just met. Decide how well each statement relates to you, then put a TICK in the box that you have chosen. NOTE: If there is something you have never experienced, imagine how much you *would* enjoy it. Please try to answer all questions.

	Strongly disagree	Disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Agree	Strongly agree
1. I enjoy being around people who think I am an important, exciting person							
2. I enjoy treating others fairly							
3. I enjoy making someone angry							
4. I enjoy going to parties							
5. I enjoy being nice to someone only if I gain something out of it							
6. I enjoy feeling emotionally close to someone							
7. I enjoy it if others look up to me							
8. I enjoy tricking someone out of something							
9. I enjoy being a member of a group/club							
10. I enjoy being around people who are impressed with who I am and what I do							
11. I enjoy letting someone else tell me what to do							
12. I enjoy embarrassing others							
13. I enjoy many people wanting to invite me to their social events							
14. I enjoy keeping promises I make to others							
15. I enjoy seeing others get hurt							
16. I enjoy getting praise from others							
17. I enjoy it if someone accepts me as I am, no matter what							
18. I enjoy someone else making decisions for me							
19. I enjoy making someone feel happy							
20. I enjoy following someone else's rules							

Social Reward Questionnaire (SRQ; Foulkes et al., 2014)

Instructions: Here is a list of statements about what you enjoy when you interact with other people. The statements refer to all people in your life, e.g. friends, partners, family, colleagues or people you have just met. Consider how well each statement relates to you and indicate your answer with a tick. NOTE: If there is something you have never experienced, imagine how much you *would* enjoy it.

	Strongly disagree	Disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Agree	Strongly agree
1. I enjoy being around people who think I am an important, exciting person							
2. I enjoy treating others fairly							
3. I enjoy making someone angry							
4. I enjoy going to parties							
5. I enjoy being nice to someone only if I gain something out of it							
6. I enjoy feeling emotionally connected to someone							
7. I enjoy it if others look up to me							
8. I enjoy tricking someone out of something							
9. I enjoy having erotic relationships							
10. I enjoy being a member of a group/club							
11. I enjoy being around people who are impressed with who I am and what I do							
12. I enjoy letting someone else tell me what to do							
13. I enjoy having many sexual experiences							
14. I enjoy embarrassing others							
15. I enjoy many people wanting to invite me to their social events							
16. I enjoy keeping promises I make to others							
17. I enjoy seeing others get hurt							
18. I enjoy achieving recognition from others							
19. I enjoy it if someone accepts me as I am, no matter what							
20. I enjoy having an active sex life							
21. I enjoy someone else making decisions for me							
22. I enjoy making someone feel happy							
23. I enjoy following someone else's rules							

Scoring

On both the SRQ and SRQ-A items are scored from 1 (Strongly disagree) to 7 (Strongly agree). The mean score is then calculated for each subscale (see below). Total mean score is not calculated. Data from the Sexual Relationships subscale of the adult version was not analysed.

SRQ A:

Admiration: Q1, Q7, Q10, Q16 Negative Social Potency: Q3, Q5, Q8, Q12, Q15 Passivity: Q11, Q18, Q20 Prosocial Interactions: Q2, Q6, Q14, Q17, Q19 Sociability: Q4, Q9, Q13

SRQ:

Admiration: Q1, Q7, Q11, Q18 Negative Social Potency: Q3, Q5, Q8, Q14, Q17 Passivity: Q12, Q21, Q23 Prosocial Interactions: Q2, Q6, Q16, Q19, Q22 Sexual Relationships: Q9, Q13, Q20 Sociability: Q4, Q10, Q15