COGNITIVE CONTROL DEVELOPMENT IN ADOLESCENCE

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DECLARATION

I, Lucía Inés Magis Weinberg, 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.

Lucía Magis Weinberg
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Publications

Information presented in Chapters 2 and 3 is being written up for publication in collaboration with my supervisors.

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ABSTRACT

Adolescence is a transitional period in which an increasing ability to coordinate basic cognitive control abilities is also particularly challenged by contextual factors in the environment. The aim of this dissertation was to examine the development of complex cognitive control in adolescence in relation to different socio-affective contexts at the behavioural and neural level. The dissertation presents three functional magnetic resonance imaging (fMRI) experiments. The first studies explored transient and sustained aspects of cognitive control, and how the context influences behaviour and brain activation during cognitive control tasks. Study 1 used a prospective memory task where the cues were more or less salient, affecting the need to proactively monitor the stimuli vs. react to more distinctive cues. Study 2 used a working memory task and manipulated the reward context, on a trial-by-trial or run-by-run basis. Study 3 used a relational reasoning task to investigate manipulation and integration of information and its sensitivity to the nature of this information, in particular whether making judgements in the social domain elicited specific brain activations compared to the non-social domain. All three studies were run in adolescent and adult participants, to allow the study of developmental changes in complex cognitive control at the behavioural and brain level.

Study 1 found behavioural evidence for development of prospective memory in adolescence and neuroimaging evidence for sustained and transient activation of the frontoparietal network associated with monitoring costs for cue detection whilst being engaged in a different task. Study 2 found that in the context of sporadic rewards, both adolescents and adults combine a proactive and a reactive strategy to maximise performance. Reward had both sustained and transient effects on frontoparietal regions as well as subcortical regions involved in reward processing. Study 3 showed parallel recruitment of the social brain and the relational reasoning network during the relational integration of social information in adolescence and adulthood. Across the three studies, there was evidence for behavioural improvement with age, but no strong differences of haemodynamic brain changes between adolescence and adulthood.

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Abbreviations

AAL	Automated anatomical labelling
AIns	Anterior insula
ANOVA	Analysis of variance
BA	Brodmann area
BOLD	Blood oxygen level dependent
DA	Dopamine
dACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
DMC	Dual mechanisms of control
DTI	Diffusion tensor imaging
EEG	Electroencephalography
ERP	Event related potentials
EVC	Expected value of control
FA	Fractional anisotropy
FD	Framewise displacement
FIR	Finite impulse response
fMRI	Functional magnetic resonance imaging
FWHM	Full width at half maximum
GLM	General linear model
HRF	Hemodynamic response function
ICBM	International Consortium for Brain Mapping
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
ITI	Inter-trial interval
LPFC	Lateral prefrontal cortex
LTM	Long term working memory
MD	Mean diffusivity
MNI	Montreal Neurological Institute
MPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
NAcc	Nucleus accumbens
OFC	Orbitofrontal cortex
OT	Ongoing task trials
PFC	Prefrontal cortex
PM	Prospective memory
PPC	Posterior parietal cortex
Pre-SMA	Pre-supplementary motor area
pSTS	Posterior superior temporal sulcus
RLPFC	Rostrolateral prefrontal cortex
RMS	Root mean square
ROI	Region of interest
RPFC	Rostral prefrontal cortex
RPM	Raven's progressive matrices
RS	Reward sensitivity
RT	Reaction time
SD	Standard deviation
SE	Standard error
SPM	Statistical parametric mapping
SPSS	Statistical Package for the Social Sciences
SWM	Short-term working memory
TE	Echo time

TPJ	Temporo parietal junction
TR	Repetition time
VLPFC	Ventrolateral prefrontal cortex
VMPFC	Ventromedial prefrontal cortex
VS	Ventral striatum
WASI	Wechsler Abbreviated Scale of Intelligence
WHO	World Health Organisation

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1 INTRODUCTION

Adolescence is a transitional period that follows childhood and is a preparation for adulthood. Individuals are expected to develop independence and maturity in terms of social roles and goals. Adolescence is characterised by marked physical changes in body mass and size, and the sexual maturation triggered by the rise in sexual hormone levels associated with puberty. These physical changes prepare the individual for reproduction, which requires the formation of relationships outside the primary family group and rapid adjustment to changing social environments. As a result, there are important psychological changes in cognition and affect, particularly in sensitivity to the social environment, with distancing from adults and children by prioritising peer interactions (Ernst, Pine, & Hardin, 2006). It is through these events that adolescents move toward social and economic independence, develop a sense of self and identity, and the cognitive skills for adult roles. While the start of adolescence is biologically defined as puberty, which usually occurs between 10 and 12 years of age (1.5 years earlier for girls, on average), the end of adolescence is informed by cultural factors and defined in terms of attainment of mature social goals, which varies largely and occurs between the ages of 20 and 25 years old (Crone & Dahl, 2012). Adolescence is not only an important plastic period for enhanced learning and growth, but also a period of vulnerability for impulsivity and risk taking behaviour, in which the socio-affective context exerts a powerful influence (Patton et al., 2016).

Adolescence is a period of immature incentive processing coupled with limited cognitive control, as components of executive function continue to develop. Specific patterns of behaviour emerge in adolescence in the form of risk-taking, novelty and reward seeking, and impulsivity (Ernst et al., 2006). These adaptive behaviours are a key aspect in the establishment of adolescents' identity and navigation of a quickly changing and increasingly complex social environment (Blakemore & Mills, 2014). However, they are also the principal source of morbidity and mortality in this age group (Gardner & Steinberg, 2005). These behavioural patterns have been explained in terms of differential developmental trajectories of different brain networks. Extensive structural and functional brain development continues throughout adolescence (Blakemore & Mills, 2014), with gradual decreases in cortical grey matter volume and increases in white matter volume and density (Mills et al., 2016). Structural changes are thought to reflect ongoing myelination of long-range axonal pathways and intra-cortical connections and continued synaptic pruning in specific neural systems (Mills et al., 2016; Mills & Tamnes, 2014).

There is evidence that the brain regions involved in socioemotional incentive and reward processing mature before brain regions necessary for cognitive control, which undergo protracted development, and reach adult levels by the third decade of life (Casey, 2014; Mills, Goddings, Clasen, Giedd, & Blakemore, 2014; Steinberg et al., 2017; Vazsonyi & Ksinan, 2017). Maturation imbalance theories posit that this asynchrony makes adolescents overly influenced by features of their social environment without the suitable regulation of an immature control circuitry (Casey et al., 2010; Steinberg, 2008; van Duijvenvoorde, Peters, Braams, & Crone, 2016). A different view by Crone and Dahl (2012) does not support a simple model of frontal cortical immaturity but conceptualises adolescence as a period of increased flexibility in the interaction between motivation and cognition, framed by differences in socio-affective processing (Crone & Dahl, 2012).

The aim of this PhD was to explore development between adolescence and adulthood of different complex cognitive control abilities in varying contexts, with a focus on the neural underpinnings of these interactions. In this introductory chapter, I *firs*t provide an overview of structural brain changes in adolescence, discussing how disparities in maturational rates have informed neurocognitive models of adolescent behaviour. I relate this with more general contextual differences of cold and hot cognition. *Second*, I review some models of cognitive control that have been particularly influential for the presented studies. Here, I describe development of basic and complex executive functions involved in cognitive control, highlighting the role different frontoparietal regions play. *Third*, I review behavioural changes in motivation during adolescence in the form of reward sensitivity and social information processing, and relate these findings to developmental differences in reward-processing regions. *Finally*, I focus on the interaction between these two spheres, cognitive control and motivation, highlighting adolescence as a key transitional period of increased influence of the socio-affective context on cognitive control.

1.1 STRUCTURAL BRAIN CHANGES DURING ADOLESCENCE

Human brain anatomy changes significantly during the first decades of life, involving dynamic changes in grey and white matter. Grey matter is made up by neurons (bodies, dendrites and axons), glial cells, capillaries and extracellular space, and is high in water content, while white matter is higher in fat content and made up by myelinated axons, glial cells, and extracellular space. Magnetic resonance imaging (MRI) can pick apart different signals arising from these differences in water and fat content, allowing the investigation of changes in grey and white matter during development (Houston, Herting, & Sowell, 2014). Macroscopic developmental changes observed with imaging studies (with a current resolution of approximately 1 mm^3) are thought to reflect synaptic pruning, myelination, and glial cell proliferation, which have been identified in developmental histological post-mortem studies (Mills & Tamnes, 2014). Different, but related, indices of brain anatomy may be quantified using structural MRI: *grey matter volume, cortical thickness*, and *surface area*, *white matter volume,* and *white matter tracts,* and each has a particular developmental trajectory (Mills & Tamnes, 2014). Structural MRI has revealed that adolescence is a period of continuous change of brain structure in which there is greater specialisation and strengthening of connectivity between brain regions.

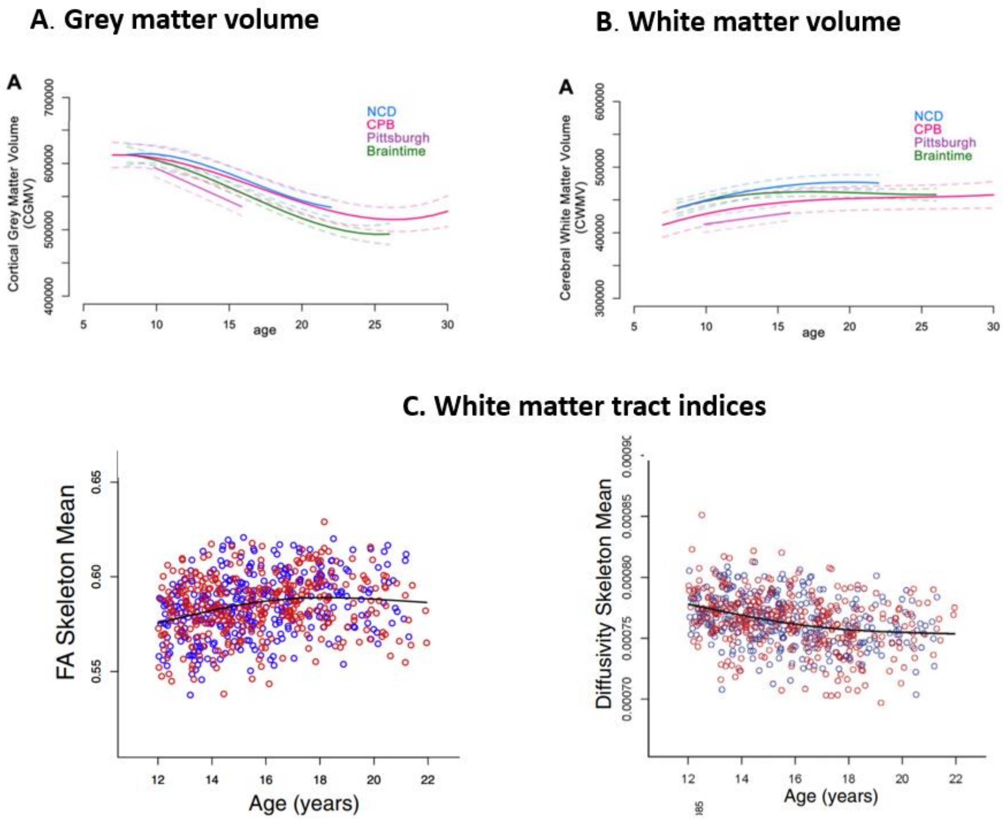


Figure 1.1. *Developmental trajectories of grey and white matter changes in adolescence*. Cortical grey matter volume in mm^3 (A) and cortical white matter volume in mm^3 (B) plotted against age in an accelerated longitudinal sample across 4 sites (pooled age range: 7 – 29.9 years). Different colours indicate different sites (Figure taken from Mills, et al.,2016, reproduced under a CC-BY 4.0 license). (C) White matter tract indices: changes in fractal anisotropy (FA) and mean diffusivity (MD) in a cross-sectional study (age range: 12 -21), boys in blue; girls in red. (Figure taken from Pohl, et al., 2016, reproduced by permission of Elsevier).

1.1.1 Cortical grey matter changes

1.1.1.1 Cortical volume

Histological studies indicate that, following synaptogenesis during childhood, synaptic density reaches a peak in late childhood and decreases throughout adolescence and early adulthood, likely reflecting region-specific synaptic pruning (Huttenlocher, 1990; Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011). This results in an overall reduction of grey matter volume and cortical thickness (Giedd et al., 1999; Gogtay et al., 2004; Mills & Tamnes, 2014; Raznahan et al., 2011; Tamnes et al., 2010), which can be observed in MRI studies.

Cortical grey matter volume is greatest in mid-to-late childhood, decreases more sharply in adolescence, and less pronouncedly in the mid-twenties (see **Figure 1.1.A)** (Mills et al., 2016; Tamnes et al., 2017). Grey matter development decreases show strong regional patterns in an overall posterior to anterior developmental gradient (see **Figure 1.2**) and seems to be driven by cortical thinning and not changes in surface area (Tamnes et al., 2017).

1.1.1.2 Cortical thickness and surface area

Cortical thickness is thought to reflect the packing density of neurons and other components of the neuropil and exhibits regional and temporal specificity over development (Sowell et al. 2003). It is measured as the distance between the border between white matter and cortical grey matter, and the border between grey matter and the pia mater (Mills & Tamnes, 2014). It varies between 2 and 4 mm: the insular and temporal cortex exhibit the thickest cortex, while the frontal and occipital poles are the thinnest (Ribeiro et al., 2013).

Previous longitudinal studies have found contrasting results in regard to cortical thickness trajectories. While some earlier studies suggest an inverted U-shape pattern of maximal cortical thickness in adolescents (Raznahan et al., 2011; Shaw et al., 2006, 2008) recent findings from longitudinal studies with methodological improvements in terms of quality control and standardisation, support a pattern of decreasing cortical thickness with increasing age during late childhood and across adolescence (see **Figure 1.2**) (Tamnes et al., 2017). Cortical surface area increases in childhood, and decreases subtly during adolescence (Mills et al., 2014; Raznahan et al., 2011; Wierenga, Langen, Oranje, & Durston, 2014).

1.1.2 Subcortical development

Compared to studies of the cortex, understanding of subcortical development is still limited. There is evidence that subcortical regions, including areas of sensorimotor processing (thalamus and caudate), and limbic regions of emotion and memory, undergo significant changes in childhood and adolescence with different developmental trajectories for males and females (Giedd et al., 1996; Koolschijn & Crone, 2013; Sowell, Trauner, Gamst, & Jernigan, 2002; Toga, Thompson, & Sowell, 2006), which might reflect effects of puberty.

In terms of limbic neurodevelopment, a large cross-sectional study of 442 typically developing individuals between 8 and 39 years, found that putamen volume decreased with age while thalamus volume increased with age. Independent of age, males had larger amygdala and thalamus volumes than females (Koolschijn & Crone, 2013). In contrast, a large cross-sectional study of participants between 4 and 18 years, found larger amygdala volumes with age in males only, and large hippocampal volumes with age in females only, with no overall volume differences between sexes when controlling for total brain volume (Giedd et al., 1996). In a longitudinal study of 618 participants, males and females showed significant differences in both absolute subcortical volume and the timing of developmental changes in subcortical volume, with earlier peaks for females than males in the majority of regions between 5 and 25 years (Raznahan et al., 2014). The pallidum was the first to peak in volume in late childhood (M_{females} = 9.5 yo, M_{males}= 7.7 yo), followed by striatum (M_{females} = 12.1 yo, M_{males} = 14.7 yo) and finally by the thalamus (M_{females}=13.8 yo, M_{males} = 17.4 yo). Similarly, in a longitudinal study by Lenroot et al., caudate volumes were found to peak earlier in females than males ($\mathrm{M}_{\text{females}}$ = 10.5 yo, $\mathrm{M}_{\text{males}}$ = 14 yo), following an inverted U-shape (Lenroot et al., 2007).

1.1.3 White matter changes

White matter changes that can be measured with MRI include increasing volume, and extension of tracts and myelin, measured as increasing fractional anisotropy (FA), decreasing axial diffusivity (L1), decreasing radial diffusivity (LT), or decreasing mean diffusivity (MD) with diffusion tensor imaging (DTI) (Barnea-Goraly et al., 2005; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005).

White matter increases in volume and maturation at the micro-structural level from birth to late adolescence and early adulthood (Hasan et al., 2010; Lebel et al., 2008; Pfefferbaum et al., 2013; Sowell, Thompson, & Toga, 2004; Yeatman, Wandell, & Mezer, 2014). There is evidence of continued myelination throughout childhood and adolescence (Benes, 1989; Benes, Turtle, Khan, & Farol, 1994), resulting in an increase and reorganisation of white matter connections with age between 5 and 25 years, stabilising around this time (Simmonds, Hallquist, Asato, & Luna, 2014). Cortical white matter volume shows an increase between late childhood and mid-adolescence, and starts to stabilise in mid to late adolescence (Mills et al., 2016).

FA is an index of local fibre organization and increases with age from birth (Sadeghi et al., 2013) through late adolescence (Lebel et al., 2008) and beyond (Tamnes et al., 2010; Yeatman et al., 2014). A recent large cross-sectional multisite study inspected tractography trajectories in 671 adolescents, confirming a pattern of higher FA and lower diffusivity measures in older adolescents, with findings that the boys' indices were higher than the girls (**Figure 1.1.C**) (Pohl et al., 2016). FA and axonal calibre increase have been associated with pubertal changes in hormones: there is a positive correlation with testosterone in boys, and a negative correlation with oestradiol in girls (Herting et al., 2014; Herting, Maxwell, Irvine, & Nagel, 2012; Perrin et al., 2008).

1.1.4 Inverse relationship between grey and white matter measures and regional specificity

Maturation of a given brain region has been defined in terms of both grey and white matter changes. Age-related increases in white matter and measures of extension of tracts and myelin follow an inverse pattern with the observed decreases in cortical grey matter volume and thickness and regional variability. Giedd et al. (1999) found that grey/white matter exhibited nonlinear/linear relationships, respectively, for the frontal, occipital, and parietal regions. By contrast, both grey and white matter mature linearly in the occipital region. Consistent with these reports, inverse relations have been reported between white matter MD and subjacent cortical thickness (Vandekar et al., 2015), local FA and grey matter density (Giorgio et al., 2008) and cortical thickness (Tamnes et al. 2010). These patterns are thought to reflect environmental effects on grey matter pruning concurrent with creation and extension of fibre connections (Pohl et al., 2016).

Regional timing of maturation adds to the complex pattern of neurodevelopment of grey matter volume decline and white matter volume increase (for review, (Giedd et al., 2015; Stiles & Jernigan, 2010; Toga et al., 2006). Gogtay et al. (2004) described a gradient where primary sensory and motor cortices matured earlier than association cortices in a longitudinal study in participants aged 4 – 21 years. Tamnes et al., 2013 also showed a posterior-to-anterior gradient with higher rates of grey matter decreases at the youngest age in the parietal and lateral occipital lobes relative to higher rates of decreases at older ages in the frontal lobes and anterior temporal lobes in participants between 8 – 22 years.

Regional specificity in cortical development exists in terms of cortical thickness, surface area and cortical volume from late childhood to early adulthood (Tamnes et al., 2017). From age 7 to 29 years, widespread nonlinear decreases in cortical volume and thickness, which varied by lobar region (frontal, parietal, temporal, occipital), alongside smaller steady decreases in surface area was observed (see **Figure 1.2**). Regional specificity in when tracts reach maximal values was also reported in DTI measures, particularly FA (Hasan et al., 2010; Lebel et al., 2008; Yeatman et al., 2014).

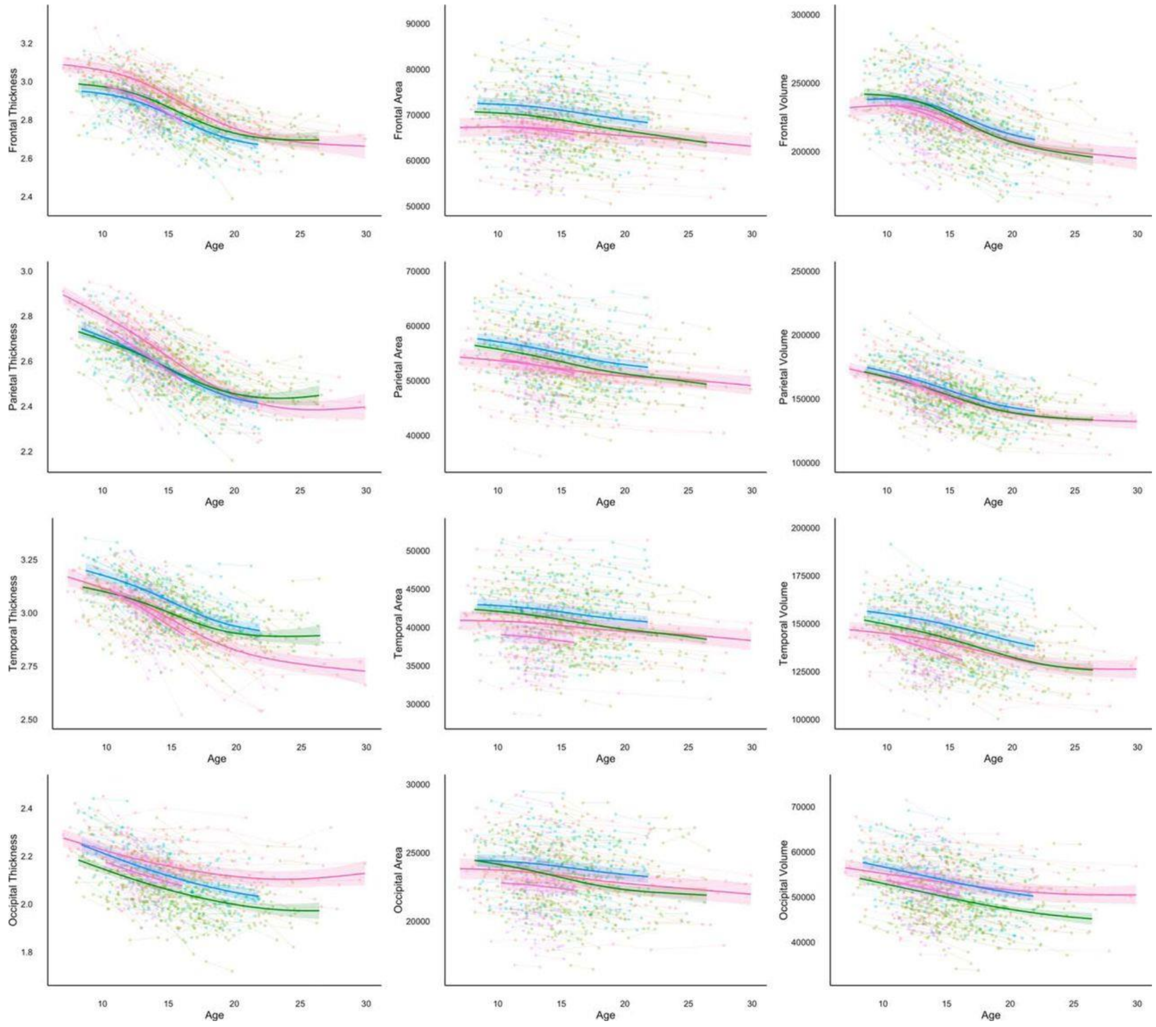


Figure 1.2. *Developmental trajectories for lobar cortical measures*. Spaghetti plots of lobar cortical thickness, surface area, and volume, controlling for sex. The coloured lines represent the GAMM fitting while the lighter coloured areas correspond to the 95% confidence intervals. Different coloured lines represent different samples (Figure from Tamnes et al., 2017, reproduced under a CC-BY 4.0 license).

1.1.4.1.1 The misconception of prefrontal systems maturing last

A common misconception in the field is that the prefrontal cortex matures last in this posterior-anterior developmental gradient, when in reality other temporal and parietal regions also exhibit prolonged developmental trajectories (see **Figure 1.2**) (Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015). This misconception arose from early histological findings which compared the middle frontal gyrus with Brodmann area 17 and Heschl's gyrus (Huttenlocher & Dabholkar, 1997). However, this study was not extensive of all brain regions, and other cortical associations were not investigated, making conclusions across the whole brain unwarranted. While the MRI evidence discussed above does support a longer maturational trajectory for the prefrontal cortex, other regions, such as temporal areas and subcortical regions show an even more protracted trajectory (Gogtay et al., 2004; Raznahan et al., 2014), which is supported with histological evidence of prolonged myelination in prefrontal cortex, parietal and temporal regions (Yakovlev & Lecours, 1967). By cortical thickness indices, posterior temporal cortices have the most protracted maturation (Tamnes et al., 2017). Studies of structural connectivity using diffusion tensor imaging show that while dorsal prefrontal cortex (PFC) regions have white matter integrity comparable to adolescence, there are still changes in connectivity between ventral and medial PFC and limbic and temporal regions which continue into emerging adulthood (Lebel et al., 2008; Simmonds et al., 2014)

1.1.4.1.2 Developmental mismatch

In a longitudinal study of 33 individuals, Mills et al. (2014) found structural evidence for a developmental mismatch. At both the group and individual levels, the volume of subcortical structures developed earlier than the PFC. There was a stronger amygdala/PFC imbalance than NAcc/PFC (Mills, Lalonde, Clasen, Giedd, & Blakemore, 2012). PFC grey matter volume remained fairly steady in childhood, but started to decrease in adolescence and continued to decrease until young adulthood. In contrast, amygdalar volume increased between late childhood and late adolescence, with a shallower slope of growth after age 16. NAcc volume decreased linearly between ages 8 and 25. However, at an individual level, the study did not find a relationship between structural maturational patterns and self-reported risk-taking or sensation seeking (Mills et al., 2014).

In summary, brain maturation in humans is protracted with distinct developmental trajectories in different tissue types, brain structures, and neural circuits. The general pattern of change is of highest volumes of cortical grey matter in childhood which decrease steadily through adolescence with decelerating decreases in emerging adulthood. In contrast, there is increased white matter volume and tract extension with age until mid-to-late adolescence, before showing relative stability. Maturational rates of white and grey matter show regional specificity.

1.2 NEUROCOGNITIVE MODELS OF THE INTERACTION BETWEEN COGNITIVE CONTROL AND MOTIVATION IN ADOLESCENCE

Neurocognitive models of adolescence highlight changes in motivation in terms of increased reactivity of affective-motivational systems (Crone & Dahl, 2012; Dahl & Vanderschuren, 2011; van Duijvenvoorde et al., 2016). Developmental trajectories of decision making in adolescence differ when they are made in an affective or hot experimental context (e.g., when emotions or reward are involved, or peers are present) or a non-affective or cold context. Imbalance models explain adolescent motivated behaviour as a result of a mismatch between earlier maturing subcortical regions, associated with socio-affective processing, and later-maturing cortical structures involved in cognitive control regions (Casey, Jones, & Somerville, 2011; Ernst, 2014; Steinberg, 2008). Consistent with these neurocognitive models, adolescents are more prone to taking risk in a variety of arousing situations compared to adults, including immediate rewards (Defoe, Dubas, Figner, & van Aken, 2015; Figner, Mackinlay, Wilkening, & Weber, 2009), peer presence (Gardner & Steinberg, 2005; Peake, Dishion, Stormshak, Moore, & Pfeifer, 2013), or in uncertainty (Blankenstein, Crone, Van Den Bos, & van Duijvenvoorde, 2016; Tymula et al., 2012).

Below, I briefly outline the different models that have been proposed which are generally based on the imbalance in maturation between different systems, but which stress different aspects of changes in motivated behaviour in adolescence (van Duijvenvoorde et al., 2016).

1.2.1 Dual-system model

The seminal dual-system model, coined by Steinberg et al. (2008) identified that while sensation seeking peaks in mid to late adolescence, self-regulation capacity continues to develop until the mid- twenties (Steinberg et al., 2008). Steinberg and colleagues draw on Metcalf and Mischel's (1999) two-system model of will power, which identifies a cold system, which is neutral, strategic and flexible, and a hot system, which is affectively driven and more automatic (Metcalfe & Mischel, 1999). McClure et al. (2004) extended this two-system model to explain how the limbic system, associated with midbrain dopamine levels, dealt with immediate rewards, while prefrontal circuitry was associated with the ability to delay rewards (McClure, York, & Montague, 2004).

In the dual-system model (Steinberg et al. 2008), the earlier maturing limbic system, triggered by puberty, interacts with an immature prefrontal system, challenging the capacity to exert control in hot contexts (such as the presence of peers). Steinberg et al. (2008) propose that the socio-affective system reactivity follows an inverted U-shape trajectory, declining in early adulthood. In their view, the decrease in reactivity to reward is independent from the development of the cognitive control system.

1.2.2 Imbalance model

Building on the dual-system model, and by framing adolescence as a period of transition and integrating comparisons with both children and adolescents, Casey et al. (2008) propose that imbalances within brain circuitry explain nonlinear changes in adolescent behaviour. Casey and colleagues (2015, 2016) have highlighted brain connectivity within and between limbic, affective-motivational, and cognitive control brain circuits. In this view, development and sensitivity of subcortical circuits precede top-down cortical control circuits (Casey, 2015; Casey, Galván, & Somerville, 2016). In contrast to Steinberg et al. (2008), Casey et al. suggests that the increasing arousability of the socio-affective system plateaus in mid-adolescence, due to the strengthened capacity of the cognitive control system.

1.2.3 Triadic model

Proposed by Ernst et al. in 2006, the triadic model of motivated behaviour recognises two hot subsystems: reward (associated with activity in the VS) and avoidance (associated with activity in the amygdala). Behaviour emerges from the balance between the harm avoidance and reward-driven subsystems, in counterbalance with the prefrontal regulatory circuit. During adolescence, there is a bias towards the reward-driven subsystem, because of puberty triggered sexual hormonal changes (Ernst, 2014; Ernst et al., 2006).

1.2.4 Social reorientation models

Extending on the dual-system model (Steinberg et al. 2008), Shulman et al. (2016) and Nelson et al. (2016) acknowledge the crucial role of the social context in influencing neural sensitivities. Nelson et al. (2016) suggests that the focus of social goals shifts across development with underlying changes in motivation to promote certain social experiences (e.g. the predominance of interactions with parents in childhood to peers in adolescence). Hot contextual factors, such as the presence of peers in adolescence, might expose the cortical/subcortical imbalance, which might not occur in cold contexts. In this view, subcortical activity highlights distinct experiences or stimuli that are *developmentally relevant* in the social environment (Leppänen & Nelson, 2009; E. E. Nelson, Jarcho, & Guyer, 2016; Scherf, Smyth, & Delgado, 2013).

1.2.5 Flexible interaction model

Crone and Dahl (2012) argue against a simple increase in cognitive control in favour of a less automatic and more flexible engagement in adolescence. They posit that increases in pubertal hormones trigger changes in cortical-subcortical flexible interactions, where frontoparietal cognitive control regions are recruited in line with the motivational context. For example, peers or affective appraisal of stake, might promote differential engagement of cognitive control systems in line with adolescent goals (Crone & Dahl, 2012).

Beyond the particularities of each model briefly described above, all propositions identify adolescence as a time of particular influence of hot systems over cold cognition, which is less apparent in childhood, when presumably the systems are immature, or adulthood, when both systems have matured. During adolescence, regional brain development and strengthened connectivity, results in increased capacity to exert top-down regulation of limbic, hot systems. These models have provided a nice, albeit simplistic, heuristic to frame research on adolescent behaviour. Traditionally, research has focused on the negative aspects of increased reward-related motivation in adolescence to explain increased aberrant decision making and risk taking, and sensation seeking which are associated with morbidity and mortality in adolescence. Research has also focused on explaining the emergence of psychopathology in this age group in the light of dual-system (Keshavan, Giedd, Lau, Lewis, & Paus, 2014; Patton et al., 2016; Paus, Keshavan, & Giedd, 2010) . However, increased influence of hot contexts can also mean increased motivation and capacity for learning during adolescence, perhaps pointing towards a second window of opportunity (Fuhrmann, Knoll, & Blakemore, 2015). Increased motivation during this period promotes exploration of new environments and social relationships, and more positive, pro-social, risk-taking behaviour (Crone & Dahl, 2012; Do, Guassi Moreira, & Telzer, 2017). Thus, cognitive control sensitivity to context may underlie positive developmental trajectories as well (Telzer, 2016; van Duijvenvoorde et al., 2016). **In this dissertation, I aimed to characterise in more detail how complex cognitive control abilities may be flexibly adaptable to varying contexts during development.**

1.3 MODELS OF COGNITIVE CONTROL

Cognitive control is the ability to guide behaviour in line with goals and plans. This ability relies on executive functions, which are high-level cognitive processes that control lower level implementational processes to enable goal pursuit. Often, multiple goals need to be managed concurrently with different time scales and levels of abstraction. Cognitive control coordinates the maintenance of current goal representations and its shielding against distraction, while also allowing for flexible updates of goals if environmental changes should arise (Chiew & Braver, 2017).

A comprehensive review of the numerous models that exist is beyond the scope of this **Introduction**. Here I briefly describe four models of cognitive control function that have particularly influenced the experimental paradigms employed in this dissertation: (1) Unity/diversity model (Friedman and Miyake), (2) Hierarchical cognitive control model (Badre/Koechlin), (3) Dual mechanisms of control (Braver), (4) Cost benefit analysis model (Shenhav and Botvinick). I also review the existing evidence for development of some key processes that relate to aspects from each model in relation to the experiments described in this dissertation.

This dissertation investigated examples of complex cognitive control that cut across these different models with a focus on the sensitivity to the socio-affective context. **Chapter 2** describes a prospective memory study with a focus of the RLPFC in the context of branching (see **Section 1.3.2.3** below) and the sensitivity of proactive and reactive control to cue salience (**Section 1.3.3**). **Chapter 3** investigated the interaction of reward with working memory performance (**Section 1.3.1**) and the sensitivity of proactive and reactive control to the motivational context (**Sections 1.3.3)**. Finally, **Chapter 4** describes an experiment of relational reasoning which can be framed as a different example of branching and manipulation of various levels of abstract information (**Section 1.3.2**), and whether it was sensitive to the type of information being manipulated (social/non-social).

1.3.1 Unity/diversity model of executive functions

Executive function (EF), sometimes synonymous with cognitive control, is a broad umbrella term that comprises capacities such as inhibiting responses, resisting distraction, switching between task sets, aspects of working memory processes (such as maintenance, manipulation and updating), dual tasking, planning, monitoring, and verbal fluency (Banich, 2009; Diamond, 2013; Jurado & Rosselli, 2007). Friedman and Miyake proposed a model of unity and diversity where EFs are robustly correlated but load into separable latent factors which reflect common EF and specific abilities (switching and updating) and activate both common and specific neural areas (Friedman & Miyake, 2017; Miyake & Friedman, 2012). In their seminal study, Miyake et al. (2000) examined the separability of three key EFs: shifting, updating and inhibition and how they related to nine experimental executive tasks in young adults. Confirmatory factor analysis indicated that the three target executive functions were moderately correlated with one another, but were clearly separable, and contributed differentially to performance on complex executive tasks as is indicated in **Figure 1.3 (panel A)**. However, as the authors recently noted, the selection of these three EFs was driven by the fact that they are commonly discussed in the literature and not to suggest that they are the exclusive elementary processes of cognitive control. Other authors have since investigated how other EFs relate to one or more of these three EFs (Fisk & Sharp, 2004; Fournier-Vicente, Larigauderie, & Gaonac'h, 2008; Friedman & Miyake, 2004), revealing the general principle of unity and diversity not only in inhibition, updating and shifting, but also in EFs not originally investigated by Miyake et al., such as fluency and dual task coordination.

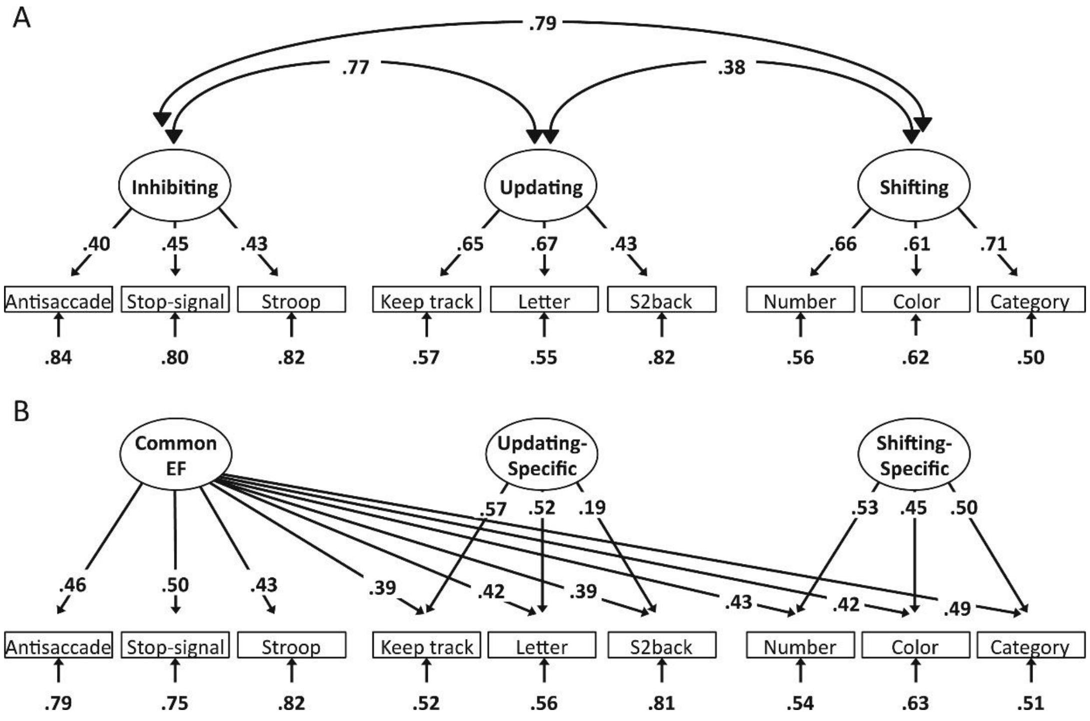


Figure 1.3. *Latent variable models of executive functions*. In the correlated factors parameterisation (panel A), three latent variables (represented with ellipses) each predict separate tasks (represented with rectangles). All of the correlations are significantly larger than zero (indicating unity), but none of the factors can be collapsed without significantly harming model fit (indicating diversity). In the bifactor parameterization (panel B), unity is captured with a common factor that predicts all nine tasks, and diversity is captured by orthogonal factors that capture remaining correlations among the updating and shifting tasks, respectively, once the Common EF variance is removed. Parameters taken from Friedman et al. (2011); all $p < .05$. Letter = letter memory; S2back = spatial 2-back; Number = number–Letter; Color = Color–shape; Category = category-switch. (Figure and caption from Friedman & Miyake, 2017, reproduced by permission of Elsevier).

In the original model, each task loaded on one of the three correlated EF latent factor as is indicated in **Figure 1.3**, **panel A**. A revision model (Friedman et al., 2008), proposed an alternative parametrisation of unity and diversity as latent variables (**Figure 1.3**, **panel B**). In this model, a common EF factor predicts all tasks and captures Unity, while remaining variance in task performance is captured by two specific factors, updating and shifting. The common EF factor relates to the ability to select and apply the correct task set. In this view, the Common EF factor relates to individual differences in goal maintenance and implementation of control ongoing processing (Friedman et al., 2008; Miyake & Friedman, 2012). While the ability to maintain and manage goals is important for any EF task, it is crucial in tasks that require inhibition of prepotent responses or distracting information, which may explain the absence of an inhibition specific latent factor (Friedman & Miyake, 2017). The shifting factor is suggested to underlie the capacity to rapidly change task sets or goals. Individual differences might be in goal changing speed, but also in the strength of activation, or maintenance, of a goal, as stronger goals might take longer to replace. The opposite effects of inhibition and switching speak to a stability/flexibility trade-off that is likely regulated by the common EF factor.

The updating factor is related to the ability to replace some information in working memory while general goal-related information is maintained. In contrast, in shifting tasks, the general goal is constantly being updated. Individual differences in both memory specific factors, such as retrieval, as well as more general updating processes, support this ability (Friedman & Miyake, 2017; Miyake & Friedman, 2012). Evidence supporting an inhibition-specific factor is not robust, as some studies do not find the factor at all (Hull, Martin, Beier, Lane, & Hamilton, 2008; Valian, 2015; van der Sluis, de Jong, & van del Leij, 2007), and have suggested that inhibition is the common EF factor as many EF tasks require some sort of inhibition. Friedman and Miyake (2017), however, suggest that inhibition particularly requires goal maintenance, and therefore it might not load on an additional specific factor (Friedman & Miyake, 2017).

This pattern of unity/diversity has been replicated in other studies of EFs in young adults (Fournier-Vicente et al., 2008; Ito et al., 2015) and children and adolescents (Brydges, Fox, Reid, & Anderson, 2014; Huizinga, Dolan, & van der Molen, 2006; Huizinga & Smidts, 2010; K. Lee, Bull, & Ho, 2013; Lehto & Elorinne, 2003). The majority of these studies have focused on inhibition, shifting and updating in line with Miyake et al., (2000), although with differences in the specific experimental tasks used. Results indicate that EF tasks load into separate factors that are correlated, although the precise factor architecture varies between studies. Developmental studies suggest that EF in pre-schoolers has a simple unitary structure (Brydges et al., 2014; Wiebe et al., 2011), but a more fractioned structure in children and adolescents (Huizinga et al., 2006; Lehto & Elorinne, 2003), where shifting can be separated from updating. Improvements in EF efficiency might be related to structural changes of EF factors (Friedman & Miyake, 2017).

An important limitation of this approach based on the identification of latent EF factors is that low correlations between tasks could also reflect methodological considerations such as lower reliability of tasks, different strategy use or task impurity given that performance in experimental tasks necessarily reflects the non-executive processes under control of EFs as well (Shallice, Burgess, & Robertson, 1996). In addition, as Hedge et al. (2017) have recently suggested in their “reliability paradox”, experimental tasks are optimised to minimise between-participants variability. It is precisely this low between-participants variability that undermines the capacity to detect individual differences (Hedge, Powell, & Sumner, 2017).

1.3.2 Hierarchical cognitive control

1.3.2.1 Hierarchical organisation of the PFC

Hierarchical models of cognitive control have aimed to explain how we are able to concurrently manage multiple goals that might differ in time scale and level of abstraction in terms of hierarchically organised representation of behavioural rules. Neuroimaging studies have suggested that this hierarchy from high-level to low-level control might emerge from a functional organisation of the frontal lobe along a rostrocaudal axis, as schematised in **Figure 1.4**. (Badre, 2008; Badre & D'Esposito, 2009; M. M. Botvinick, 2007; Summerfield & Koechlin, 2008) . Cognitive control allows the flexible adaptation of behaviour in response to the task context, which is represented by frontal neurons. This representation of the context in relation to the desired goal resolves competition between conflicting courses of action (see for a review Miller & Cohen, 2001).

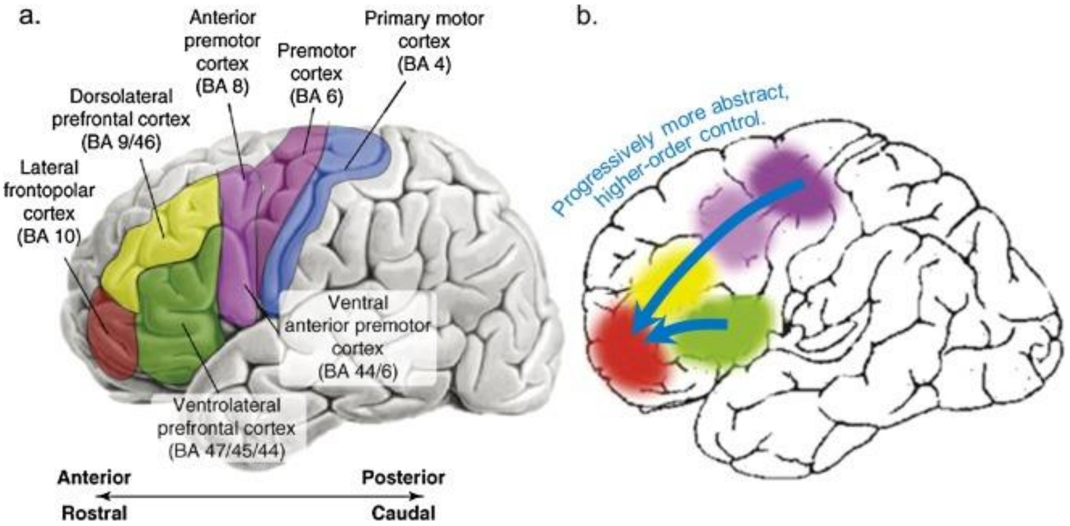


Figure 1.4. *Sub-divisions of the frontal lobes*. (A) Schematic representation of the major anatomical sub-divisions of the frontal lobes. Following a caudal to rostral direction. Boundaries and Brodmann areas (BA) are approximate. (B) Schematic representation of the rostro-caudal gradient of the organisation of the LPFC. Progressively more anterior PFC regions support cognitive control of more abstract and temporally extended representations (Figure from Badre, 2008, adapted by Dumontheil, 2014, reproduced by permission of Elsevier).

Task sets are the sets of cognitive processes that are actively maintained to guide behaviour (Sakai, 2008). Cognitive control coordinates the encoding, storage and retrieval of task sets in long-term memory to regulate goal-oriented behaviour (Collins & Koechlin, 2012). An important distinction is between the *actor task set*, which is regulating behaviour at any given moment, and the competing *alternative (counterfactual) task sets*, which may need to become the actor task set in response to the changing environment. The term *policy* was introduced by Botvinick (2007) to describe a rule that connects the state, the action and the desired outcome. According to Badre et al. (2008), cognitive control is largely occupied with understanding how the brain acquires, selects and implements these action policies. In the hierarchical approach, an abstract goal can be broken down into a series of specific subgoals, which can be broken down further into a highly specific sequence of motor outputs necessary to achieve a goal. In this way, choices at the higher levels constrain possible actions at lower levels, reducing complexity and demands. In this view, second-level policies (more abstract rules) can specify which sets of first-level policies should be implemented in each task state.

Cognitive control, operationalised as the selection, maintenance and implementation of the task set in line with the desired goal, is thought to be organised in the PFC according to three main anatomical dissociations (see **Figure 1.5** for schematic and details) (Duverne & Koechlin, 2017a): (1) the most anterior prefrontal regions, (2) medial frontal regions, and the (3) lateral prefrontal cortex.

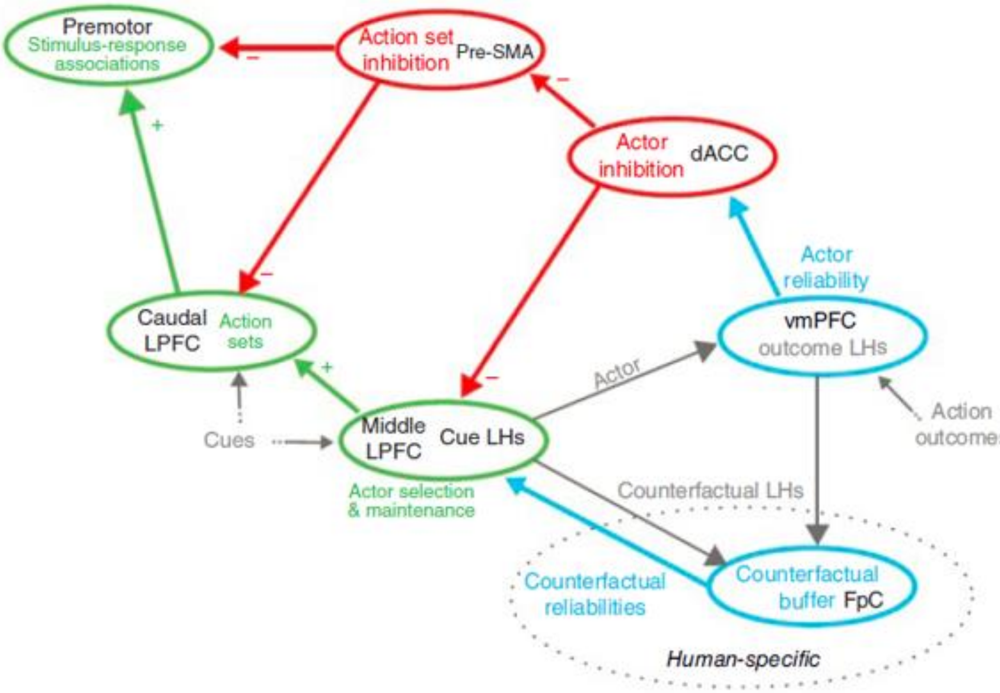


Figure 1.5. *Functional architecture of cognitive control in the prefrontal cortex.* The ventromedial prefrontal cortex and the frontoparietal cortex compare whether a few task sets match the current external state. The middle lateral prefrontal cortex and dACC and other posterior frontal regions control the switching between task sets. The MPFC controls the predominating actor task set which drives behaviour and monitors external contingencies to evaluate how reliable the predominant task set is. The lateral PFC controls the alternative, counterfactual, task sets that might be chosen in the future, should the actor task set result inefficient. If the VMPFC deems the actor task set unreliable, the dACC will inhibit the actor set, while the middle LPFC will retrieve one of the alternative task sets that the frontoparietal cortex has deemed reliable. Finally, there is a posterior-anterior organisation gradient for medial and lateral regions. One stream extends from the preSMA, passing through the dACC and unto the ventral MPFC, and is implicated in inhibiting component of the actor task set. In the lateral PFC, the functional gradient extends from the caudal to the middle LPFC and is involved in selecting subordinate components of the counterfactual set that are becoming reliable. (Figure from Duverne & Koechlin, 2017, reproduced by permission of John Wiley and Sons).

Related to the rostrocaudal gradient in the LPFC, Badre et al. (2010) reviews neuroimaging evidence suggests that policy abstraction affected locus of activation within the lateral frontal cortex, with progressively rostral regions supporting representations with added levels of abstraction (see **Figure 1.4**). Activity in rostral regions influences neural activity in caudal regions more than in the opposite direction, providing further evidence for a hierarchical gradient of representations. This structure seems to emerge from a series of nested cortico-striatal loops that permit more rostral regions to gate the activity on the caudal regions. (Badre et al.,2010; Koechlin, Danek, Burnod, & Grafman, 2002) (Badre & D'Esposito, 2007; Koechlin et al., 2003). Badre et al. (2010) has suggested that this nested gating architecture allows a reduced number of cortico-striatal loops to control large policy structures, giving rise to cognitive flexibility (Badre et al., 2010).

1.3.2.2 Motivational influences on control hierarchy

While the role of subcortical dopamine-rich structures in reward processing has been robustly documented (reviewed below in **Section 2.5.1**) the hierarchical model of cognitive control has begun to recognise the role of several PFC structures in reward-related modulations of goal maintenance in lateral PFC at the cortical level. Medial structures are thought to encode motivational signals that regulate engagement of LFPC according to rewards at stake (Bahlmann, Aarts, & D'Esposito, 2015; Kouneiher, Charron, & Koechlin, 2009) in different time frames. VMPFC encodes rewarding values of outcomes contingent on task-set execution (Duverne & Koechlin, 2017b). The anterior cingulate cortex (ACC) encodes the potential reward advantage of switching to alternative task-set to help guide selections (Boorman, O'Doherty, Adolphs, & Rangel, 2013; Kolling et al., 2016) The pre-SMA also encodes appetitive values for task-sets through reinforcement learning, to drive task-set selection in line with "cached" value rather than those inferred to result from a given action (Duverne & Koechlin, 2017b). The pre-SMA is associated with more immediate task-switching, while dACC is associated with sustained control

Reward expectations associated with a given task-set are encoded by the DMPFC and relayed to LPFC to guide strategy selection. At the same time, the LPFC encodes learned rules related to strategy selection, which feed back into the MPFC. This functional loop ensures that strategy selection is in line with learned rules instead of reward expectations only (Duverne & Koechlin, 2017b). Bahlmann et al. (2015) suggest that different levels of cognitive control and motivation in medial and lateral frontal subregions interact. In their study, reward enhancement was maximal for flexible updating, which corresponds to mid-level cognitive control. Only this level showed functional coupling between LPFC and dopamine-rich subcortical regions. Motivation may therefore differentially affect different hierarchical levels of cognitive control influencing the recruitment of frontal cortical control regions depending on specific task demands (Bahlmann et al., 2015).

1.3.2.3 Cognitive branching

Cognitive branching, or multitasking, refers to the ability to keep information about a pending, incomplete task, in memory while alternative subtasks are completed and their progress is being monitored (Mansouri, Koechlin, Rosa, & Buckley, 2017; Ramnani & Owen, 2004) . When alternative subtasks are completed, this ability allows the individual to return to the pending task. Cognitive branching is a key aspect of other related cognitive abilities such as planning and problem solving and those which are the topic of this dissertation: relational reasoning (i.e. the capacity to infer relations between categories or objects), prospective memory (i.e., the ability to remember to remember), and the ability to exert proactive and reactive control.

Koechlin et al. have suggested that cognitive branching is mediated by the frontopolar cortex or the rostrolateral PFC (RLPFC) (Donoso, Collins, & Koechlin, 2014; Koechlin, 2011; Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999). In a related view, Braver and Bongiolatti (2002) suggested that the frontopolar cortex is implicated in managing and monitoring sub-goals while maintaining information in working memory, by successively allocating resources between concurrent tasks. Furthermore, Braver and Bongiolatti found that other regions, like the DLPFC, were also involved in cognitive branching, in addition to the RLPFC (Braver & Bongiolatti, 2002). While cognitive branching enables multitasking, Koechlin et al. argue that it is different from dual-task performance, in which the individual is not required to keep task A in mind while performing task B. Further, they argue that branching, but not dual-task processing, is associated with activation in the RLPFC (Donoso et al., 2014; Koechlin, 2011; Koechlin et al., 1999). This was explored in **Chapters 2 and 4**.

1.3.3 Dual mechanisms of control

1.3.3.1 The Gating Model

This model describes the role of the interaction between the PFC and the dopamine rich (DA) subcortical modulatory system in selecting, updating and maintaining behaviour guiding context (Braver & Cohen, 1999). Information access to active representations in the PFC is subserved by phasic bursts from the striatum, which acts as an input gate (Braver, Barch, & Cohen, 1999). In addition, DA plays a key role in reinforcement learning in which phasic firing to response prediction errors signal relevant environmental information for context (task set) selection (Braver & Cohen, 1999), optimising reward pursuit and goal-oriented behaviour.

The model has been refined by the addition of two output gates (in addition to the previously described input gate). Striatal signalling can control the output of PFC representations to lower-levels in the system for the behavioural implementation of the goal or to relocate resources when recent events make the current representations irrelevant (Chatham & Badre, 2015; Desrochers, Chatham, & Badre, 2015)

1.3.3.2 Proactive and reactive control

In the dual mechanisms of control (DMC) framework, cognitive control operates in two modes: proactive and reactive. In proactive control, sustained context representations (task sets) are maintained in the PFC. Information input and maintenance is supported by the phasic DA gating mechanism, which also relatively protects proactive control form interference. Proactive control is characterised by sustained neural activity in anticipation of the relevant stimuli. Reactive control, in contrast, is a transient corrective measure in response to changes in demands or stimulus-triggered associative retrieval, and acts without a gating mechanism. It is characterised by quick deployment of transient neural activity triggered by the stimuli just immediately before the individual makes their response (Braver, 2012; Chiew & Braver, 2017). Briefly, proactive control has been robustly associated with sustained activity in the PFC (Braver, 2012), whereas reactive control is associated with a more distributed network of regions, including the PFC, and the ACC, which is thought to monitor performance and detect errors, signalling changes in demands (Botvinick & Braver, 2015). This will be treated in extensive detail in **Chapter 3**.

The two modes of control can dynamically shift in response to multiple within-individual, within group and between groups influences (Braver, 2012). The DMC has been most extensively used to understand variability in tasks where contextual cues indicate how to respond (Chiew & Braver, 2017). For example, in cued task switching paradigms, trials following cues that allow participants to prepare to switch task, are associated with reduced switching costs, suggesting the recruitment of proactive control (Meiran, Chorev, & Sapir, 2000; Monsell, 2003). Residual costs, which are also impacted by target features, suggest reactive control still plays a role (Kessler & Meiran, 2008; Meiran, Kessler, & Adi-Japha, 2008).

Working memory tasks can fit this contextual framework to the extent that they have a *cue → target* structure. Items that need to be stored over a delay guide responding to the target acting as contextual information. In working memory paradigms, proactive control is involved in maintaining the target set in memory over the delay. Proactive control is involved in the selection of specific items in short-term storage for further attentional processing, or bias attention toward task-relevant features of probe items (Irlbacher, Kraft, Kehrer, & Brandt, 2014). In addition, the potential interference effects that targets can have suggest the demand for additional reactive control (Craig, Berman, Jonides, & Lustig, 2013; Irlbacher et al., 2014; Jonides & Nee, 2006). **Chapter 3** explored these ideas in detail.

The DMC framework can be used to understand variability in memory tasks with much longer delays. Within the domain of prospective memory, the multi-process account (Einstein et al., 2005) distinguishes between sustained attentional monitoring and spontaneous retrieval in maintaining an intention throughout a delay. This distinction maps well into the proactive and reactive framework (McDaniel, LaMontagne, Beck, Scullin, & Braver, 2013) This will be treated in extensive detail in **Chapter 2**.

1.3.3.3 Motivational influences and the DMC

Rewards are associated with phasic (Schultz, Dayan, & Montague, 1997) and tonic (Niv, Daw, Joel, & Dayan, 2007) DA responses which could enhance proactive control of goals in lateral PFC, in line with the gating model. To the extent that proactive control optimises the use of contextual, reward-predictive cues, as well as tonic indicators of current reward, and enhances performance, it should maximise reward in motivational tasks (Chiew & Braver, 2017).

In adults, reward-related improvements in performance, likely mediated by enhanced proactive control across tasks has been observed, including the AX-CPT (Chiew & Braver, 2013; Locke & Braver, 2008), task-switching (Umemoto & Holroyd, 2015) and working memory tasks (Beck, Locke, Savine, Jimura, & Braver, 2010; Savine, Beck, Edwards, Chiew, & Braver, 2010). Tonic enhancement at the trial level, likely related to reactive control, has also been observed in working memory paradigms (Jimura, Locke, & Braver, 2010). This informed the reward manipulations employed in **Chapter 3**.

1.3.3.4 Methodological considerations

The fMRI mixed block/event design was developed to allow characterisation of block and event-related neural activity (Visscher et al., 2003). This design allows to characterise both sustained and transient neural activity associated with proactive and reactive cognitive control, which supports the DMC framework (Chiew & Braver, 2017). For example, Braver, Reynolds & Donaldson (2003) documented sustained frontoparietal activity associated with blocks of task switching (compared to single-task blocks), with additional transient activity with trial demands. Similarly, in a prospective memory experiment, sustained activity in RLPFC and DLPFC was observed in non-focal conditions, where the delayed intention is not related to the ongoing task, with transient activity in VLPFC, ACC and medial parietal regions in focal conditions (Braver, Reynolds, & Donaldson, 2003). Further, motivational-related shifts in dynamics within the same regions have been observed in the AX-CPT (Braver, Paxton, Locke, & Barch, 2009) and working memory (Jimura et al., 2010).

In the current dissertation, we employed this design to dissociate block and event-related neural activity in prospective memory and how this is influenced by cue salience (see **Chapter 2**) and the impact of reward in working memory (see **Chapter 3**) in adolescence and adulthood.

1.3.4 Cognitive control as a Cost-Benefit Decision Making

Motivational factors modulate the degree to which mental effort is deployed ((Matthew M. Botvinick & Braver, 2015; Padmala & Pessoa, 2011; Shenhav, Botvinick, & Cohen, 2013). In addition, it has been shown that there is reluctance to exert cognitive control (Kool, McGuire, Rosen, & Botvinick, 2010). The Cost-Benefit Decision Making Model posits that control allocation is jointly determined by the payoffs, which are positive and negative outcomes of a certain action, and the intrinsic costs associated with cognitive control. The selection of the amount of cognitive control is such that it maximises the expected value of control (EVC) (Shenhav, Botvinick & Cohen, 2013). The EVC results from the expect payoff and the cost of exerting control, and contemplates three dimensions: intensity, length and kind.

Increasing the intensity of control changes the probability of performance outcomes, which can lead to greater expected payoffs (i.e., increased accuracy in a task or faster response times). Intensity of control also produces a subjective “effort-like” cost, which might increase nonlinearly. EVC is derived by taking the difference between payoffs and these subjective costs of control (in a cost-benefit analysis). As a result, there is an optimal window in which factors that indicate increased demand for control (such as incongruency in the stimuli) or increased rewards can recruit greater cognitive control (Kool, Shenhav, & Botvinick, 2017).

In this view, cognitive control must be supported by monitoring (inputs to control decision making), specification (decision making) and regulation (execution of control). The dorsal ACC (dACC) has emerged as the key region in this model as it has been implicated in monitoring and specification (Holroyd & Yeung, 2012; Kouneiher et al., 2009; Ullsperger, 2017). The authors suggest that the dACC would calculate the EVC to optimise control allocation, outputting decision to downstream regions (Kool et al., 2017; Shenhav et al., 2013).

Although in this framework the dACC plays the central role, it is supported by other regions. Input to the dACC would come from regions that are involved in valuation and monitoring, such as the anterior insula (AIns), ventral striatum (VS), orbitofrontal cortex (OFC) and ventromedial PFC (VMPFC) (Haber & Knutson, 2010) Output from the ACC would be implemented by specific regions determined by the type of required control, for example the LPFC if attention to a particular task set needs to be enacted (Miller & Cohen, 2001).

1.4 CHANGES IN COGNITIVE CONTROL IN ADOLESCENCE

Cognitive control emerges during childhood and continues to develop throughout adolescence (Diamond, 2013; Huizinga, Dolan, & van der Molen, 2006). Protracted development of cognitive control arises from the need to coordinate different levels of functions: assembling “simpler” components such as working memory, inhibition and monitoring (Miyake et al., 2000) into more complex processes such as reasoning, sustaining control across extended periods of time, abstract thinking and decision and judgement making (Crone and Dahl, 2012).

Even though evidence of cognitive control over thoughts and actions is found in early development, the ability to consistently exert cognitive control steadily improves during childhood and adolescence (Luna, Paulsen, Padmanabhan, & Geier, 2013). Sustained cognitive control requires monitoring of performance, identification of errors, and readjustment of behaviour. These abilities continue to develop in adolescence, and reach optimal levels only during adulthood (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010). The increase in cognitive control in adolescence underlies advancements in learning and successful adaptations to varied social contexts and cultural influences (Crone & Dahl, 2012).

The PFC has been associated with cognitive control ever since the finding that patients with damage to the region exhibit executive function deficits (Crone & Steinbeis, 2017). The structural and functional development of the PFC, in interaction with more posterior parietal brain regions, underlies the maturation of higher cognitive abilities and goal oriented behaviour (Casey, Galvan, & Hare, 2005; Crone, 2009; Rubia et al., 2006). Protracted changes in the recruitment of the PFC in general are consistent with the extended maturation of cognitive control. Furthermore, the developmental trajectory of cognitive functions can be related to subregions of the PFC: working memory and inhibitory control are often related to increased activity in dorsolateral and ventrolateral PFC (DLPFC and VLPFC, respectively), while error monitoring is associated with the ACC (Crone & Steinbeis, 2017).

Cognitive control relies on a top-down modulation of subcortical structures (VS, thalamus, cerebellum, and brain stem) by the LPFC and parietal cortex (Hwang, Velanova, & Luna,

2010) . The parietal cortex shows a consistent pattern of increased activation in cognitive control tasks with age. However, there are different patterns of developmental changes in PFC activation observed (see **Figure 1.6.A**), which will be examined in detail in the following sections.

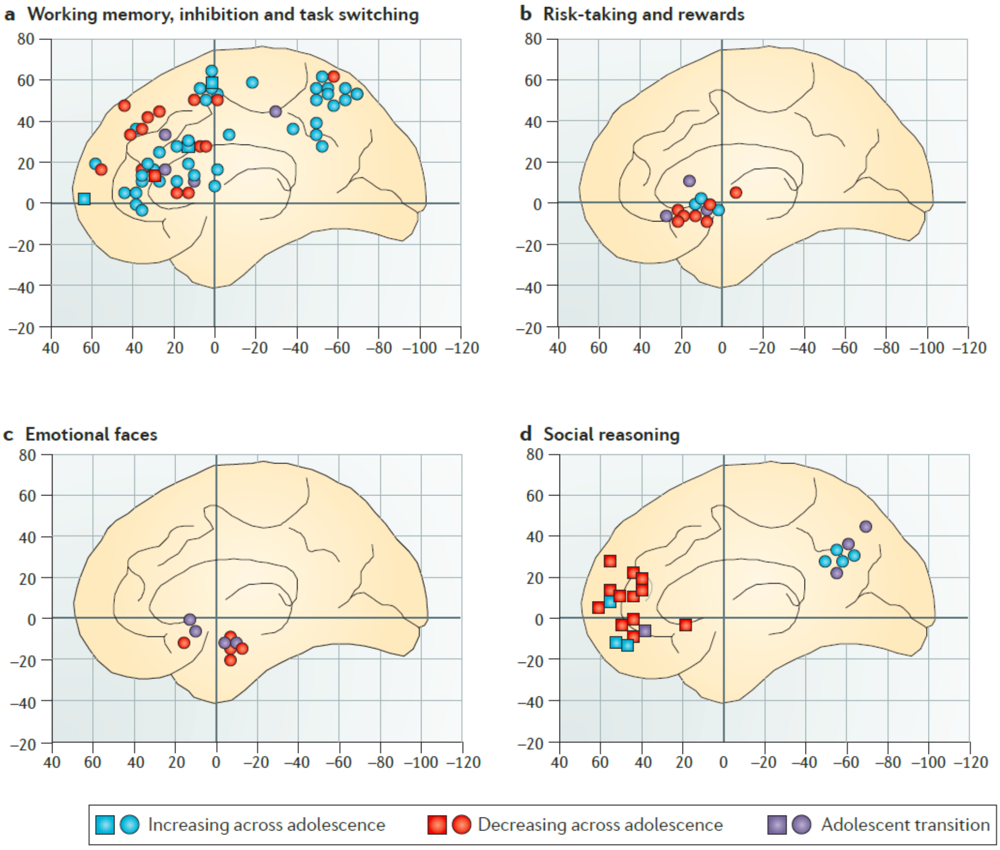


Figure 1.6 *Meta-analysis of functional MRI studies in adolescents.* (A) Frontoparietal and anterior cingulate cortex activation in working memory, inhibition and interference suppression and task switching studies. **(B)** Striatum activation in reward processing studied. (C) Amygdala and striatum activation for face processing studies. (D) Anterior medial prefrontal cortex and temporoparietal junction activation in social–cognitive reasoning studies (Figure from Crone & Dahl, 2012, reproduced by permission of Nature Publishing Group).

Research has shown increased frontoparietal activation with age might be associated with increased specificity of brain networks for certain cognitive processes, along with increased cortico-cortical and cortico-subcortical connectivity (Crone & Dahl, 2012; Ordaz, Foran, Velanova, & Luna, 2013). Some studies have found age-related decreases in frontal cortical activity in early adolescents compared with children and adults, in the superior part of the LPFC and MPFC in working memory, response inhibition, and task switching (see for Crone & Dahl, 2012 for review, see **Figure 1.5**). It has been suggested that this could reflect that networks are becoming more efficient over time. However, given that these brain activation patterns are not always related to behavioural differences, this hypothesis remains unconfirmed (Luna, Padmanabhan, & O'Hearn, 2010). Mixed findings might be explained by methodological considerations as well as interpretations of developmental changes in BOLD signal (Luna et al., 2010). While some fMRI studies investigate differences at the whole-brain level, many studies focus exclusively in regions-of-interest analysis (ROI). Many of the earlier studies had much smaller samples, which as well as statistical thresholds that have become more stringent recently (see **Chapter** 5 for a detailed discussion of limitations).

1.4.1 Developmental trajectories of basic executive functions

Working memory, inhibition, and performance monitoring are supported by different underlying neural regions within the PFC and each has a separate developmental profiles, and act as building blocks for complex cognition (Crone & Steinbeis, 2017). These basic processes are stimulus driven and need to work in concert to achieve complex, deliberative processes, which relate to strategy use. While these basic abilities appear early in childhood, more concerted use continues to improve into adulthood (Dumontheil, 2014; Luna, 2009). Here, I present a brief overview of some of the abilities that have been studied the most in developmental populations to provide the context for interpreting results from the experimental chapters regarding complex cognitive abilities such as prospective memory (**Chapter 2**), proactive and reactive control (**Chapter 3**) and relational reasoning (**Chapter 4**).

1.4.1.1 Working memory

Working memory is the ability to keep information in mind while ignoring distractions (Baddeley & Logie, 1999) and is an essential element of more complex abilities such as problem solving and reasoning (Bayliss, Jarrold, Baddeley, & Gunn, 2005; Swanson, 2004). According to the model by Baddeley and Hitch (1974), working memory is subserved by a central executive, which allocates resources between two slave systems which process different types of incoming information: the phonological loop and the visuo-spatial sketchpad. The slave systems are tested with short-term memory tasks, such as digit span, word recall, Corsi blocks and visual-pattern tasks, which require maintenance and reproduction of limited amounts of information after a certain delay. The central executive is assessed through tasks that require updating and manipulation of information, such as span tasks, backward digit span and n-back task (Zanolie & Crone, 2018).

Behaviourally, working memory capacities emerge early in childhood (Diamond & Goldman-Rakic, 1989), and exhibit prolonged development through adolescence, with accrued precision and flexibility (Luna, 2009). Children and adolescents can exhibit adult-level performance in working memory, particularly in simpler tasks that do not entail information manipulation. However, related attentional, monitoring and updating capacities continue to develop with age, revealing continued maturation in adolescence of more complex working memory abilities (Luna et al., 2010).

Developmental fMRI studies of working memory have shown mixed findings (see **Figure 1.6** for meta-analysis). Across studies, there are reports of developmental changes in DLPFC activation in working memory tasks, with additional involvement of the parietal and visual cortices (Geier, Garver, Terwilliger, & Luna, 2009; Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002; Olesen, Macoveanu, Tegner, & Klingberg, 2006; Scherf, Sweeney, & Luna, 2006). However, there are discrepant reports in the literature (Simmonds, Hallquist, & Luna, 2017), with findings of increased activity across the delay period in children and adolescents compared to adults (Geier et al., 2009), reports of the opposite pattern, with adults showing more activity than children, (Klingberg et al., 2002; Kwon et al., 2002; Olesen et al., 2006), as well as inverted U-shaped developmental trajectories, with maximal activity for adolescents (Geier et al., 2009; Scherf et al., 2006). Simmonds et al. (2017) found evidence for continued improvements in performance in working memory in the antisaccade task into the early 20s. Behavioural improvements in accuracy were associated with event-related increases in encoding/retrieval activity in the visual cortex between childhood and adulthood. Decreases in sustained maintenance activity in executive regions were observed from childhood through mid-adolescence and were associated with reaction times (Simmonds et al., 2017).

Important developmental differences emerge in the capacity to sustain activation beyond the trial-by-trial level. Studies using a visuo-spatial n-back task demonstrated that activity in the LPFC and parietal cortex increased linearly across ages 7-22 years (Kwon, Reiss, & Menon, 2002; Spencer-Smith et al., 2013), which might be associated with adults' capacity to sustain activation in these regions over more extended periods (Brahmbhatt, White, & Barch, 2010). Developmental differences in sustained and transient cognitive control in relation to memory will be more fully described in **Chapter 2 and 3**.

1.4.1.2 Response inhibition and interference control

Voluntary control of behaviour relies on the ability to supress a response that is irrelevant to the task or goal. A related ability, interference control, is that of ignoring distractions from irrelevant information. Response inhibition has been extensively studied in development using tasks which require participants to inhibit response to competing prepotent responses, which might be reflexive (the antisaccade task) or learned (the Go/No go task). Interference control can be assessed with tasks such as the Flanker or Simon task (see Zanolie & Crone, 2018, for review). Response inhibition capacities in the Go/No go task (Hester, Fassbender, & Garavan, 2004), antisaccade task (Luna, 2009) and Stop-signal task

(Rubia, Smith, Taylor, & Brammer, 2007), are particularly challenging in childhood (Diamond, 2013; Simmonds, Pekar, & Mostofsky, 2008), (H. W. Lee, Lo, Li, Sung, & Juan, 2015) and continue to develop until early-mid adolescence, where adult accuracy and speed are usually obtained (Casey, 2014; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Schel & Crone, 2013; Schel, Scheres, & Crone, 2014). Interference control seems to have earlier changes as it undergoes considerable improvement in childhood between 7 and 10 (Cragg, 2016).

Response inhibition has been associated with activity in the right inferior frontal gyrus (IFG) and DLPFC (Crone & Steinbeis, 2017). fMRI studies employing the Go/No go task, show that adolescents have less activity in the right VLPFC than 18-24 yo adults (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Rubia et al., 2006; Tamm, Menon, & Reiss, 2002), with additional recruitment of the DLPFC (Durston et al., 2006). Studies with the stop-signal task (Rubia et al., 2013, 2007) and the antisaccade task (Luna, 2009) found comparable results.

1.4.2 Developmental trajectories of complex executive functions

Less is known about the development of more complex cognitive control abilities that require the coordination of basic executive functions. While improvements in response inhibition, error monitoring and working memory are typically observed until late childhood and early adolescence, developmental improvements in some more complex cognitive control abilities that have been studied, such as working memory manipulation, delay discounting, emotion regulation and feedback learning are observed throughout adolescence until adulthood.

To the extent that it influences which goal(s) is(are) guiding behaviour, context might particularly impact complex cognitive control abilities which require the coordination of basic executive functions. Developmental studies of cognitive control focusing on basic cognitive functions indicate that PFC has a slow developmental trajectory and is not engaged to the same extent in children and adolescents as in adults (Crone & Dahl, 2012). In contrast, studies of complex cognitive control tasks including monitoring and relational reasoning found that the PFC was engaged to the same extent in participants of different age groups but under different experimental conditions. In one study, positive performance feedback activated the PFC and parietal cortex in early adolescents, while the same regions responded to negative feedback in adults (van Duijvenvoorde, Zanolie, Rombouts, Raijmakers, & Crone, 2008). A similar nonlinear pattern was found in a relational reasoning task in early adolescents, mid-adolescents and young adults (Dumontheil, Houlton, Christoff, & Blakemore, 2010). Increasingly, studies interpret the observed qualitative changes in brain activation as reflecting different *cognitive strategies* to perform tasks efficiently, which points towards flexibility in the engagement of cognitive abilities during adolescence (Crone & Dahl, 2012). **This highlights the importance of investigating context and its impact on performance in complex cognitive tasks, which was the main aim of this dissertation.**

1.4.2.1 Working memory manipulation

In developmental fMRI studies, protracted improvements in working memory have been observed until late adolescence, especially for tasks that require updating, associated with increased recruitment with age of the VLPFC and DLPFC (Crone & Steinbeis, 2017). DLPFC is particularly important for improvements in performance during working memory manipulation (Crone, Wendelken, Donohue, Van Leijenhorst, & Bunge, 2006).

These more protracted developmental patterns might be explained by the fact that when working memory tasks require cognitive operations, such as manipulation of the contents of WM, these can lead to learning compensatory strategies that are unrelated to working memory but continue to develop, such as verbal processing and inhibitory control abilities (Crone et al., 2006; Thomason et al., 2009).

1.4.2.2 Performance monitoring

Performance monitoring is essential for flexibly adapting behaviour in line with a goal. In monitoring studies, participants make a choice and then receive feedback. In adults, monitoring has been associated with the dorsal MPFC, the pre-SMA and the dACC (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Internal and external performance monitoring are already apparent by age 7 and continue to develop as children grow older (Crone & Steinbeis, 2017; Zanolie & Crone, 2018). Another feature that continues to develop into adolescence is the ability to distinguish between different types of feedback (van Duijvenvoorde et al., 2008) Behavioural improvements are associated by increased dACC/pre-SMA activity in the dorsal MPFC and LPFC with age (Crone & Steinbeis, 2017; Zanolie & Crone, 2018).

1.4.2.3 Cognitive flexibility and valued based learning

Cognitive flexibility is typically assessed as performance in task switching paradigms, especially with task with sudden shifts in reward contingencies which are indicated by external feedback (Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015). Probabilistic reversal learning tasks have been used to study cognitive flexibility in adults, where participants learn changes in reward probabilities based on feedback, which elicits positive or negative reward prediction errors (Gläscher, Hampton, & O'Doherty, 2009; Hauser et al., 2014)

In general, cognitive flexibility has been associated with activity in the pre-SMA and inferior frontal junction. There is evidence of improvements in performance until early adolescence (Cepeda, 2001; Crone & Steinbeis, 2017). Most studies have found robust performance improvements in childhood, but less behavioural differences between adolescents and adults (Crone, Zanolie, Van Leijenhorst, Westenberg, & Rombouts, 2008; Hämmerer, Li, Müller, & Lindenberger, 2011).

Neural correlates of reward prediction errors in probabilistic reversal learning tasks have been found in the striatum and ventral MPFC (positive correlations) and dorsal MPFC and AIns (negative correlations) in adults (Gläscher et al., 2009; Hauser et al., 2014). Hauser et al. (2015) found that young and mid adolescents learned more quickly than adults from negative reward prediction errors in a reversal learning paradigm that required cognitive flexibility. Adolescents had increased AIns responses to negative reward prediction errors than adults, with no other differences in other regions such as striatum and ventral MPFC (Hauser et al., 2015). A decline in the influence of negative feedback with age might provide an adaptive advantage in terms of persistence in spite of occasional negative feedback (Hartley & Somerville, 2015).

Positive outcome weighting increases between childhood and adulthood in associative learning tasks (van den Bos, Cohen, Kahnt, & Crone, 2012; van der Schaaf, Warmerdam, Crone, & Cools, 2011). Thus, adolescents lie at the intersection of opposing developmental trajectories and exhibit variable weighting of valenced feedback (Hartley & Somerville, 2015). This asymmetric weighting of positive and negative feedback can optimise performance in accordance to individual task demands and enhance cognitive flexibility. However, it can also contribute to risk-seeking behaviour (Hartley & Somerville, 2015).

1.5 CONTEXT DEPENDENCY OF ADOLESCENT BEHAVIOUR

As was described in **Section 2.2**. of this introduction, adolescents may approach adult-like levels in some cognitive control tasks in neutral contexts, but their performance can be readily disrupted by social and reward related contexts (Crone, 2009; Dumontheil, Apperly, & Blakemore, 2010; Gardner & Steinberg, 2005). Research suggests that adolescents' cognitive control may be more strongly modulated by affective or social context than is observed in adults (Somerville, 2013), in line with dual process theories. Here, I present an overview of two important motivators of adolescent behaviour, contexts of heightened arousal due to the presence of rewards and social information (Hartley & Somerville, 2015).

These topics will be treated in more detail in relation to the studies described in **Chapter 3** (rewards) and **Chapter 4** (social information).

Research on motivation in adolescence has been extensively influenced by cognitive neuroscience models. As such, it focuses on the neural representations of reward, typically using monetary incentives (Braver et al., 2014). In the standard approach, experiments compare adolescents' adult-like performance in cold cognition conditions with disrupted performance in hot cognition conditions (in an affective-motivational context) (Gladwin, Figner, Crone, & Wiers, 2011)

1.5.1 Reward context

Reward sensitivity is a broad construct which tries to capture a person's reactivity to either the presence or manipulation of rewards, and has been operationalised in different experimental paradigms. Delay discounting tasks investigate the preference for later but larger rewards compared to smaller but sooner incentives, other tasks measure how willing participants are to perform risky actions in exchange of rewards, finally some tasks measure performance indices in rewarded and non-rewarded trials. Many paradigms differentiate between the anticipation, outcome or evaluation reward stage and the positive or negative valence of reward processing (Haber & Knutson, 2010).

The majority of developmental studies investigating reward show heightened sensitivity for the anticipation and receipt of rewards during adolescence in affective tasks, when emotions are involved or peers are present (Cauffman et al., 2010; Ernst et al., 2006; Figner et al., 2009; Galván, 2013; Van Leijenhorst et al., 2010). This sensitivity goes in parallel with increased levels of available dopamine during this stage, which has been suggested in animal and human studies (Luciana & Collins, 2012; Spear, 2000). During adolescence, dopaminergic modulation of incentive processing circuits is maximally activated biasing the dynamic interactions within subcortical–cortical neural circuits (Braver et al., 2014).

1.5.1.1 Neural correlates of reward sensitivity

Heightened sensitivity to reward in adolescence is underpinned by sensitised VS and OFC during this period (Andersen, Dumont, & Teicher, 1997; Brenhouse, Sonntag, & Andersen, 2008). Blood oxygen level dependent (BOLD) responses to reward in the ventral striatum in adolescents are greater than what is observed in children and adults (Casey, Jones, & Somerville, 2011; Galvan et al., 2006), who also have exaggerated prediction error learning signals (Cohen et al., 2010). As a result, socio-affective information is more salient and exerts a disproportionately strong modulation of decisions, actions and regulation in adolescence (Blakemore & Mills, 2014; Casey et al., 2010; Spear, 2000).

In adults, a meta-analysis of 142 fMRI studies in adults identified core regions involved in reward processing including the NAcc, caudate, putamen, thalamus, OFC, bilateral AIns, ACC and posterior cingulate cortex (PCC), alongside regions that are typically involved in cognitive control such as the PFC and inferior parietal lobule. The NAcc was insensitive to either stage or valence or reward. Positive rewards activated the medial OFC and PCC, and negative rewards were associated with ACC, AIns, and LPFC. In terms of reward stages, anticipation was associated with ACC, AIns, and the brain stem. Reward outcome was associated with the NAcc, medial OFC and amygdala (Liu, Hairston, Schrier, & Fan, 2011) .

Following a similar methodology, Silverman et al. (2015) conducted a meta-analysis of 26 reward-related studies with adolescent participants. Their results found that adolescents activate a similar network of regions to adults, including ventral and dorsal striatum, AIns, and PCC. In terms of stages, adolescents were more likely to activate the AIns in anticipation compared to outcome, and the putamen and amygdala in the opposite contrast. Adolescents showed increased activation likelihood for PCC and VS for positive relative to negative reward valence (Silverman, Jedd, & Luciana, 2015). Developmental differences between adolescents and adults were observed. Adolescents had increased likelihood for activation in limbic, frontolimbic and striatal regions relative to adults. In addition, adults were more likely to activate frontal and parietal regions in reward processing than adolescents (Silverman et al., 2015).

1.5.1.2 Cognitive control in the context of reward

A handful of studies have investigated the impact of extrinsic rewards (generally monetary incentives) on adolescents' performance and neural activity. Geier et al. (2010) studied the effects of monetary incentives on response inhibition using the antisaccade task. They found an enhancement effect on performance in mid to late adolescents (13 – 17 yo), but not in adults (18 – 30 yo). In terms of neural correlates in an event-related fMRI design, adolescents had showed reduced VS activity when assessing the cue, but increased preparatory activity for reward vs non-rewarded trials compared to adults in the frontal cortex along the precentral sulcus (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010).

In a follow up study, which included a child sample as well, Padmanabhan et al. (2011) found general age improvements in performance in the antisaccade task which was enhanced by monetary incentives in children and adolescents, but not adults, when compared to non-rewarded trials. Event-related fMRI results found that children, adolescents and adults recruited similar reward processing regions, including VS and OFC, as well as inhibitory control regions, including frontal eye fields, PPC and PFC. Trial-by-trial rewards were associated with transient increases in striatal regions for adolescents, and

OFC for adults, while children had more activity in prefrontal regions (Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011).

Teslovich et al. (2014) investigated the effects of rewards on a perceptual discrimination task of a cloud of moving dots with low and high incentives (1 vs 5 points) for accurate detection of the direction of motion. Compared to adults, adolescents were slower to make decisions when there were large rewards at stake. This pattern was associated with higher activity in prefrontal and parietal cortices in adolescents, while both age groups exhibited higher activity in the ventral striatum for high vs low rewards. These results suggest that adolescents let more evidence accumulate before making a decision when incentives are high (Padmanabhan et al., 2011).

Paulsen et al. (2015) studied the effects of monetary incentives in inhibitory control performance in the antisaccade task in a longitudinal study including 10 – 22 yo participants. Consistent with previous work with the antisaccade task, they found improved performance with age (Geier & Luna, 2012; Luna et al., 2004), and found individual differences in response to incentives. Reward-modulated cognitive control was supported by activity in the amygdala which interacted with age, having a positive effect on inhibitory control in youth, but detrimental effect in adults (Paulsen, Hallquist, Geier, & Luna, 2015).

Pollak et al. (2014) found that children (9 – 11 years), adolescents (14 -16 years) and adults (25 – 30 years) improved in a cognitive control task in the rewarded trials relative to non-rewarded trials. This improvement was enabled by a shift to a proactive control strategy, and associated with increased and sustained activity in the right lateral PFC. These results indicated continuity in reward-related enhancement of cognitive control from 9 to 30 years of age, in contrast with previous findings (Strang & Pollak, 2014). These findings will be treated in more detail in **Chapter 3**.

1.5.1.3 Delay of gratification

Delay discounting has been assessed with a feedback-learning card task in which participants can choose between immediate high rewards and high long term losses, or immediate low reward with low long term losses (Zanolie & Crone, 2018). Children typically favour immediate rewards, while adults favour the delayed rewards. A developmental shift is seen in adolescents aged 16-18 yo who can delay gratification more than children but do not match adult levels of performance (Cauffman et al., 2010; Hooper, Luciana, Conklin, & Yarger, 2004). Similarly, developmental improvements during adolescence are observed in temporal discounting tasks, where participants choose between smaller immediate rewards and larger delayed rewards. While children are more impulsive and favour the immediate reward, adolescence show an increasing ability to make long term choices (Achterberg, Peper, van Duijvenvoorde, Mandl, & Crone, 2016; Banich et al., 2013; Steinbeis, Haushofer, Fehr, & Singer, 2016).

In fMRI studies, adolescents exhibit more activity in the VS than adults when making immediate choices (Christakou, Brammer, & Rubia, 2011). Connectivity studies reveal that the ability to override impulsive choices of the immediate, but lower, reward, is associated with functional coupling between the ventral MPFC (which is associated with valuing reward) and the DLPFC (which is associated with regulation). This connection strengthens with age (Steinbeis et al., 2016). Increased structural connectivity between the frontal cortex and the ventral striatum is associated with decreased impulsivity, and also strengthens with age (Achterberg et al., 2016; van den Bos, Rodriguez, Schweitzer, & McClure, 2015).

1.5.2 Social context

1.5.2.1 Social information relevance

A major developmental task in adolescence is the transition away from the primary family unit and into extended circles of friends, colleagues, peers and partners. This transition relies on developing and refining the ability to navigate an increasingly complex social world and investing in social relationships. Through increased social interactions, adolescent behaviour is more and more informed by the actions and influences of peers, as well as the potential impact on others (Blakemore & Mills, 2014; Burnett, Sebastian, Cohen Kadosh, & Blakemore, 2011).

During adolescence, social interactions become increasingly important and peer affiliation motivation peaks (Brown, 1990, 2004). Adolescents spend more time interacting with their peers when compared to children and adults. In addition, they exhibit the highest degree of happiness when in the context of their peers and ascribe great significance to the adherence to peer behaviour norms(Dodge & Albert, 2012; Wood, Larson, & Brown, 2009). Taken together with studies on peer influence and conformity, this provides indirect evidence of the preponderant role of social goals in motivating behaviour in adolescence (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011; E. E. Nelson, Leibenluft, McClure, & Pine, 2005). Furthermore, this can be mechanistically explained by the fact that adolescents show especially heightened activation of limbic, paralimbic, and MPFC areas in response to emotional and social stimuli, emotional expressions and social feedback (Chein et al., 2011).

Peers have been shown to significantly influence adolescent behaviour (Brechwald & Prinstein, 2011). In creating opportunities to try out novel experiences, peer relationships are both an important social goal in adolescence and an important determinant of other personal goals). Peers can also promote health behaviours. Heightened sensitivity to peer influence has been evidenced in behavioural and self-report questionnaire studies in early and mid-adolescence (Gardner & Steinberg, 2005; Steinberg & Monahan, 2009). Resistance to peer influence remains constant between the ages of 10 to 14 , increases linearly between the ages of 14 and 18, and plateaus again between the ages of 18 and 30 (Steinberg & Monahan, 2009). Susceptibility to peer pressure, the opposite measure, peaks in early adolescence (around 14 years of age) and decreases through late adolescence (Berndt, 1979; Brown, 1990). In the same line, a study on social influence of risk perception found that young adolescents (12 – 14 years) were influenced more by their peers' ratings than by adult ratings when assessing the risk of different situations, whereas children, older adolescents, young adults and adults were more influenced by adult ratings (Knoll et al., 2015). These studies illustrate that the mere presence, or mention, of peers influences risk perception and increases risk taking in adolescence, even when the peers are not explicitly encouraging any particular behaviour, an effect that is not seen among adults. The study described in **Chapter 4**, aimed to explore basic processes underlying social interactions, and investigated whether differences exist in making social judgements about self, and other and comparing between self and other.

1.6 SUMMARY OF EXPERIMENTAL CHAPTERS

Adolescence is a period of transition in which the protracted development of cognitive control interacts with increased influence of the motivational context. These interactions result in normative increases in motivated cognition, sensation and novelty-seeking, but also maladaptive consequences in which suboptimal engagement of cognitive control result in lack of behavioural regulation. In this chapter, I reviewed the literature on the development of basic and complex cognitive control abilities. In addition, I reviewed the interaction between brain systems supporting cognition and motivation, as an initial step in understanding how engagement of complex cognitive control might be modulated by affectively charged contexts of incentives and social information. This literature review highlighted the need to go beyond instances in which hot contexts might impair behavioural regulation, which has been the focus of adolescent research, to consider more positive outcomes of increased motivation. The investigation of more complex cognitive control tasks, which require the coordination of basic executive functions over more extended periods of time, might allow to more fully characterise the effect of context on cognitive control.

In the following chapters, I describe experiments conducted during my PhD to investigate the development of more complex aspects of cognitive control during adolescence. **Chapter 2 and Chapter 3** focus on transient and sustained aspects of cognitive control related to prospective and working memory, while **Chapter 4** focuses on relational reasoning. All three studies explored how various aspects of context (type of cues, reward and information) influence behaviour and brain activation during cognitive control tasks. The studies were run in adolescent and adult participants, to allow the study of developmental changes in complex cognitive control at the behavioural and brain level.

Chapter 2 describes an fMRI prospective memory study that examined the effect of cue salience on the need to proactively monitor stimuli vs. react to more distinctive cues to implement a delayed intention. Evidence in adults suggests that cue salience can modulate monitoring strategies and enhance prospective memory performance. It was hypothesised that non-salient cues would particularly challenge adolescents, who have more immature monitoring capacities as a result of protracted cognitive control development.

Chapter 3 examines the development of the neural basis of proactive and reactive control in the face of incentives. The study employed a working memory task and manipulated the reward context, on a trial-by- trial or run-by-run basis. This chapter compares the neural correlates of sustaining cognitive control throughout blocks with additional transient reaction to individual trials in the presence and absence of monetary incentives. This manipulation has been shown to enhance proactive control in adults. It was hypothesised that, due to reward-responsiveness in adolescence to reward, their cognitive abilities would be particularly modulated by incentives, with developmental changes in these neural correlates.

Chapter 4 investigates whether manipulation and integration of information in a relational reasoning task was sensitive to the type of information, in particular, whether making judgements in the social domain elicited specific brain activations compared to making judgements in the non-social domain. It was hypothesised that general developmental improvements in relational reasoning would be observed in line with results from a similar behavioural study. With evidence from an adult study of separable involvement of frontoparietal networks for relational reasoning and social brain networks for social information, it was predicted that a similar dissociation pattern would be observed in adolescence.

2 PROSPECTIVE MEMORY IN ADOLESCENCE AND ADULTHOOD: IMPACT OF CUE SALIENCE

Abstract

PM is the ability to remember to perform an intended action after a delay. FMRI studies in adults have associated PM with activity in the RLPFC, including BA 10, in addition to other frontoparietal regions. There are a few behavioural studies investigating event-based PM in adolescence, with mixed evidence regarding further behavioural development after age 13. To our knowledge, there are no fMRI studies of PM in adolescence, which could help characterise development, especially considering that frontoparietal regions exhibit protracted functional and structural development until adulthood. In this study, we compared changes in PM performance and associated sustained and transient neural correlates in 28 typically developing adolescents (12-17 years) and 19 adults (23-30 years). In addition, we investigated the impact of cue salience on event-based PM. In the ongoing task (OT task), participants had to indicate the relative position of a triangle compared to another shape. In a small percentage of trials (PM task), participants had to remember to press a different key if both shapes were the same colour (salient cue condition) or one chess knight move away (non-salient cue condition).

There was behavioural evidence for improved performance for prospective memory trials across cue salience conditions between adolescence and adulthood. Further, we documented reaction time costs for the ongoing trials, which were highest for the low salience cue condition. These performance costs did not vary between age groups.

A mixed block/event-related fMRI design was employed to explore neural correlates of PM in adolescence and adulthood. Intention maintenance was associated with sustained activity in the frontoparietal network, including bilateral RLPFC, with similar patterns across salience levels. PM trials recruited additional transient activity in the frontoparietal network, as well as in medial regions, including preSMA, ACC and precuneus. Adolescents and adults had similar patterns of hemodynamic changes.

The study provides evidence, for the first time, of shared similar frontoparietal activation for implementing intentions after a delay in adolescence and adulthood.

2.1 INTRODUCTION

PM enables the execution of intended actions after a delay, e.g. remembering to respond to an email after reading this chapter (Meacham & Singer, 1977). PM is a multiphase process where each step is associated with underlying executive functions: 1) intention formation (planning), 2) intention retention/maintenance (retrospective memory), 3) intention initiation (monitoring, switching and inhibition) and 4) intention execution (switching) (Ellis, 1996; Kliegel, Martin, McDaniel, & Einstein, 2002). Event-based PM refers to instances in which the action needs to be performed in response to an event in the environment, such as remembering to send the email when you sit down at your desk (Einstein, Holland, McDaniel & Guynn, 1992). An event-based laboratory task typically embeds a PM task, in which participants are instructed to do a different action in response to a target cue, in an ongoing task, which could require, for example, classification of stimuli. Event-PM can be split into two components: cue identification (e.g., the computer, in this real-life example, or same-colour stimuli, in an experimental task) and intention retrieval, (e.g. what to do in response to the cue, i.e., send email, or press different key) (Simons, Scholvinck, Gilbert, Frith, & Burgess, 2006).

According to the Multiprocess Framework (McDaniel & Einstein, 2000), PM is supported by both strategic monitoring, which includes top-down processes of intention maintenance and monitoring to detect a PM cue (Guynn, 2003; Smith, 2003), and spontaneous retrieval associated with bottom-up processes (McDaniel and Einstein, 2007; Scullin et al., 2013) in which intentions “pop to mind” (McDaniel and Einstein, 2007; Moscovitch, 1994). The extent to which individuals rely on strategic monitoring or spontaneous retrieval depend on task factors that impact intention initiation and execution phases, such as focality, valence and salience of PM cues, the cognitive load and the importance of the ongoing task, as well as individual factors such as cognitive capacity and personality traits (Cona, Scarpazza, Sartori, Moscovitch, & Bisiacchi, 2015; Einstein et al., 2005).

Detecting cues that are non-focal, non-salient or less important, is dependent on proactive engagement of preparatory attentional processes, which are resource consuming, but lead to monitoring of the environment for PM cues (Einstein et al., 2005; McDaniel & Einstein, 2000; McDaniel, Umanath, Einstein, & Waldum, 2015b). The “PM task interference effect”, the slowing of ongoing task RTs when a PM task is embedded, might reflect redistribution of cognitive resources from ongoing task performance to PM cue monitoring (Einstein et al., 2005; Smith, 2003). In contrast, PM targets that are focal, salient or important might encourage spontaneous, automatic retrieval which does not load on cognitive demands and relies on reactive control triggered by the cue. Scullin and colleagues (2013) have considered the “Dynamic Multiprocess Framework” which contemplates that strategic monitoring and spontaneous retrieval could be both recruited in the same PM task, but at different times and/or in distinct contexts. Thus, the degree of PM interference is sensitive to the context of both the cue and the ongoing task and can be manipulated experimentally. Here we investigated the effects of manipulating the salience of a non-focal cue on strategic monitoring mapped into proactive and reactive cognitive control processes (Braver 2012; McDaniel et al., 2013).

2.1.1 PM in Adolescence

Age related differences are apparent in PM performance across the lifespan, where the majority of studies to date have focused on childhood improvements and aging impairments. Cross-sectional studies using the same experimental task for all age groups have found evidence for an inverted U-shape function in performance, where the peak is achieved by adolescence and maintained through early adulthood (Kliegel, Mackinlay, & Jäger, 2008; Zimmermann & Meier, 2006, 2010; Zöllig et al., 2007). Studies in early childhood have traditionally employed age-specific tasks. By age 4 (and perhaps earlier) PM capacity emerges (Kvavilashvili et al., 2001) and continues to increase during preschool years (Ford, Driscoll, Shum, & Macaulay, 2012; Guajardo & Best, 2000; Kliegel & Jäger, 2007; Mahy & Moses, 2011; Somerville, Wellman, & Cultice, 1983). In middle childhood, performance continues to improve (Kerns, 2000; Mackinlay, Kliegel, & Mäntylä, 2009; Mäntylä, Carelli, & Forman, 2007; Martin & Kliegel, 2003; Smith, Bayen, & Martin, 2010; Voigt, Aberle, Schönfeld, & Kliegel, 2011). Not many studies have focused on adolescent and young adulthood samples, and the evidence regarding continued development in this age group is mixed. Some studies show further improvement on PM performance in adolescence (Shum, Cross, Ford, & Ownsworth, 2008; Wang, Kliegel, Yang, & Liu, 2006; Bowman et al., 2015). In contrast, some studies do not find strong evidence for development after early adolescence (around 13 years) (Zimmerman and Meier, 2006) with adolescents and adults performing similarly better than children. Data suggests that performance is quite stable in young to mid adulthood (Kliegel, Mackinlay, & Jäger, 2008).

It has been argued that PM tasks that impose greater executive control demands to monitor for the PM cue should particularly tax adolescent performance (Bowman, Cutman and Shum, 2015) and there is evidence that adolescents have poorer PM performance on tasks that have utilised non-focal cues (Altgassen et al., 2015; Wang et al., 2011; Zöllig et al., 2007). In contrast, some studies have suggested that age differences in performance are due to the retrospective component of the task (i.e. remembering what to do when the cue is detected), and not to the PM component (i.e. maintaining the intention in mind), a process which may already be developed by adolescence (Mattli, Zöllig, & West, 2011; Smith, Bayen, & Martin, 2010; Zöllig et al., 2007). Developmental differences in PM performance might be related to an immature ability to sustain cognitive control in adolescence, as it has been suggested that adolescent participants rely more on reactive strategies than do adults (Andrews-Hanna et al., 2011) (for details see **Chapter 3**). This imbalance might impact the ability to monitor for PM cues, as salient and non-salient cues may recruit reactive and proactive control differentially. Here, we directly tested this relationship by manipulating cue salience.

2.1.2 Neural bases of PM

To our knowledge, there are no previous fMRI studies of PM in adolescence. To provide the background for interpreting the developmental results of the current study, here I briefly review different patterns of activation that have been observed in studies with adult participants. Distinguishing between sustained and transient activations provides a link to more general proactive and reactive mechanisms of cognitive control (Braver, 2012).

PM performance is robustly associated to a series of frontoparietal regions in adults including the RLPFC (Burgess, Gonen-Yaacovi, & Volle, 2011; Burgess, Quayle, & Frith, 2001; Okuda et al., 2003; Reynolds, West, & Braver, 2009), posterior parietal and precuneus (Burgess et al., 2011, 2001; Martin et al., 2007; Reynolds et al., 2009), and temporal regions including the hippocampus (Gordon et al., 2011). More generally, other cortical regions are associated with processes that might support PM, including other regions of the PFC, which are involved in executive function and working memory (Ghetti & Bunge, 2012, Owen, 2005), the parietal cortex, which plays a role in retrospective and working memory (Gottlieb & Snyder, 2010) and the temporal cortex, which is key for retrospective memory (Alvarez & Emory, 2006).

2.1.2.1 Sustained activity

FMRI PM sustained activity is assessed by contrasting blocks of uncontaminated trials with blocks that are "contaminated" with an embedded PM task. Specially with PM cues that require strategic monitoring, sustained activity is observed in dorsal frontoparietal regions in the RLPFC (BA 10), which has been the key region associated with PM processes (P. W. Burgess, Dumontheil, & Gilbert, 2007; Burgess, Scott, & Frith, 2003; Gilbert, 2011; Gilbert et al., 2006; Simons et al., 2006), as well as regions that are associated with more general cognitive control processes, DLPFC (BA46), ACC, parietal lobules (BA 7), inferior parietal lobe (BA 40), precentral gyrus, and the frontal eye fields (FEF, BA 6) (Burgess et al., 2001, Rea et al., 2011, Reynolds et al., 2009, McDaniel et al, 2013, Beck et al., 2014).

McDaniel et al. (2015) argue that contextual task features in PM paradigms can encourage participants to actively monitor for the PM cue even when the cue is focal, which is why it is possible that focal PM tasks may show sustained activity. Suggestive of strategic monitoring even for focal cues, there is evidence of sustained increased activity in bilateral PFC, bilateral insula, ACC, and decreased medial RPFC (Gilbert, 2011). There is also evidence for activity in the FEFs and superior parietal lobe which can be considered regions of the top–down attentional network (Kalpouzos, Eriksson, Sjölie, Molin, & Nyberg, 2010), and more general cognitive control parietal areas (Gilbert, 2011; Gilbert, Armbruster, & Panagiotidi, 2012).

2.1.2.2 Transient activity

Non-focal PM trials have been associated with transient activation in the AIns, right inferior parietal cortex, bilateral RPFC, bilateral temporal cortex, left lateral occipital cortex (Gilbert et al., 2009), and bilateral marginal gyrus (Rea et al., 2011). The parietal cortex has been implicated previously in retrieval of intentions in PM, specially BA 40 (Burgess, Gonen-Yaacovi, & Volle, 2011). In line with this observation, there are reports of transient activation in the left inferior parietal gyrus (Rea et al., 2011) and bilateral inferior parietal lobule (Rusted, Ruest, & Gray, 2011). BA 40 has also been implicated in non-focal PM tasks in tasks that made no explicit distinction between sustained and transient processes (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; Cona et al., 2015; Gilbert et al., 2006). In these cases, BA 40 was associated with the maintenance phase of PM (Reynolds, West, & Braver, 2009) as well as retrieval for non-focal tasks only (except see McDaniel et al., 2013). The ACC has also been implicated in non-focal tasks during retrieval (Beck, Ruge, Walser, & Goschke, 2014; McDaniel, LaMontagne, Beck, Scullin, & Braver, 2013; Rusted et al., 2011), and has been recognized as a critical area for PM (Burgess et al., 2011).

In relation to environmental cues, cued (vs self-initiated) PM has been associated with transient activity in more medial aspects of RPFC (as well as activity in the left premotor cortex, left superior temporal cortex, right insula and right occipital cortex) (Gilbert, Gollwitzer, Cohen, Oettingen, & Burgess, 2009). Similarly, Simons et al. (2006) also found activity in the medial RPFC associated with cued conditions. These results suggest that medial RPFC is associated with environmentally driven behaviour (Burgess et al., 2003; Gilbert, Frith, & Burgess, 2005, Gilbert, Simons, Frith, & Burgess, 2006, Gilbert, Spengler, Simons, Frith, et al., 2006; Gilbert et al., 2007).

2.1.2.3 Other regions with overall changes

The anterior insula is frequently activated in non-focal tasks with both sustained and transient activation (Burgess et al., 2001; Simons et al., 2006; Gilbert et al., 2009; Rea et al., 2011; Beck et al., 2014) and in focal tasks (Kalpouzos et al., 2010; Gilbert, 2011). McDaniel et al. (2015) have suggested that the AIns is involved in monitoring for cues but might also increase the salience of the cue in a sustained way (Cona et al., 2015). Activation of the medial lateral PFC (BA9) has also been associated with both focal (Okuda et al., 1998, 2007; Benoit et al., 2011) and non-focal PM (Simons et al., 2006; Hashimoto et al., 2011; Rea et al., 2011). Mc Daniel et al. (2015) suggest BA 9 activation might reflect spontaneous retrieval process of the delayed intention.

2.1.2.4 Neural bases of PM in Adolescence

Neural correlates of PM function in adolescence remain insufficiently investigated (Dumontheil, 2014). A few studies using electrophysiology across the life span report differences with age in behavioural measures of PM and differences in neural EEG activity between children, adolescents and adults (Mattli et al., 2011; Zöllig et al., 2007). Event-related potentials (ERPs) generated in PM error trials have different sources in children and adolescents compared to adults. This suggests that various processes might have contributed to PM errors in younger participants (Mattli et al., 2011; Zöllig et al., 2007). Bowman and colleagues (2015) described development of two key PM ERP components (N300 and parietal positivity) across the whole range of adolescence, comparing 12-13 yo, 14-15 yo, 16-17 yo, and 18-19 yo in an ongoing task of lexical decision contaminated with different coloured font PM stimuli. They did not find age differences for N300 amplitude, but parietal positivity was higher for the youngest compared to the oldest adolescent group, suggesting that cognitive processes associated with parietal positivity, which might be associated with general cognitive control capacities and working memory, are still developing.

2.1.3 The present study

Simons et al. (2006) investigated whether cue identification and intention retrieval components could be separable in terms of brain activation. Despite finding behavioural differences in both accuracy and RTs, they found that both conditions, one with a high cue identification load and a low intentional retrieval load and one with opposite demands, elicited very similar patterns of increased BOLD signal in lateral aspects of RLPFC associated with the contaminated ongoing task, and increased activation of medial aspect of RLPFC, including MPFC, in the uncontaminated ongoing task. Their evidence suggests that lateral BA 10 is associated both with maintenance throughout the ongoing task and retrieval of prospective intentions. Here, we adapted the paradigm designed by Simons et al. (2006) to focus on cue identification and investigated behavioural and neural development of PM between adolescence and adulthood. In this version of the task, we kept intention retrieval demands constant, but manipulated cue salience, to directly investigate proactive and reactive processes in PM. Since the PM cue salience can modulate the degree of strategic, proactive monitoring, we used non-salient and salient PM cues.

As has been extensively discussed in **Chapter 1, Section 1.2.3**, in adolescence there is important development of frontoparietal regions in relation to basic and complex executive functions that have been associated with PM in adults. In particular, protracted development of the RLPFC into adulthood has been documented and associated to cognitive abilities that might be related to PM, such as abstract processing, integration and coordination of information (Dumontheil, 2014; Dumontheil, Burgess, & Blakemore, 2008). These led us to hypothesis that adolescents would show poorer PM performance and associated differences in brain activity compared to adults.

We compared performance for an ongoing task in which participants indicated whether a triangle was left or right of another shape with performance in infrequent PM trials, which required pressing a different key if both shapes were the same colour (salient cue condition), or if they were a chess knight move apart (non-salient cue condition). We employed a mixed block-event fMRI design to investigate sustained and transient changes in BOLD signal associated with intention maintenance across the task block and PM trials execution, respectively.

Our aim was to assess (1) how performance on a task requiring event-based prospective memory develops between adolescence and adulthood, and (2) how neural activity underlying these processes develops between early adolescence and young adulthood, and (3) whether there are separable behavioural or neural patterns for salient and non-salient cues associated with PM trials.

In terms of behaviour, we predicted differences in PM performance with age, with the best performance for adults. We further predicted a cost of PM event-based prospective memory task on the ongoing task in adolescents and adults. We predicted that non-salient PM cues would produce a lower levels of PM performance compared with salient cues (McDaniel & Einstein, 2000), in particular for adolescent participants. In terms of BOLD signal, we expected condition-general activations associated with prospective memory in the RLPFC, dorsolateral PFC and parietal cortex in adults (in line with Simons et al. 2006), and modulation of sustained and transient activity by cue salience. We explored whether adolescents exhibited a different pattern of activation.

2.2 METHODS

2.2.1 Participants

Forty-seven participants took part in the study: 28 adolescents (15 females) between 12 and 17 years old (*M* = 14.6 ± 1.4 (*SD*)) and 19 adults (9 females) between 22 and 30 years old (*M* = 27.1 ± 1.9). Data from two additional adolescents were not included in the analysis as they had less than 3 correct PM trials, and data from one adult participant were discarded due to technical problems with presentation during scanning. Participants were reimbursed £20 and their travel expenses for taking part in the study. This study was approved by the UCL Research Ethics Committee. Adolescent (*M* = 67.2 ± .9 (SE)) and adult (*M* = 65.0 ± 1.7) groups did not differ on estimated t-scores ($t(45) = 1.28$, $p = .246$) on the Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence II (WASI; Wechsler, 2011).

2.2.2 Design and materials

We adapted the shapes task from Simons et al. (2006). Each task consisted of ongoing task trials (OT) and prospective memory (PM) trials with the same intention retrieval demands and either salient or non-salient cues.

There was first an OT only run, and then the two PM conditions occurred in separate runs. In each trial, two coloured shapes, a triangle and another shape, appeared in various positions in a 4 × 4 grid (see **Figure 2.1**). Each shape had one of six possible colours. For OT trials, participants had to indicate whether the triangle shape was located to the left or the right of the other shape. In the salient cue PM condition, if the shapes were the same colour, participants had to press a third key with their thumb (Colour PM). In the non-salient cue PM condition, participants had to press a different key if the shapes were one chess knight's move away from each other (Knight PM). Responses were indicated by pressing one of three buttons on a handheld response box (right index finger = left, right middle finger = right, right thumb = PM trial). Shapes were never the same colour in the Knight PM condition and in the knight configuration in the Colour PM condition, to avoid competing cues and confusion for the participants.

Within each run, the shapes task was administered in five short blocks of approximately 35 s, intercalated with an unrelated X task which was used as an active baseline across all scanning runs. In this task, participants had to alternately press two keys to make a row of

Xs flip between the horizontal and vertical axes as quickly as possible. The inter-trial interval in the X task was varied randomly along a uniform distribution between 0 and 400 ms.

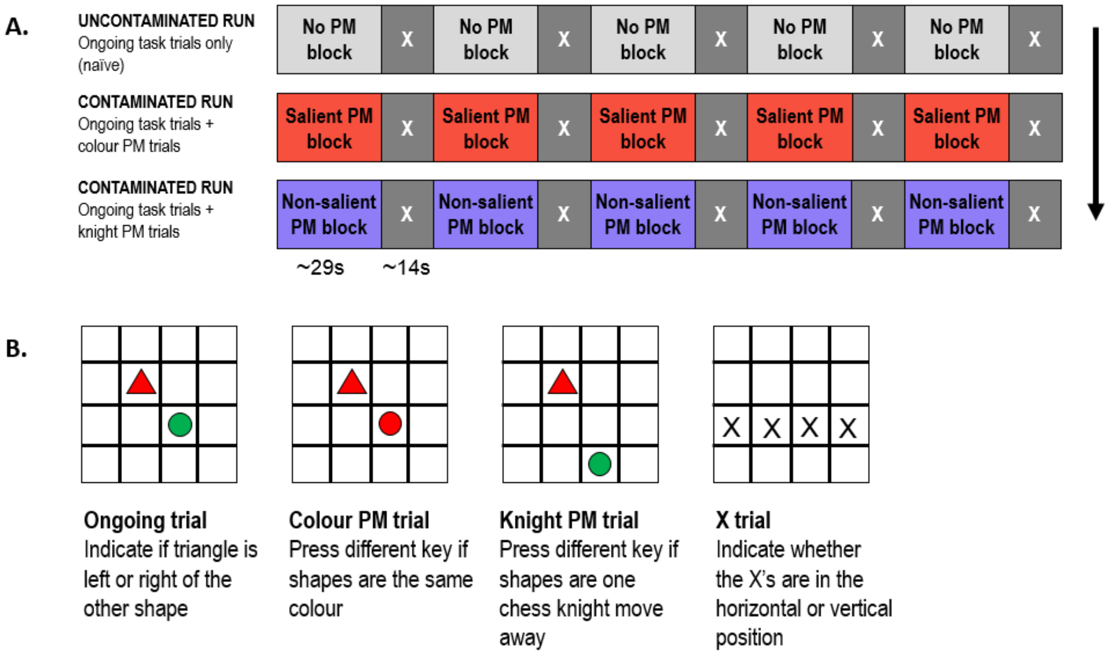


Figure 2.1 *Shapes task*. (A) Experimental design. Participants performed three runs of a visuospatial ongoing task (OT), making judgements regarding the relative location of two shapes in a grid. The first run was uncontaminated. In the second and third runs the OT was contaminated with colour and knight PM trials. (B) Example stimuli. In the Ongoing task trials, participants had to indicate whether the triangle was left or right of the other shape. In Colour PM trials, participants had to press a third key if both shapes were the same colour (salient cue condition). In Knight PM trials, participants had to press a third key if both shapes were a knight move away (non-salient cue condition). In X trials, participants had to indicate whether the Xs were along the horizontal or vertical axis.

2.2.3 Procedure

All runs were preceded by instructions and a practice round. Each trial started with 500 ms of a fixation cross, followed by presentation of the stimulus (the two shapes in the 4x4 grid) for a maximum of 3000 ms, followed by 250 ms of a fixation cross at the inter-trial interval. The tasks were self-paced to prevent instruction rehearsal (Burgess et al., 2003) and ensure variable onset times of the trials. The tasks were administered in three runs. The first run consisted of “uncontaminated” OT trials without any expectation of a PM trial (the PM conditions were not mentioned in the instructions of this first run). Two PM runs followed, one run containing “contaminated” OT trials and Colour PM trials (salient cue), and one run containing “contaminated” OT trials and Knight (non-salient cue) PM trials. The order of the PM runs was counterbalanced between subjects. Each run consisted of blocks of approximately 30 s of the shapes task alternating with around 15 s of the unrelated X task, with a 2s pause between blocks which displayed an indication of the nature of the upcoming block (“Triangle task”, “X task”, “Colour task” or “Knight task”). Given the self-paced nature of the design, participants differed in total number of completed ongoing trials. Blocks of the two PM runs consisted of approximately 18 ongoing trials interspersed with two PM trials per 30 s block, which appeared no earlier than after 10 s of OT, to ensure that the participant would be fully engaged in the ongoing task and to control for the time between PM trials of successive blocks. In total, 10 PM trials were presented per run.

2.2.4 Other behavioural measures

In the scanner, participants completed the Shapes task following the administration of the Reward Task, for an unrelated study, which is reported in **Chapter 3**. Associated with the Reward task study, participants completed computerised versions of the Behavioural Activation Scale (BAS; Carver & White, 1994) and Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia, Ávila, Moltó, & Caseras, 2001).

For the current study, participants completed the (1) Prospective and Retrospective Memory Questionnaire (PRMQ; Smith, Della Sala, Logie, & Maylor, 2000), (2) Future Orientation and Delayed Discounting Scale (FOS; Steinberg et al., 2009), and (3) WEBEXEC, a web based short self-report of executive functions (Buchanan et al., 2010). Participants also completed a computerised simple Go/No Go task (Simmonds, Pekar, & Mostofsky, 2008) in which a “Go” stimulus (green square) is presented in high frequency and requires a rapid, dominant, response, which needs to be inhibited when a less frequent “No Go” stimulus (red square) is shown. Lastly, participants were administered the Forward and Backward Digit Span task in which they were required to listen to a sequence of numbers and repeat them in the same or reversed order.

2.2.5 Image acquisition

Multi-slice T2-weighted multiband (with level 2 acceleration) EPI volumes (Demetriou et al., 2016) with BOLD contrast (44 axial slices with a voxel resolution of 3 × 3 × 3 mm covering most of the cerebrum; TR = 2 s; TE = 45 ms; TA = 2 s) were obtained using a 1.5 T MRI scanner (Siemens TIM Avanto, Erlangen, Germany). Functional images were acquired in three scanning runs lasting approximately 4 min each in which around 125 volumes were obtained (time and number of volumes varied per participant given the self-paced nature of the task). The first 4 volumes of each run were discarded to allow for T1 equilibrium effects. A 3D T1-weighted fast-field echo anatomical image lasting 5 min 30 s was acquired before the acquisition of the functional runs for each participant. The structural scan was preceded by two runs of approximately 8 min of the Reward task, which is reported separately in **Chapter 3**.

2.3 DATA ANALYSIS

2.3.1 Behavioural data

Accuracy and RT data for correct trials were analysed using mixed repeated measures ANOVA on the relationship between within-subjects factors (Task, OT condition, PM condition) of interest and PM performance. All models included Age group (Adolescents versus Adults) as the between-subjects factor. Models were fitted in R (R Development Core Team, 2016) using afex package (Singmann, Bolker, Westfall, & Aust, 2017), and post hoc pairwise comparisons were performed with lsmeans (Lenth, 2016). Where necessary, Greenhouse-Geisser correction was employed for violation of sphericity and Tukey correction for multiple comparisons. Performance costs were calculated as ($RT_{Ongoing} - RT_{PM}$) and ($Accuracy_{Ongoing} - Accuracy_{PM}$) and subjected to correlational analyses with other behavioural measures.

2.3.2 MRI data

2.3.2.1 MRI data preprocessing

MRI data were preprocessed and analysed using SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Images were realigned to the first analysed volume with a second-degree B-spline interpolation to correct for movement during the run. The bias-field corrected structural image was coregistered to the mean, realigned functional image and segmented on the basis of Montreal Neurological Institute (MNI)-registered International Consortium for Brain Mapping (ICBM) tissue probability maps. Resulting spatial normalisation parameters were applied to the realigned images to obtain normalised functional images with a voxel size of 3 x 3 x 3 mm, which were smoothed with an 8-mm full width at half maximum Gaussian kernel.

Realignment estimates were used to calculate framewise displacement (FD) for each volume, which is a composite, scalar measure of head motion across the six realignment estimates (Siegel et al., 2014). Volumes with an FD > 0.9 mm were censored and excluded from general linear model estimation by including a regressor of no interest for each censored volume. No runs met criteria for exclusion (scanning runs with more than 10 % of volumes censored or a root mean square (RMS) movement over the whole run greater than 1.5 mm). Adolescent and adult participants did not differ significantly in mean RMS rotational movement (adolescents = 0.17 rad ± 0.01 (SE), adults = 0.18 rad ± 0.01; *p* = .605). There were age group differences in the mean number of censored scans (adolescents = 0.61 ± 0.16, adults = 0.14 ± 0.08; *p* = .013), and mean FD (adolescents = 0.11 mm ± 0.01, adults = 0.09 mm ± 0.01; *p* = .023), and mean RMS translational movement (adolescents = 0.17 mm ± 0.02, adults = 0.24 mm ± 0.03; *p* = .042).

2.3.2.2 FMRI general linear model

The volumes acquired during the three sessions were treated as separate time series. For each series, the variance in the BOLD signal was decomposed with a set of regressors in a GLM that examined sustained (block-related) and transient (event-related) activity during task performance. Three boxcar regressors represented sustained ongoing task activity during the five blocks of each run: Uncontaminated OT, OT in Colour PM run, and OT in Knight PM run. Two event-related regressors represented transient PM activity in correct trials only: Colour PM, Knight PM. Two additional event-related regressors represented transient activity in 10 randomly selected OT trials in each session, to serve as a comparison for the PM trials. Other regressors included for each run in the GLM were: an event-related regressor representing the start instructions of each block and another representing the end of each block (see Dumontheil, Thompson, & Duncan, 2011); a boxcar regressor representing blocks of the X task, which served as the baseline for comparison across runs; regressors representing censored volumes as covariates of no interest; and the mean over scans. Both block and event-related regressors were convolved with the canonical haemodynamic response function. The data and model were high-pass filtered to a cut-off of 1/128 Hz.

Second-level whole-brain analyses were performed to assess sustained and transient prospective memory-related brain activation. A first set of analyses investigated the sustained effects of maintaining intentions and compared three first-level contrasts: [Uncontaminated OT block – X task block in Uncontaminated run]; [Colour OT block – X task block in Colour run]; and [Knight OT block – X task block in Knight run]. A second set of analyses investigated transient effects in PM trials and analysed the Colour PM trials and Knight PM trials event-related first-level contrasts: [Colour PM trials – OT trials] and [Knight PM trials – OT trials].

These contrasts were then entered into two flexible factorial random-effects analyses using two factors of interest with the design Subject x Age group (Adolescent, Adult) x Run type (OT uncontaminated, OT in Colour PM, OT in Knight PM) or Trial type (Colour PM, Knight PM), modelling Subject as a main effect (to account for the repeated-measure nature of the data) and the Age group x Block type or Age group x Trial type interaction.

Overall OT-related activation (average across three block types) and PM trial activation (average across both trial types), main effects of Block type and Trial type, and the interactions with Age group were determined using the *t* statistic on a voxel-by-voxel basis. Statistical contrasts were used to create SPM maps thresholded at $p < .001$ uncorrected at the voxel level and whole-brain cluster family-wise-error (FWE) correction at $p < .05$ (corresponding to a minimum cluster size of 60 voxels for event-related analyses and 91 voxels for block-related analyses). All coordinates are given in MNI space.

Correlations were run between an average of the contrasts of contaminated runs [Colour OT block – X task block in Colour run]+[Knight OT block – X task block in Knight run] and corresponding RT and accuracy costs, and other behavioural measures: FOS and PRMQ.

2.4 RESULTS

2.4.1 Behavioural results

Accuracy and RTs were analysed using a series of mixed repeated measures ANOVAs (rmANOVAs) which included group as a between-subjects factor and different within-subjects factors as indicated below.

2.4.1.1 Contaminated vs uncontaminated trials

First, the effects of contamination with PM instructions and interactions with age were assessed in ongoing trials only by running mixed rmANOVAs with Condition (Uncontaminated OT, Colour OT, Knight OT) as a within-subjects factor, and Age group as a between-subjects factor. There was a main effect of Condition on OT RT data ($F(1.53,68.89) = 215.41$, $p < .0001$, $\eta^2 = .37$). All post-hoc pairwise comparisons were significant (*p*'s < .001). Participants were fastest for Uncontaminated OT ($M = 580$ ms), followed by Colour OT ($M = 644$ ms), and slowest for Knight OT ($M = 722$ ms). Neither the main effect of Age group ($F(1,45) = 2.35$, $p = .13$) nor the interaction between Age group and Condition ($F(1.53, 68.89) = 0.23$, $p = .73$) were significant (**Figure 2.2.A**).

There was no main effect of Condition on OT accuracy data ($F(1.56, 70.22) = 1.87$, $p =.17$). The main effect of Age group was significant ($F(1,45) = 6.86$, $p = .01$, $\eta^2 = .11$) such that adolescents ($M = 93.9\%$) were less accurate than adults ($M = 96.9$ %). The interaction between Condition and Age group was not significant ($F(1,45) = 1.97$, $p = .17$) (**Figure 2.2.B**).

2.4.1.2 Cue salience effects on PM and OT

Second, the effects of age and cue salience on PM and OT performance were tested by running mixed rmANOVAs including Task (OT vs PM) and Condition (Colour versus Knight) as within-subjects factors and Age group as a between-subjects factor, and ignoring the Uncontaminated OT.

For RT data there was a main effect of Task ($F(1,45) = 212.3$, $p < .0001$, $\eta^2 = .34$): participants were considerably faster for OT trials ($M = 686 \pm 14$ ms) than PM trials ($M = 837 \pm 14$ ms). There was a main effect of Condition ($F(1,45) = 99.1$ $p < .0001$, $\eta^2 = .24$): participants were faster for Colour ($M = 703 \pm 14$ ms) than for Knight ($M = 821 \pm 14$ ms). However, the interaction between Task and Condition was significant ($F(1,45) = 27.5$, $p < .0001$, $\eta^2 = .03$): the difference between Knight and Colour was significantly higher for PM trials ($M_{\text{Knight – Colour}} = 156 \pm 14$ ms) than for OT trials ($M_{\text{Knight – Colour}} = 77 \pm 14$ ms) (**Figure 2.2.A**).

There was a main effect of Age group ($F(1,45) = 5.66$, $p = .02$, $\eta^2 = .08$): adolescents ($M = 793 \pm 18$ ms) were slower than adults ($M = 731 \pm 18$ ms). However, there was a significant interaction between Task and Age group ($F(1,45) = 8.81$, $p = .005$, $\eta^2 = .02$). This was followed up in separate rmANOVAS for each task (PM or OT) with Age group as a between factor. For OT, there was no difference between age groups ($M_{\text{Adolescents - Adults}} = 27 \pm 20$, $F(1,45) = 1.70$, $p = .20$). For PM, adolescents were significantly slower than adults ($M_{\text{Adolescents - Adults}} = 84 \pm 28$, $F(1,45) = 8.74$, $p = .005$, $\eta^2 = .16$). Neither the interaction between Condition and Age group ($F(1,45) = 0.04$, $p = .85$) nor the three-way interaction were significant ($F(1,45) = 0.09$, $p = .77$) (**Figure 2.2.A**).

For accuracy data there was a main effect of Task ($F(1,45) = 152.6$, $p < .0001$, $\eta^2 = .44$): participants were more accurate for OT trials ($M = 95.5 \pm 1.2\%$) than PM trials ($M = 76.5 \pm 1.2\%$). There was no main effect of Condition ($F(1,45) = 2.93$ $p = .09$, $\eta^2 = .01$) (**Figure 2.3**).

There was a main effect of Age group ($F(1,45) = 8.82$ $p = .005$, $\eta^2 = .06$): adolescents ($M = 83.3 \pm 1.2\%$) were less accurate than adults ($M = 88.6 \pm 1.2\%$). There was no significant interaction between Task and Age group ($F(1,45) = 1.94$, $p = .010$, $\eta^2 = .17$). There was no significant interaction between Condition and Age group ($F(1,45) = 0.04$, $p = .85$). Neither the Task by Condition ($F(1,45) = 2.32$, $p = .14$), nor the three-way interactions were significant ($F(1,45) = 0.00$, $p = .96$) (**Figure 2.2.A**).

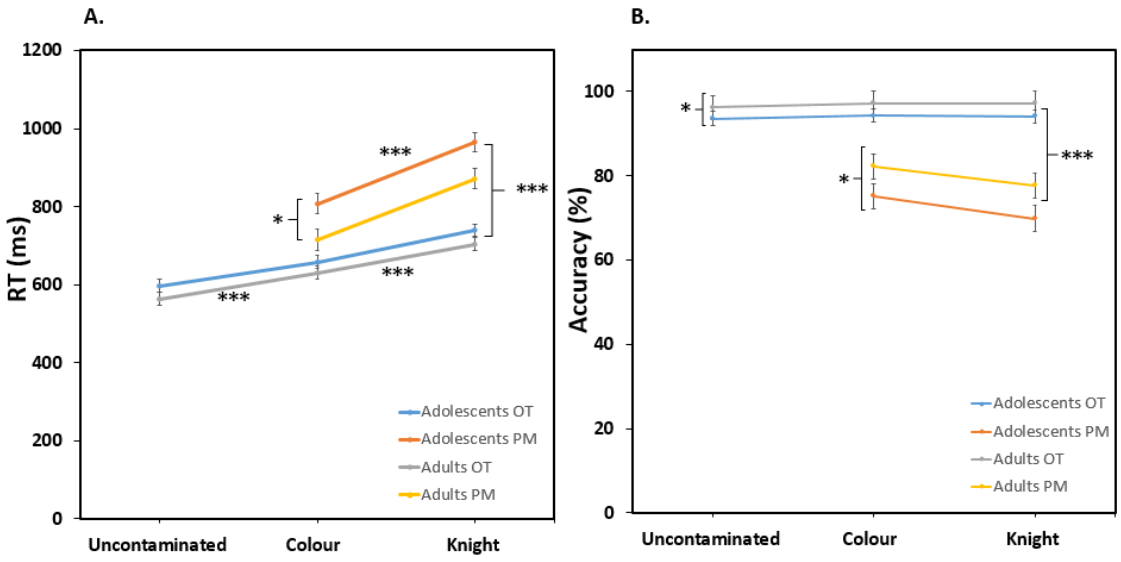


Figure 2.2: *Mean RT (A) and accuracy (B) as a function of Task, Condition and Age group*. Error bars represent *SE*. $^{\dagger}p < .1$, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$ (Tukey corrected). OT = Ongoing task trials, PM = Prospective memory task trials.

2.4.1.3 Other behavioural measures

Adults had greater backwards digit span capacity than adolescents, but the two age groups did not differ on forward digit span capacity, accuracy in No go trials in the Go/No go task or on WEBEXEC scores (**Table 2.1**). Adolescents did not differ in the self-reported levels of prospective memory failures in daily life assessed with the PRMQ (**Table 2.1**). There was no correlation between PRMQ scores and RT costs ($RT_{Ongoing} – RT_{PM}$, *r*(47) = .21, *p* = .15) or accuracy costs ($Accuracy_{Ongoing} – Accuracy_{PM}$, *r*(47) = -.242, *p* = .10). There was a trend for increased future orientation with age (**Table 2.1**), but no correlation between FOS and RT costs (*r*(47) = -.237, *p* = .12) or accuracy costs (*r*(47) = .174, *p* =.25).

Table 2.1: *Behavioural measures.* Summary statistics of measures collected in adolescent and adult participants.

	Adolescents (Mean ± SE)	**Adults (Mean ± SE)**	**Statistics**
PRMRQ (Possible range: 8 – 35)^{a}	22 ± .71	21 ± .65	n.s. (*p* = .14)
FOS (Possible range: 1 – 4)^{b}	2.9 ± .07	3.1 ± .09	t(43) = 1.95, *p* = .057
WEBEXEC (Possible range: 6 -24)^{c}	13.5 ± .47	12.8 ± .73	n.s. (*p* = .45)
Forward digit span total score (Possible range: 1-22)	16.8 ± .65	18.2 ± .80	n.s. (*p* = .18)

Backward digit span total score (Possible range: 1-22)	9.0 ± .58	12.2 ± .75	*t*(44) = 3.46, *p* = .001
No Go accuracy (%)	87.7 ± .02	91.2 ± .02	n.s. (p = .16)

[a] Higher scores indicate more prospective memory failures
[b] Higher scores indicate stronger future orientation
[c] Higher scores indicate more EF failures

2.4.1.4 Exploratory analyses: young, mid adolescents and adults

In post-hoc analyses we explored whether developmental differences would become apparent by focusing on the youngest participants. In the following analyses, we split the planned adolescent group into young (12.34 - 14.05 yo, n = 14) and mid (14.8 – 17 yo, n = 14) adolescents and compared them with the adults and re-ran the analyses reported previously.

2.4.1.4.1 Uncontaminated OT vs Colour OT vs Knight OT

First, the effects of contamination with PM instructions and interactions with age were assessed in ongoing trials only by running mixed rmANOVAs with Condition (Uncontaminated OT, Colour OT, Knight OT) as a within-subjects factor, and Age group as a between-subjects factor.

For RT data, neither the main effect of Age group (*F*(2,44) = 1.71, *p* = .19) nor the interaction between Age group and Condition (*F*(3.07, 67) = 0.30, *p* = .83) were significant.

For accuracy data, the main effect of Age group was significant (*F*(2,44) = 3.88, *p* = .03, η^2 = .12) such that young adolescents (*M* = 93.8 %) were less accurate than adults (*M* = 97.4 %, p = .02). There were no differences between mid-adolescents and young adolescents or adults (all *p's* >.21). The interaction between Condition and Age group was not significant (*F*(3.12,68.65) = 0.19, *p* = .91).

2.4.1.4.2 Colour PM vs Knight PM

Second, the effects of age and cue salience on PM and OT performance were tested by running mixed rmANOVAs including Trial (OT vs PM) and Condition (Colour versus Knight) as within-subjects factors and Age group as a between-subjects factor, and ignoring the Uncontaminated OT.

For RT data, the significant main effect of Age group (*F*(2,44) = 4.05, *p* = .02, η^2 = .11) was driven by the youngest age group. Young adolescents (*M* = 807 ± 22 ms) were significantly slower than adults (*M* = 721 ± 21 ms; *p* = .0181). Mid adolescents (*M* = 758 ± 22 ms) did not differ from either young adolescents or adults (*p*'s > .29). The interaction between Trial and

Age group was significant (*F*(1,44) = 6.33, *p* = .67, η^2 = .03): the difference for Young adolescents between PM and OT was significantly higher than the difference for Adults (M = 85 ± 24 ms, *p* = .0026), with no difference between Mid adolescents and Young adolescents (M = 47 ± 26 ms, *p* = .169,) or Mid adolescents and Adults (M = 37 ± 24 ms, *p* = .2634) (**See Figure 2.3**).The interaction between Condition and Age group was not significant (*F*(1,44) = 0.120, *p* = .88) .

For accuracy PM data, there was no main effect of Age group (*F*(2,44) = 1.29, *p* = .29). The interaction between Condition and Age group was not significant. (*F*(2,44) = .38, *p* = .69).

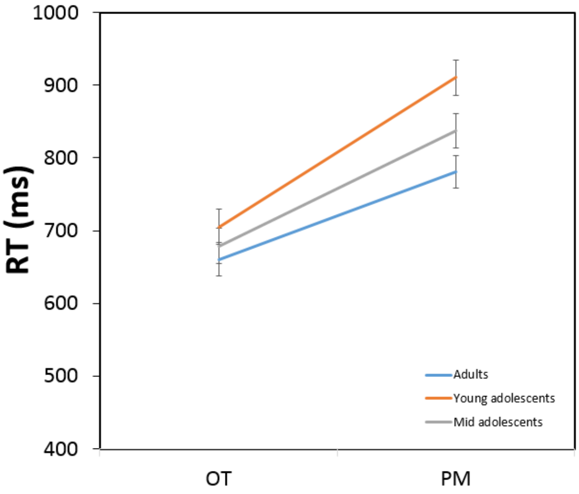


Figure 2.3: *Mean RT as a function of Task and Age group (Young adolescents, Mid adolescents and Adults)*. Error bars represent *SE*. OT = Ongoing trials, PM = Prospective memory trials.

2.4.2 Neuroimaging results

2.4.2.1 Sustained effects

2.4.2.1.1 Colour OT blocks

Compared to the Uncontaminated run, Ongoing task trials in the Colour run were associated with BOLD signal in a right lateral prefrontal cluster in the middle frontal gyrus extending rostrally into the frontal pole. There was activation in the left occipital fusiform gyrus. The other observed clusters were bilateral and located in the anterior insula/frontal operculum, in the inferior parietal lobules and along the medial wall in the pre-SMA, inferior frontal gyrus. No age effects were observed (**Table 2.2, Figure 2.4.A**).

2.4.2.1.2 Knight OT block

Compared to the Uncontaminated run, Ongoing task trials in the Knight run exhibited a similar but stronger pattern of activation than the Colour condition contrast described previously. There was greater overall activation, strong bilateral occipital activation and an additional cluster in the left precentral gyrus, and a more dorsal aspect of the middle frontal gyrus. No age effects were observed (**Table 2.2, Figure 2.4.B**).

2.4.2.1.3 Comparison between salient and non-salient cues

Contrasting Knight OT with Colour OT revealed higher posterior activation of bilateral superior and inferior parietal lobule. The opposite contrast revealed higher activation in bilateral angular gyri, left supramarginal gyrus and a cluster in the superior medial frontal cortex (**Table 2.2, Figure 2.4.C and 2.4.D**).

Table 2.2. *Sustained fMRI results across age groups*. Coordinates and *t* scores are listed for regions showing a significant difference in sustained BOLD signal for [Colour OT block > Uncontaminated OT block], [Knight OT block > Uncontaminated OT block], and the comparison between the two. Region labeling was done using automatic anatomical labeling (Tzourio-Mazoyer et al., 2002). BA labeling of peak of activations was done using MRIcron. L/R = left/right hemisphere. [a] Voxels are significant at $p_{FWE} < .05$ at the voxel level. [b] Clusters are significant at $p_{FWE} < .05$ at the cluster level, with a cluster-defining threshold of $p < .001$ uncorrected at the voxel level.

Region	L/R	Extent	t-score	x	y	z	BA
Colour OT > Uncontaminated OT							
Insula	R	1111[b]	8.21[a]	33	26	2	47
Inferior frontal gyrus (operculum)	R		7.16[a]	42	8	29	44
Middle frontal Gyrus	R		5.82[a]	39	2	53	6
Pre-SMA	R	218[b]	6.09[a]	6	20	50	8
Inferior parietal lobule	L	505[b]	5.90[a]	-45	-37	50	40
Superior parietal lobule	L		5.32[a]	-27	-64	56	7
Inferior parietal lobule	R	546[b]	5.64[a]	33	-55	53	7
Supramarginal gyrus	R		5.26[a]	45	-34	44	40
Insula	L	147[b]	5.45[a]	-30	26	-1	47
Cerebellum	L	186[b]	4.99[a]	-6	-79	-19	
Cerebellum	L		4.87[a]	-27	-73	-22	
Knight OT > Uncontaminated OT							
Inferior parietal lobule	L	1515[b]	10.56[a]	-45	-37	47	40/2
Superior parietal lobule	L		9.92[a]	-15	-67	56	7
Middle occipital gyrus	L		6.81[a]	-27	-70	29	19
Supramarginal gyrus	R	1944[b]	9.90 [a]	39	-37	44	40
Superior parietal lobule	R		9.26 [a]	27	-64	53	7
Middle occipital gyrus	R		5.87 [a]	33	-79	14	19
Insula	R	1703[b]	9.79 [a]	33	26	2	47

Precentral gyrus	R		9.19[a]	45	8	29	44
Middle frontal gyrus	R		6.54[a]	33	2	59	6
Inferior frontal gyrus	L	162[b]	7.38[a]	-30	20	-1	47
Pre-SMA	R	295[b]	7.21[a]	6	20	50	8
Inferior frontal gyrus (operculum)	L	189[b]	6.88[a]	-42	5	26	44
Inferior temporal gyrus	R	751[b]	6.75[a]	48	-52	-7	37
Fusiform	L		6.42[a]	-30	-73	-19	19
Cerebellum	L		5.91[a]	-9	-79	-19	
Superior frontal gyrus	L	244[b]	6.29[a]	-24	2	62	6.
Colour OT > Knight OT							
Mid cingulate cortex	L	365[b]	4.83[a]	-12	-49	35	23
Mid cingulate cortex			3.97	0	-22	41	23
Mid cingulate cortex	R		3.93	12	-46	35	23
Angular gyrus	R	191[b]	4.83[a]	57	-58	35	39
Angular gyrus	R		4.07	45	-67	50	39
Superior frontal gyrus	L	108[b]	4.68	-15	41	47	1
Angular gyrus	L	159[b]	4.62	-45	-70	44	39
Supramarginal gyrus	L		3.71	-60	-55	32	40
Knight OT > Colour OT							
Precuneus	L	2067[b]	7.37[a]	-15	-67	56	7
Superior parietal lobule	R		6.79[a]	18	-61	56	7
Supramarginal gyrus	R		6.60[a]	36	-40	44	40
Superior Frontal gyrus	R	95[b]	4.63	24	8	56	6/8

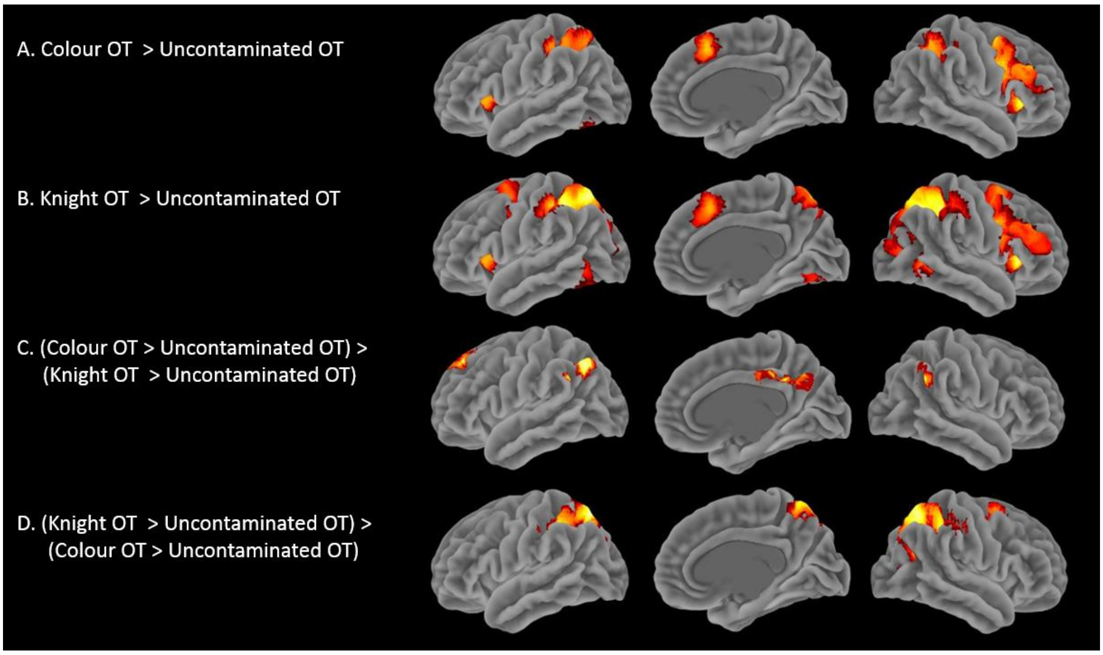


Figure 2.4. *Sustained fMRI results across age groups*. Regions showing increased BOLD across blocks are rendered on the SPM12 mesh template. From left to right: lateral view of the left hemisphere, and medial and lateral view of the right hemisphere.

2.4.2.2 Transient effects

2.4.2.2.1 Colour PM > OT trials (salient PM cue)

Colour PM trials were associated with frontal activation in the left inferior and middle frontal gyrus, and bilateral anterior AIns. There was activation in the mid cingulate cortex and SMA, as well as activation along the precentral and postcentral gyri bilaterally, extending into the supramarginal gyri, and the right superior temporal sulcus (See **Table 2.3** an**d Figure 2.5.A**).

2.4.2.2.2 Knight PM > OT trials (non-salient PM cue)

Strong widespread activity was seen in frontal, parietal and some temporal regions associated with non-salient PM cue retrieval. A more conservative threshold of p < .0001 was used to differentiate the clusters observed in this contrast (See **Table 2.3** and **Figure 2.5.B**).

There was bilateral activity in the frontal poles (RLPFC) which extended posteriorly into inferior and middle frontal gyri including DLPFC and VLPFC. There was activation of bilateral AIns. In the medial wall, there was activation that extended from anterior cingulate cortex through SMA into midcingulate cortex... In the parietal lobes, bilateral superior and inferior activation was observed, as well as precentral and postcentral gyri activation. There was activation of the right middle temporal gyrus, as well as subcortical structures: caudate and putamen (See **Table 2.3** and **Figure 2.5.B**).

2.4.2.2.3 Comparison between salient and non-salient cues

No regions survived in the contrasts examining the impact of salience.

2.4.3 Sustained and transient overlap

A series of regions showed an influence of the PM context (block contrasts) as well as greater activation during PM trials, including left AIns, superior parietal lobule (BA 40) and right superior frontal (BA 44) and DLPFC (BA 46), and, to a minor extent, a middle region in the ACC and SMA.

Table 2.3. *Transient fMRI results across age groups*. Coordinates and *t* scores are listed for regions showing a significant difference in transient BOLD signal for Colour PM trials, Knight PM trials, and the comparison between the two. Region labeling was done using automatic anatomical labeling (Tzourio-Mazoyer et al., 2002). BA labeling of peak of activations was done using MRIcron. L/R = left/right hemisphere. [a] Voxels are significant at $p_{\mathrm{FWE}} < .05$ at the voxel level. [b] Clusters are significant at $p_{\mathrm{FWE}} < .05$ at the cluster level, with a cluster-defining threshold of $p < .001$ uncorrected at the voxel level.

Region	L/R	Extent	t-score	x	y	z	BA
Colour PM trials > Colour OT trials							
Postcentral gryus	L	1489 [b]	7.45[a]	-60	-22	41	3
Precentral gyrus	L		6.61 [a]	-33	-22	71	6
Postcentral gyrus	L		6.13 [a]	-48	-31	59	3/2
Insula	R	158 [b]	5.76 [a]	36	17	-1	48
Postcentral gyrus	R	574 [b]	5.60 [a]	57	-22	53	3
Postcentral gyrus	R		4.48	60	-16	32	43
Postcentral gyrus	R		4.43	42	-40	62	2
Mid cingulate cortex	L	274 [b]	4.98	-9	5	38	24
SMA	R		3.99	3	11	62	6
Superior frontal gyrus	R	94 [b]	4.95	33	-7	65	6
Mid temporal gyrus	R	166 [b]	4.84	48	-25	-7	21
Mid temporal gyrus	R		4.47	57	-43	2	22
Precentral gyrus	R	80 [b]	4.76	57	11	32	6/44
Middle frontal gyrus	L	99 [b]	4.46	-36	41	29	46
Mid cingulate cortex	L	72 [b]	4.23	-12	-28	47	23
SMA	R		3.96	9	-22	47	23
Knight PM trials > Knight OT trials							
Insula	R	3243[b]	7.82 [a]	39	17	-1	48
Mid temporal gyrus	R		6.87 [a]	57	-40	2	22

Middle frontal gyrus	R		6.61[a]	42	50	8	46/10
Postcentral gyrus	L	1476[b]	6.14[a]	-45	-28	50	3
Postcentral gyrus	L		6.01[a]	-57	-19	35	48
Precentral gyrus	L		5.25	-33	-22	71	6
Mid cingulate cortex	R	1379[b]	6.35[a]	9	29	32	32
Mid cingulate cortex	L		5.52[a]	0	-10	32	23
SMA	R		4.87	6	17	56	6
Insula	L	700[b]	9.40[a]	-33	20	-7	47
Insula	L		5.44[a]	-36	-1	2	48
Middle frontal gyrus	L	444[b]	5.59[a]	-33	47	17	5
Middle frontal gyrus	L		5.13	-39	32	35	46
Precentral gyrus	L		4.70	-45	5	44	6
Fusiform gyrus	R	269[b]	5.27	24	-58	-16	37
Vermis			3.83	3	-67	-28	
Caudate	R	100[b]	5.61[a]	12	2	17	
Thalamus	R		3.84	9	-19	8	
PM trials > Contaminated OT trials **Youngest adolescents > Adults**							
Superior occipital gyrus	R	75[b]	4.77	21	-82	17	19
Precuneus	R		4.29	18	-70	47	7
Fusiform gyrus	R	57[b]	4.34	36	-52	-13	37

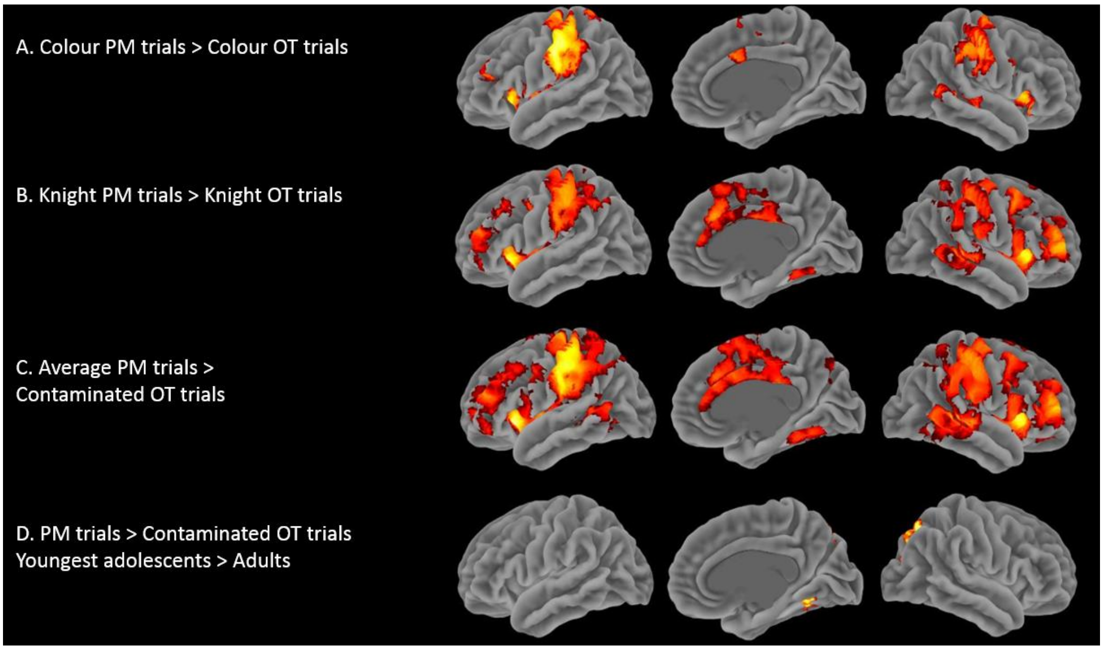


Figure 2.5. *Transient fMRI results across age groups*. Regions showing increased BOLD across blocks are rendered on the SPM12 mesh template. From left to right: lateral view of the left hemisphere, and lateral and medial view of the right hemisphere.

2.4.3.1 Developmental differences

Adolescents and adults did not differ in the patterns of activation in any of the contrasts. Given some indication of changes at earlier ages in a previous EEG report (Bowman et al., 2015), and the behavioural differences we observed, we decided to run additional exploratory analysis comparing brain activity of the youngest adolescent group (12.34 - 14.08 yo) with the adult group. There were no age differences for Contaminated OT trials. PM trials were associated with increased activity in the young adolescents compared to the adults in right occipital clusters suggestive of the need to recruit extra regions to support detection of PM cues and execution of PM trials in this condition (**Table 2.2, Figure 2.3.D**).

2.4.3.2 Covariate analyses

Whole-brain analyses were performed to investigate correlations between the self-reported measure of FOS and PRMQ and BOLD signal during contaminated trials (averaging across cue salience). No correlations were observed.

2.5 DISCUSSION

The current study examined PM performance and associated neural correlates in adolescents and adults. In addition, we investigated the impact of cue salience on event-based PM, in a non-focal task, where the delayed intention was unrelated to the OT. The study assessed sustained effects associated with maintaining PM intentions across blocks, and transient effects associated with PM trial execution. We explored, for the first time, whether developmental fMRI differences exist between adolescents and adults.

2.5.1 Behavioural results

2.5.1.1 Performance across age groups

2.5.1.1.1 Intention maintenance (OT trials)

While PM performance is measured at the PM trial level, OT trials can be informative of potential interference effects. Indeed, intention maintenance throughout contaminated runs was associated with slower RTs, but similar accuracy, for OT trials for both adolescents and adults. These RT costs have been well documented in PM paradigms (Massar, Lim, Sasmita, & Chee, 2016) and can been interpreted as evidence for monitoring activities in the context of competition for limited cognitive control resources (Altgassen, Kretschmer, & Schnitzspahn, 2017). An alternative interpretation is that increased latencies can be related to target-checking strategies before and after the ongoing decision (Horn & Bayen, 2015).

2.5.1.1.2 PM execution (PM trials)

Both adult and adolescent participants were slower and less accurate for PM trials than OT trials, in line with similar performance differences observed by Simons et al. (2006). This pattern is consistent with the additional demands of PM trials including cue identification, intention retrieval, inhibition of ongoing task, and branching into subtasks necessary for successful performance.

2.5.1.1.3 Cue salience effects

Monitoring costs and PM execution varied as a function of cue salience, with no evidence of age-specific effects. In the ongoing task, participants were slower for trials contaminated with salient cues, and slowest for trials contaminated with non-salient cues, with no differences in accuracy between conditions. This suggests that non-salient cues had higher intention maintenance demands and more general difficulty that detracted from speed, but not accuracy, performance of the ongoing task. Similarly, in the PM trials, participants were slower for non-salient than for salient cues, with no accuracy differences.

The impact of non-salient cues compared to salient cues on RT was greater for PM than OT. However, it is hard to make a comparison between the two tasks as the mechanisms underlying the impact might be driven by different causes. For OT, non-salient cues arguably require more proactive monitoring than do the salient cues, which could be detected based on more reactive mechanisms of later detection and correction, potentially at the moment of pressing the key response. For PM, in the Knight condition participants potentially had to count number of squares between the shapes and/or do mental rotation of the configuration just to detect the cue, which necessitates longer RT to resolve. It is likely that RT delays for non-salient cues are due to both demands on monitoring for the delayed intention, and additional processing needed to detect the cue. However, our design does not allow us to investigate this and should be explored in future studies.

The current results are in line with reports of strong influence on PM by manipulations surrounding the PM cue (Kliegel et al., 2013; McGann et al., 2005). High salience has been demonstrated to enhance PM in pre-school (Kliegel et al., 2013) and school-aged children (McGann et al., 2005, Mahy et al. 2017) as well as in adults (Brandimonte & Passolunghi, 1994, Einstein & McDaniel, 1990, McDaniel & Einstein, 1993). Here, we demonstrate similar enhancement effects of salient cues for both adolescents and adults.

2.5.1.2 Developmental effects on OT trials

Adolescents were less accurate than adults in the ongoing task for both contaminated and uncontaminated trials, with no effects on RT. These results of general age improvements in accuracy which did not interact with contamination are in contrast with reports of lower accuracy in contaminated OT that has been reported for adolescents compared to adults in a task that manipulated cognitive demands and PM importance (Ward et al., 2005). In their case, age differences between adolescents and adults were only evidenced in the ongoing task with high-demands, and not when the demand were low. Similarly, there are reports of increased accuracy with age between 12 and 19 years in an ongoing lexical decision task (words vs non-words) which was contaminated with the intention of pressing a different button in response to different ink colours (Bowman, Cutmore, & Shum, 2015).

2.5.1.3 Developmental effects on PM trials

PM abilities improved with age: adolescents were both slower and less accurate for PM trials than adults. Previous findings have reported increased PM performance with age between adolescence and adulthood in terms of accuracy (Wang, Kliegel, Yang, & Liu, 2006, Maylor & Logie, 2010) and RTs (Bowman et al., 2015). In contrast, other studies have found studies improvements between childhood and adolescence, with no further maturation in PM after adolescence (Zimmermann & Meier, 2006, Ward, Shum, McKinlay, Baker-Tweney, & Wallace, 2005). Further, performance differences between PM and OT trials were found to be greater for adolescents than adults, which suggests that age differences in PM are not just due to general processing speed difference between the age groups. PM and OT performance are not directly compared in other developmental studies. We believe this analysis is useful to distinguish between general and PM specific improvements in PM ability associated with age and suggest that future studies could benefit from including this analysis.

In summary, across age groups, performance was worse for contaminated OT relative to uncontaminated OT, suggesting cognitive costs associated with maintaining a delayed intention. Low cue salience led to greater monitoring costs in the OT, and had an even greater effect on performance RTs and accuracy in the PM trials, similarly for adolescents and adults. PM trial performance improved across cue salience conditions between adolescence and adulthood. Compared to adults, adolescents had a greater difference in performance between PM and OT, suggesting maturation of some PM specific processes. These findings provide further evidence for continued development of PM and associated processes during adolescence in line with findings of still developing executive resources across childhood and adolescence (Crone & Steinbeis, 2017; Luna, 2015; Dumontheil, 2014).

2.5.2 Neuroimaging findings

2.5.2.1 Intention maintenance

Intention maintenance was associated with sustained activity in regions implicated in PM, with activation in similar regions, but to varying strength, for both salient and non-salient cues. The current findings are robustly aligned with previous findings regarding regions which respond in a sustained fashion in PM task blocks, notably RLPFC, DLPFC, ACC, and inferior parietal lobe (see for a review McDaniel, LaMontagne, Beck, Scullin, & Braver, 2013; McDaniel, Umanath, Einstein, & Waldum, 2015; Reynolds, West, & Braver, 2009). Contamination with salient and non-salient cues which require a continuous internal representation of the delayed intention were associated with sustained higher BOLD signal in the right rostral aspects of the lateral PFC, including BA 46 and extending slightly into BA 10, a key region previously implicated in PM (Burgess et al., 2001, 2003; den Ouden et al., 2005; Gilbert et al., 2009; Momennejad and Haynes, 2012; Okuda et al., 1998; Simons et al., 2006).

In addition, contaminated OT were associated with activation of the DLPFC (BA 46) extending into superior frontal cortex (BA 44) as well as VLPFC (BA 47/45). In the medial wall, there was activity in the ACC associated with maintaining delayed intentions. These results are in line with the increasing recognition of the involvement of more extended frontoparietal networks in PM processes (Bisiacchi et al., 2011; Kalpouzos et al., 2010; McDaniel et al., 2013). Some authors have suggested that, in PM contexts, the DLPFC might be involved in strategic monitoring of more general cognitive control needs, while ventroparietal networks may be associated with bottom-up capture of attention in response to the cue (Beck et al., 2014; Cona et al., 2015; Kalpouzoset al., 2010; McDaniel et al., 2013). Bilateral AIns were also recruited. Activity in these regions has been reported in other PM studies in non-focal tasks (Burgess et al., 2001; Simons et al., 2006; Gilbert et al., 2009; Rea et al., 2011; Beck et al., 2014), suggestive of a role in cue monitoring (Cona et al., 2015; McDaniel, Umanath, Einstein, & Waldum, 2015a). Overall, and in line with previous accounts, activation of DLPFC, bilateral AIns, and superior parietal lobule, may relate to preparatory processes that include maintaining the task set (e.g. instructions for PM trial) in anticipation of cues to enable goal pursuit (Braver, Paxton, Locke, & Barch, 2009; Jiang, Beck, Heller, & Egner, 2015).

As has been described, there was considerable overlap for salient and non-salient cues in regions related to intention maintenance and strategic monitoring, which could be explained by the non-focal nature of the PM task. This has been argued by McDaniel et al. (2015) and is consistent with the fact that behaviourally, both had PM interference costs. However, contamination with non-salient cues did recruit more extensive regions overall, and in particular in the superior parietal lobule (BA 7 and BA 40), which has been implicated in encoding and maintenance/retrieval of PM intentions (Burgess et al., 2001; den Ouden, Frith, Frith, & Blakemore, 2005; Eschen et al., 2007; Gilbert et al., 2009; Hashimoto et al., 2010; Okuda, Gilbert, Burgess, Frith, & Simons, 2011; Poppenk, Moscovitch, McIntosh, Ozcelik, & Craik, 2010; Reynolds, West, & Braver, 2009; Simons et al., 2006). This has been supported by findings of Gilbert (2011) who identified that posterior brain regions might be encoding the content of the delayed intention (i.e. storing appropriate responses) and through functional interactions with the RLPFC, enable the realisation of the PM task.

In summary, maintaining a delayed intention across a block of trials was associated with regions implicated in PM, particularly with the processes of strategic monitoring. Cue salience modulated the extent of recruitment of the PM network and parietal regions associated with proactive control.

2.5.2.2 PM trials

RLPFC exhibited transient changes in reaction to PM trials as has been described in previous fMRI studies which have reported higher activity in RLPFC, when participants either anticipate or encounter PM cues (Burgess et al., 2001; Reynolds et al., 2009; Simons et al., 2006). Across cue salience, PM trials were associated with transient frontoparietal activity, including activation in lateral and medial prefrontal regions including DLPFC and VLPFC, suggestive of reactive recruitment of cognitive control resources to support successful retrieval.

In the current study, there was activation in non-frontal regions including the caudate nucleus, thalamus, medial temporal lobe, and inferior occipital cortex, which are consistent with the results of a study investigating effects of aging in an event-related non-focal PM in adulthood (Peira, Ziaei, & Persson, 2016). The authors interpreted these finding as suggestive of non-strategic processing of PM target detection. While there were differences in RLPFC between high and low salience cues, there were no differences in terms of general retrieval networks. One possibility is that that when the non-salient PM cue appears, there are no increased retrieval demands, since the intention has been maintained. Alternatively, it could be that the low difficulty for the delayed intention, which involved pressing a different button, did not require extensive activation to support it.

Equivalent transient activation for salient and non-salient PM trials was observed in ACC, bilateral AIns, precentral gyrus, middle frontal gyri (FEF), superior parietal lobe, basal ganglia and thalamus and midbrain, results that are strongly in line with transient activations in a non-focal PM task that investigated proactive and reactive strategies (McDaniel et al., 2013). Along with activity in VLPFC (BA 45) and AIns (BA 47), these results might speak to the involvement in bottom-up attention processes captured externally by the PM cue (Cona et al. 2015).

In summary, PM trials recruited frontal regions associated with PM processes as well as more general memory retrieval and bottom-up attention processes.

2.5.2.3 Sustained and transient overlap

The left AIns, right superior parietal lobule, DLPFC and precentral gyri and FEF, as well as middle aspect of ACC exhibited a mixed pattern of sustained and transient differences in BOLD signal as a function of the PM context or PM trials execution. AIns was previously found to show sustained and transient changes in a PM task (Gilbert et al., 2009; Cona et al., 2015; in contrast, see Burgess et al., 2001), suggestive of a role both in sustained task control as well an in increasing the salience of the cue (Cona et al., 2015). McDaniel et al. (2013) also found a mixed pattern of activation in precentral gyrus (BA 44) and FEF in the middle frontal gyrus (BA 6) for a non-focal PM task.

We found a similar pattern of regions showing both transient and sustained changes in activation when studying contextual modulations of proactive and reactive control with the same participants, as described in **Chapter 3**. More generally, these regions have been previously implicated as neural correlates of the DMC (Braver, 2012; Jiang et al., 2015), where temporal dynamic within some regions, in addition of activation of distinct brain networks, would enable the shift between modes of cognitive control. In this more general view, the AIns has been suggested to monitor current control demands and sustain task control, and rostral ACC reactively monitors level of conflict and then signals DLPFC and dorsal ACC to mediate trial-by-trial conflict driven adjustments in control (Jiang et al., 2015). Indeed, the activation observed in the ACC may reflect the detection of a conflict, or competition, between two task goals (OT and PM), as it has been described that by monitoring conflict, the ACC can signal and enact transient adjustments in cognitive processes (Shenhav, Botvinick, & Cohen, 2013). When PM cues are detected, conflict may arise between the goal of continuing to perform the ongoing task and the retrieval of the relevant PM intention followed by execution of the PM response, giving rise to transient activity during PM trial (Hashimoto et al., 2011).

In summary, the fMRI results suggest that proactive sustained attentional monitoring as well as reactive retrieval contribute to successful PM performance.

2.5.2.4 Correlations with behaviour

Given the exploratory nature of the study, we ran a series of correlations between mean brain activation in the contaminated tasks collapsing across cue salience and self-reported scales to explore potential associations.

We did not find differences in self-reported prospective memory failures in real-life settings between adolescents and adults. Some other studies report similar PM performance between adolescents and adults (Zimmermann & Meier, 2006, Ward, Shum, McKinlay, Baker-Tweney, & Wallace, 2005). However, to our knowledge, the PRMQ has only been used in adult populations in the past (Smith, Del Sala, Logie, & Maylor, 2000). Although the PMRQ was piloted in adolescent participants, and the questions were screened for age-appropriateness, further studies could more systematically investigate how suitable the PMRQ is to detect developmental differences. Adolescents scored marginally significantly lower in the FOS compared to adults. These results are in the direction of the pattern typically observed in the literature (Steinberg et al., 2009), in which adults are more oriented towards the future than adolescents. We did not find an association between either PMRQ or FOS and average activity in contaminated runs across cue salience. Future studies could explore whether other measures of individual differences in PM ability are correlated with neural correlates of PM.

2.5.2.5 Developmental differences (exploratory analysis)

We did not find developmental differences in brain activation in the planned analyses between adolescents (12-16 yo) and adults (23-31 yo). We found evidence that behavioural differences were driven by the youngest participants of the adolescent group, which is in line with previous studies that find earlier development in PM performance with a plateau between adolescence and adulthood (Zimmermann & Meier, 2006, Ward, Shum, McKinlay, Baker-Tweney, & Wallace, 2005).

Given that this is the first paper to investigate PM using fMRI in adolescence, we explored age differences between the youngest teens (12-14, n=14) and the adults (n=18). Age differences emerged for PM trials in which young adolescents had higher transient BOLD signal in occipital regions. These results suggest that early adolescents between 12 and 14 recruit additional regions for PM trials in areas associated with visuospatial processing as well as movement planning. Post-hoc analyses indicate that developmental differences might be driven by the youngest adolescent group. Future studies should explore developmental patterns in a broader sample, including children.

2.5.3 Limitations

It should be noted that PM tasks such as the one in the present study, are also dual tasks paradigms which require participants to execute the ongoing task and the PM task in parallel. In this view, behavioural and neural correlates might be reflecting general dual task demands and associated cognitive processes. There is also a cognitive branching component, in which participants disengage momentarily from the ongoing task and switch to the internal representation of the PM intention. These explanations are in line with other proposed interpretations of RLPFC function (Hyafil, Summerfield, & Koechlin, 2009; Koechlin, Ody, & Kouneiher, 2003) and ultimately PM processes cannot be entirely dissociated from branching performance processes with the current design.

There was evidence for strategic monitoring for both salient and non-salient cues. This might be due to the fact that the current paradigm employed a non-focal PM task, which has been shown to elicit strategic monitoring in previous studies (see McDaniel et al. (2015) for a review). Alternatively, as has been identified by McDaniel et al. (2015), isolating spontaneous retrieval is difficult in traditional laboratory settings. Contextual factors in the way experiments are set up and delivered might encourage monitoring even with focal cues. Monitoring which responds to instruction framing or high number of PM target cues could mask discovery of bottom–up spontaneous retrieval processes.

2.6 CONCLUSION

The aim of this study was to investigate the neural correlates of prospective memory in adolescence with fMRI for the first time. In addition, we sought to determine whether cue salience would modulate behavioural performance or sustained/transient associated brain activation associated with increased demands for strategic monitoring. The study found behavioural evidence for improved prospective memory performance with age, as adolescents made more errors and were slower to respond that adults in PM trials. High cue salience was shown to limit monitoring costs in OT and enhance PM to the same extent in both age groups.

The current results provide evidence that PM is relying on multiple dissociable transient and sustained cognitive processes which are supported by a distinct set of brain regions, and that adolescents and adults exhibited similar patterns of hemodynamic brain changes. Sustained activation was observed in frontoparietal regions typically associated with intention maintenance in prospective memory studies, including RLPFC and parietal cortex, and did not vary largely as a function of cue salience. There was also sustained activation of regions more generally involved in cognitive control, including in the dorsal frontal cortex and AIns. Transient activation was observed in RLPFC, ventral and dorsal frontal cortex and peaks in temporal and parietal regions. The findings presented here support development of prospective memory in adolescence and show evidence, for the first time, that adolescents recruit similar frontoparietal networks that have been associated with prospective memory in adults, with preliminary findings that early adolescence may be associated with increased precentral and occipital activation during PM trials in a non-salient cue condition compared to adults.

3 PROACTIVE AND REACTIVE CONTROL OF WORKING MEMORY IN ADOLESCENCE AND ADULTHOOD: IMPACT OF REWARD

Abstract

Cognitive control allows the coordination of cognitive processes to achieve goals. Control may be sustained in anticipation of goal-relevant cues (proactive control) or transient in response to the cues themselves (reactive control). While both strategies are necessary for goal pursuit, adolescents typically exhibit a more reactive pattern than adults in the absence of incentives, the context in which this dissociation is frequently studied. We aimed to investigate how reward modulates temporal engagement of cognitive control in adolescence and adulthood using both behavioural and neural measures. We compared changes in performance in a letter-array working memory task as a function of reward in 30 typically developing adolescents (12-16 years) and 20 adults (23-30 years). After a Baseline run without rewards, participants performed a Reward run in which they expected some trials (50%) to be monetarily rewarded. A mixed blocked and event-related functional magnetic resonance imaging design enabled separation of transient and sustained neural activity associated with reactive and proactive cognitive control respectively. Participants' accuracy was greater in trials of the Reward run than the Baseline run, indicating engagement of proactive control. Overall accuracy increased with age. Across age groups, participants were faster for the No reward trials of the Reward run than of the Baseline run, indicating engagement of proactive control, and even faster for Reward trials, suggesting an additional reactive engagement of cognitive control. Increased sustained activity in the bilateral anterior insula, right dorsolateral prefrontal cortex and posterior parietal cortex was observed in both adolescents and adults in the Reward run compared to the Baseline run. Widespread transient activation was observed in bilateral insula, lateral prefrontal cortex, posterior parietal cortex, supplementary motor area, and anterior cingulate cortex and putamen and caudate in response to reward. There was also evidence for regions that responded with both higher sustained activity in blocks of the Reward run than the Baseline run and transient activity for the Reward trials compared to No reward trials. These results provide evidence that proactive and reactive control are supported both by separable neural frontoparietal neural circuitries, as well as encoded by regions that can exhibit both sustained and transient temporal modulation that is sensitive to reward.

3.1 INTRODUCTION

Adolescents experience important changes in motivated behaviour: their ability to exert cognitive control is particularly susceptible to potential rewards and emotional contexts (A. O. Cohen et al., 2016; Crone & Dahl, 2012; van Duijvenvoorde et al., 2016). The maturational imbalance theory of adolescent development has focused mainly on maladaptive instances in which cognitive control systems fail to constrain reward sensitive systems typically in contexts of gambling and risky decision-making. Less is known about adaptive situations in which cognitive control might be enhanced by reward sensitivity (Strang & Pollak, 2014). In this study, we explored whether the temporal dynamics of reward (trial-by-trial vs sustained across a block) impact adolescent and adult's ability to proactively implement cognitive control in a working memory task, a demanding but effective strategy to improve performance.

3.1.1 Dual mechanisms of control

The DMC framework distinguishes between two temporally distinct cognitive control strategies (Braver, 2012 and see **Introduction**, Section **1.2.3.3** for details). Proactive control refers to the sustained maintenance of goal-relevant information in anticipation of a cue. It is generally more effective, but consumes more resources and is vulnerable to interruption. Reactive control refers to the transient reactivation of goals in response to a cue, and is less demanding than proactive control, but more susceptible to interference (Braver, 2012; Chiew & Braver, 2017). While adults vary in the recruitment of proactive and reactive control as a function of trait factors, (Chiew & Braver, 2017; Locke & Braver, 2008), they have the capacity to adapt to contextual demands by flexibly engaging the most efficient mode of cognitive control, as evidenced by changes in response to experimental manipulations (Braver et al., 2009; Chiew & Braver, 2013). Previous fMRI studies of the DMC in adults have found that sustained activation of the frontoparietal network across a block of trial is associated with behavioural indices of proactive control (Braver et al., 2009; Jimura et al., 2010).

3.1.1.1 Sustained and transient effects associated with working memory

Mixed event-related/blocked fMRI designs (Visscher et al., 2003) are specifically optimised to dissociate sustained versus transient effects in the same experimental paradigm (McDaniel et al., 2013), and have been employed to study different aspects of cognitive control without reward manipulations, e.g. long term, episodic and working memory (Brahmbhatt et al., 2010; Marklund et al., 2007), prospective memory, (McDaniel et al., 2013)and with reward manipulations (Jimura et al., 2010).

In working memory paradigms, sustained activity is thought to reflect task set and preparatory processes, and has been associated, in adults, with activity in right VLPFC (BA 47) and medial PFC (BA 6/32). Right VLPFC and ACC/pre-SMA have been implicated in task preparation and general attention processes (Marklund et al., 2007). Long term memory (LTM) and working memory (WM) were associated with the RLPFC (BA 10) and midline area (BA 8/6/32), which might represent information about the task that is important to maintain between trials. Sustained frontopolar and ACC activity has been associated with episodic retrieval and more general processes including monitoring, and preparatory processes. Transient activity in areas other than those with sustained activity were seen for memory and attention tasks (Marklund et al., 2007): the left posterior DLPFC (BA 44/9) has been implicated in item processing, perhaps reflecting general retrieval-control processes (Wheeler and Buckner, 2003). Moreover, different types of memory tasks had particular transient responses, which are thought to represent recovery of domain-specific information (Marklund et al., 2007) .

A developmental study employed the n-back task to investigate sustained versus transient activation in children and early adolescents (9-13 years) and emerging adults (18-23 years) (Brahmbhatt et al., 2010). Overall, both groups showed activation of frontoparietal WM related regions, with different patterns of sustained and transient activity across load. In 2-back trials, children and early adolescents had lower sustained but higher transient activation, which the authors suggest reflects decreased reliance on a sustained approach and impaired maintenance of information across blocks (Brahmbhatt et al., 2010).

3.1.1.2 Developmental studies of the dual mechanisms of control

3.1.1.2.1 Childhood

The majority of developmental DMC studies to date have focused in childhood. Pre-schoolers are more reactive and demonstrate some capacity to engage proactive control by age 6 (Lucenet & Blaye, 2014). While there is more stability in proactive strategies by age 8 (Chatham, Frank, & Munakata, 2009) these abilities continue to improve between 9 and 11 years of age (Lorsbach & Reimer, 2011). Reliance on reactive control in earlier childhood shifts towards a mix proactive and reactive control depending on individual differences and task demands in mid to late childhood (Chevalier, Martis, Curran, & Munakata, 2015). Younger children rely on reactive control even in situations where proactive control would be more adaptive. By age 8, children seem to have the capacity to flexibly adapt strategies to be more efficient (Blackwell & Munakata, 2014; Chatham et al., 2009; Chevalier et al., 2015).

3.1.1.2.2 Adolescence

Proactive control has been associated with the ability to maintain a task-set in anticipation of cue/stimuli presentation, while reactive control underlies the ability to adjust behaviour once the stimulus has been presented (Braver, 2012) As such, task-switching paradigms have been used to investigate participants' ability to update response rules and in cued-paradigms, prepare for the task switch, with mixed findings for the age of development of proactive cognitive control. There are a handful of studies investigating the dynamics of the DMC in adolescence.

Andrews-Hanna et al. (2011) employed a mixed block/event-related fMRI study of the Stroop task in participants between 14 and 25 years. Results indicated delayed maturation of proactive goal maintenance: younger adolescents relied more on reactive strategies than young adults. Associated with increased activation in posterior DLPFC, sustained aspects of control became more efficient through early adulthood (Andrews-Hanna et al., 2011)

Velanova et al. (2009) investigated the sustained and transient correlates of inhibitory control between 8 and 27 years of the improved rate of successful inhibitory responding in the antisaccade task with age. They found that transient trial-specific activation was mostly mature by adolescence, but sustained brain activation in frontoparietal regions followed a more protracted developmental trajectory. These results underscore the importance of the ability to maintain a task set in enabling the maturation of inhibitory control (Velanova, Wheeler, & Luna, 2009). Similarly, another study found that developmental improvements between 8 and 25 years in the antisaccade task were associated with increased activation in frontoparietal regions, including the DLPFC and ACC, in the preparatory phase when contrasted with the execution phase (Alahyane, Brien, Coe, Stroman, & Munoz, 2014).

A four-year longitudinal study using a modified version of the Stroop task demonstrated improvements in reactive control between early and mid-adolescence, which were associated with structural brain changes. Thinning of the RLPFC was associated with improvements in proactive control for both females and males, while thinning of the ACC was associated with improvements in reactive control for male participants only (Vijayakumar et al., 2014).

3.1.2 Cognitive control and motivation

Cognitive control reactive and proactive profiles are sensitive to the motivational context (Braver et al., 2014; Chiew & Braver, 2017), and interact with reward circuitry in the presence of incentives (Luna et al., 2015). Results from studies using reward cueing and blocked reward designs indicate that reward enhancement may be driven by proactive top-down control mechanisms that modulate the processing of the subsequent stimuli in preparatory fashion (Jimura et al., 2010; Locke & Braver, 2008). For example, in adults, rewards can enhance cognitive control through a shift towards proactive control (Jimura, Locke, & Braver, 2010). In addition, reward can lead to enhanced activity in task-related control areas within a given trial, suggesting that reward can enhance reactive control in a top-down fashion. There is also evidence for some contribution by more automatic bottom-up processes, suggesting increased saliency of reward-related features (Krebs, Hopf, & Boehler, 2015).

As was reviewed in **Chapter 1** in more detail (see Section **1.2.5.2**), in adolescence, rewards improve inhibitory control, in terms of accuracy and speed, and match adult levels of performance (Geier et al., 2010; Padmanabhan et al., 2011; Zhai et al., 2015). In addition to enhanced behavioural performance, research has identified differences in event-related neural activity, in which, in addition to increased activation of reward regions, adolescents also have increased recruitment of control regions when compared to adults (Geier et al. 2010, Padmanabhan et al. 2011). Smith et al. found evidence for increased activation with age in regions associated with attention control and reward processing between 10 and 73 years old, suggestive of greater integration and executive control of motivation with development (A. B. Smith, Halari, Giampetro, Brammer, & Rubia, 2011).

Moreover, a recent study found that children aged between 9 and 11 years and adolescents aged between 14 and 16 and adults aged between 25 and 30 showed better RT performance, but not in accuracy, in a cognitive control task in rewarded trials relative to unrewarded trials (Strang & Pollack, 2014). This improvement was thought to reflect a shift to a proactive control strategy, and associated with increased sustained activity in the right lateral PFC. These results indicated that in a reward-related context, there was continuity in enhancement of cognitive control from 9 to 30 years of age. However, Strang and colleagues (2014) focused on sustained brain activity only. An outstanding question is whether similar modulations of transient brain activity can be observed. The investigation of both sustained and transient brain activity and their modulation by context is needed to fully characterize the use of proactive and reactive strategies in cognitive control tasks.

3.1.3 The present study

In the present study, we aimed to investigate the development of proactive and reactive cognitive control and their modulation by a motivational (reward) context that varied trial-by-trial and across blocks. We expected adolescents to exhibit a more reactive strategy and to show greater sensitivity to a rewarding context, both in terms of behaviour, strategy and neural activity. We employed a mixed block/event-related fMRI design while adolescents and adults completed a working memory task under neutral and reward conditions, adapted from Jimura et al. (2010). First, the mixed experimental designed allowed estimates of sustained brain activity across blocks (proactive control) and transient activity in response to trials (reactive control). Second, after identifying key brain regions with context-related changes in both transient and sustained activity, we decomposed trial related activity in a time-course analysis.

We predicted overall behavioural improvements with blocked effects for adults and trial effects for adolescents, consistent with proactive and reactive strategies. We expected to find adults maintained sustained frontoparietal activity across blocks and adolescents to be more reliant on transient, trial-by-trial activity.

3.2 METHODS

3.2.1 Participants

Fifty participants took part in this study: 30 adolescents (15 females) aged between 12 and 17 years (*M* = 14.6 ± 1.4 (*SD*)) and 20 adults (10 females) aged between 22 and 30 years old (*M*= 27.1 ± 1.9). Participants were reimbursed £20 (plus up to £8 depending on their performance) and their travel expenses for taking part. This study was approved by the UCL Research Ethics Committee. Adolescent and adult groups did not differ on t-scores on the Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2011) (adolescents: *M = 66.9* ± .86 (SE); adults: *M = 64.7* ± 1.7 (SE); *t*(48) = 1.26, *p* = .213).

3.2.2 Design and Stimulus Material

3.2.2.1 Design

The fMRI task had one between-subjects factor (Age group: adults and adolescents). We will discuss two types of within-subject factors: either sustained, run effects (*Baseline run* vs *Reward run*) or transient, trial effects (*Baseline trials*, *Reward trials* vs *No reward trials*). In the *Reward run*, half of the trials had potential rewards (*Reward trials*) and half did not (*No reward trials*). Preceding the *Reward run*, participants were unaware of the potential rewards, and hence all the *Baseline trials* in the *Baseline run* were unrewarded (**Figure 3.1.A**).

3.2.2.2 *Letter array working memory task*

We employed a fixed set-size Sternberg-item recognition task that was adapted from Jimura, Locke and Braver (2010; **Figure 3.1.B**). At the beginning of each working memory trial, a cue was presented in the centre of the screen for 1.5 s. There were two different cues: **“★★★ trial**” indicating that a potential reward could be obtained on this trial (*Reward* *trial*) or “**new trial**” indicating that no reward could be obtained on this trial (*Baseline trial* or *No reward trial*). Immediately after the reward cue, five uppercase consonants were presented on the screen for a 1.5 s encoding period. A 3.5 s delay followed to serve as a retention interval. After the delay, a single lowercase probe letter was presented for 1.5 s. Participants were required to indicate whether the probe matched one of the letters from the memory set. Participants were encouraged to respond both accurately and quickly. Responses were indicated by pressing one of two buttons on a handheld response box (right index finger = match, right middle finger = no match), and were followed by a 2s delay and then feedback for 1.5 s. Four different types of feedback could be provided, indicating whether the response was incorrect, too slow, correct and not rewarded, or correct and rewarded (**Figure 3.1B**). Cut-off times were individually set for each participant, based on their own median correct reaction time (RT) on trials performed in the practice (see Procedure). The next trial started after an intertrial interval lasting 2.5, 5 or 7.5 s.

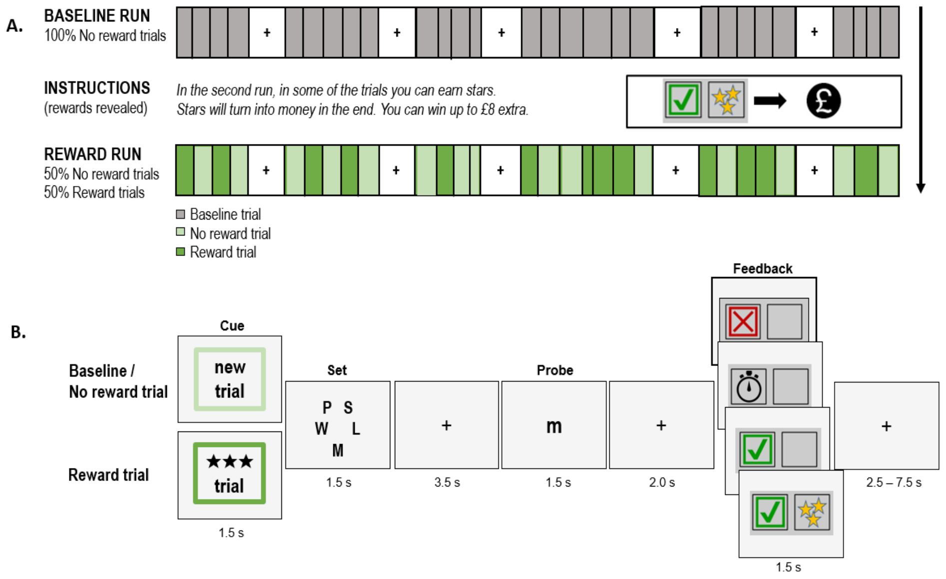


Figure 3.1: *Letter-array working memory task*. (A) Experimental design. Participants performed two runs of 30 trials each of a letter-array working memory task. In the first run, none of the trials were rewarded. In the second run, half of the trials could be rewarded. (B) Example stimuli. In each trial, participants were presented with a 5 letter set, and, after a delay, had to indicate whether the probe was present in the set. Each trial was preceded with a screen indicating whether there were potential star rewards, and followed by feedback on performance.

3.2.2.3 Individual difference measures

Participants completed computerised versions of the (1) Behavioural Activation Scale (BAS; Carver & White, 1994), (2) Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia, Ávila, Moltó, & Caseras, 2001), and (3) WEBEXEC, a web based short self-report of executive functions (Buchanan et al., 2010). For a different study on prospective memory, reported in **Chapter 2**, they also completed (4) the Prospective and Retrospective Memory Questionnaire (PRMQ; Crawford, Smith, Maylor, Della Sala, & Logie, 2003), and (5) the Future Orientation and Delayed Discounting Scale (FOS; Steinberg et al., 2009). Participants also completed a computerised simple Go/No Go task (Simmonds et al., 2008) in which a “Go” stimulus (green square) is presented in high frequency and requiring a rapid, dominant, response, which needs to be inhibited when a less frequent “No Go” stimulus (red square) is shown. Lastly, participants were administered the Forward and Backward Digit Span task in which they were required to listen to a sequence of numbers (minimum 3 items, maximum 9) and repeat them in the same or reversed order and the WASI.

3.2.2.4 Procedure

Participants were first trained on the letter-array working memory task outside the scanner. After going through the two types of trials (probe matches preceding letter array or not) and feedback (correct, incorrect, too slow), they performed one block of ten trials with a cut-off time of 2.5 s. Participants then performed one block of fifteen trials with their individual cut-off time limit (median RT in the first 10 trials). This was done to adapt task difficulty for each individual and quickly achieve a consistent level of performance to avoid practice effects.

Participants then performed two scanning runs of the letter-array working memory task. Each run comprised six blocks with either 4, 5 or 6 trials for a total of 30 trials per run (Baseline run: 30 Baseline trials; Reward run: 15 Reward trials, 15 No reward trials). The order of the conditions was fixed within the Reward run, but counterbalanced across participants, in one of two possible sequences which started with the presentation of a Reward trial but did not present more than two times of the same trial in a row (i.e. RNRRN RNRN RNRNN NRNRRN). After every block, there was a period of fixation. Task blocks lasted between 61.5 and 96.6 s, while fixation periods lasted between 20 and 30 s. Each block start and end was indicated by a 1 s instruction screen stating “BLOCK START” and “BLOCK END”. Afterwards, participants had a structural scan, and then completed an unrelated prospective memory task that is reported in **Chapter 2**. After the scanning participants completed the questionnaires, the Go/No-go tasks, Forward and Backward digit spans and the WASI.

3.2.2.5 MRI data acquisition

Multi-slice T2-weighted multiband (with level 2 acceleration) EPI volumes (Demetriou et al., 2016) with BOLD contrast (44 axial slices with a voxel resolution of 3 × 3 × 3 mm covering most of the cerebrum; TR = 2 s; TE = 45 ms; TA = 2 s) were obtained using a 1.5 T MRI scanner (Siemens TIM Avanto, Erlangen, Germany). Functional images were acquired in two scanning runs lasting approximately 8 min 40 s each in which 321 volumes were obtained. The first 4 volumes of each run were discarded to allow for T1 equilibrium effects. A 3D T1-weighted fast-field echo anatomical image lasting 5 min 30 s was acquired after the first two functional runs for each participant.

3.2.3 Data Analysis

3.2.3.1 Behavioural data

A 2 (Age group) x 3 (Trial type: Baseline, No reward, Reward) mixed-model repeated measures ANOVA was performed on mean RT and accuracy data of the fMRI letter-array working memory task. Correlational analyses were run between indices of performance ($RT_{Reward} – RT_{Baseline}$, $RT_{No\ reward} – RT_{Baseline}$) and composite indices of reward sensitivity (mean z-scores on BAS and SPRSQ), and Forward and Backward Digit Span total number of correct trials. Data were analysed with SPSS 21 (IBM Corp., Armonk, NY).

3.2.3.2 MRI data

3.2.3.2.1 fMRI data preprocessing

MRI data were preprocessed and analysed using SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Images were realigned to the first analysed volume with a second-degree B-spline interpolation to correct for movement during the session. The bias-field corrected structural image was coregistered to the mean, realigned functional image and segmented on the basis of MNI-registered International Consortium for Brain Mapping (ICBM) tissue probability maps. Resulting spatial normalisation parameters were applied to the realigned images to obtain normalised functional images with a voxel size of 3 x 3 x 3 mm, which were smoothed with an 8-mm full width at half maximum Gaussian kernel.

Realignment estimates were used to calculate framewise displacement (FD) for each volume, which is a composite, scalar measure of head motion across the six realignment estimates (Siegel et al., 2014). Volumes with an FD > 0.9 mm were censored and excluded from general linear model (GLM) estimation by including a regressor of no interest for each censored volume. No session met criteria for exclusion (scanning sessions with more than 10 % of volumes censored or a root mean square (RMS) movement over the whole session greater than 1.5 mm). Adolescent and adult participants did not differ significantly in the number of overall censored volumes (adolescents = 0.75 ± 1.21 (SD), adults = 0.56 ± 1.87; *p* = .659), mean RMS rotational movement (adolescents = 0.18 mm ± 0.07, adults = 0.19 mm ± 0.08; *p* = .633), and mean FD (adolescents = 0.11 mm ± 0.03, adults = 0.10 mm ± 0.05; *p* = .280). There was a difference between groups in terms of mean RMS translational movement, with more movements in this axis for adults than adolescents (adolescents = 0.18 mm ± 0.07, adults = 0.24 mm ± 0.12; *p* = .025).

3.2.3.2.2 Block and event-related analysis

Variance in the BOLD signal was decomposed using a mixed block/event-related GLM to investigate sustained and transient activity during task performance. Sustained activity was modelled in Reward and No reward runs separately using extended boxcars regressors representing task blocks (durations 57.5-100.0 s), and fixation blocks (duration: 21.9-29.7s). Transient activity was modelled using two boxcar regressors of duration 10.5s, representing correctly answered Reward trials and No reward trials (NB: in the Baseline run, this distinction was arbitrary). Other regressors included in this model were: start of blocks (duration 2s), end of blocks (duration 2s), a regressor representing all incorrect trials (duration 10.5), censored volumes as covariates of no interest, and the mean over scans. Block and event regressors were convolved with a canonical haemodynamic response (hrf) function. The data and model were high-pass filtered to a cut-off of 1/128 Hz.

Two second-level whole-brain analyses were performed to look at sustained and transient patterns of activation. The first random-effect flexible factorial analysis included the factors Subject, Age group and Block type ([Baseline blocks – fixation blocks], [Reward blocks – fixation blocks]), modelling Subject as a main effect (to account for the repeated-measure nature of the data) and the Age group x Block type interaction. The simple effect [Baseline blocks – fixation blocks] was used to assess the general neural correlates of working memory over the task blocks. The main effect of Block type [Reward vs. Baseline] and the interaction between Block type and Age group allowed the investigation of sustained effects of the reward context (proactive control).

The second random-effect flexible factorial analysis included the factors Subject, Age group and Trial type (Baseline trials, No reward trials, Reward trials event-related activation), modelling again Subject as a main effect and the Age group x Trial type interaction. Activation in Baseline trials was assessed to provide the transient neural correlates of the working memory trials. The contrast [Reward vs. No reward trials] was run as a measure of reactive control, and the contrast [No reward vs. Baseline trials] as a measure of proactive control. Again, interactions with Age group were tested.

Main effects of run (Reward run > Baseline run and reverse) and trial (Reward trial > Baseline trial and reverse), (No reward trials > Baseline trials), and (Reward trial > No reward trial and reverse), and the interaction between each of these effects and Age group were determined using the t statistic on a voxel-by-voxel basis. Statistical contrasts were used to create SPM maps thresholded at $p < .001$ at the voxel level with a minimum cluster size of 82 voxels. In addition, activations that survived whole-brain that survived whole-brain FWE correction at $p < .05$ are indicated. All coordinates are given in MNI space. Data visualization and contrast rendering was done in bspmview (Spunt, 2016) and SPM12, with automatic anatomical labelling using AAL2 (Rolls, Joliot, & Tzourio-Mazoyer, 2015; Tzourio-Mazoyer et al., 2002), and manual Brodmann area labelling using mricron (Rorden, Karnath, & Bonilha, 2007). Regions that exhibited mixed sustained and transient effects were identified by running the transient contrasts inclusively masked by the sustained contrasts (voxel $p_{\mathrm{uncorr}} < .001$ and cluster $p_{\mathrm{FWE}}=.05$). Reversely, to identify regions that were exclusively sustained or transient, the relevant contrast was exclusively masked ($p_{\mathrm{uncorr}} <.05$).

3.2.3.2.3 Correlations with performance and individual differences

Exploratory correlation analyses were performed between task improvement in terms of RT, Reward sensitivity (RS), and individual differences in activation in the tasks. Relevant task contrasts were entered in a two-sample t-test design modelling the two age groups separately, with the behavioural measure as a single covariate of interest. Correlations were run between the contrasts [Reward blocks > Fixation blocks] and [Reward trials > No reward trials] and RT improvement between Baseline trials and Reward trials, between No reward trials and Reward trials as well as the composite score of RS.

3.2.3.2.4 FIR analyses

To characterise the timecourse of brain activation during working memory trial, with a focus on identifying early vs later modulations of brain activity by reward. Trial-related activity (Baseline, No reward and Reward) was modelled using a finite impulse response (FIR) basis set of ten 2 s (TR) boxcars (Jimura et al., 2010). As before, block-related activity was modelled using two extended boxcar regressors convolved with a canonical hrf for each block type separately (Reward block and Baseline block). Other regressors included in this model were: boxcar regressors for instructions of each block (“Block start” or “Block end”) to capture changes in BOLD signal associated both with the start of a new blocks and also with the end of a previous block (Dumontheil, Thompson, & Duncan, 2011; Visscher et al., 2003), censored volumes as covariates of no interest; and the mean over scans. The data and model were high-pass filtered to a cut-off of 1/128 Hz.

3.2.3.2.5 ROI analyses

ROI analyses were performed on regions that were found to exhibit either a mixed pattern of activation to test for interaction effects between Task, Condition and Age group, in (1) the mixed block/events analysis, (2) and the FIR analysis. ROIs were defined as 10 mm spheres with the following centres: left anterior insula (AI; -33, 23, -4), right AIns (33,23,4), anterior cingulate cortex (ACC; 3, 35, 20), caudate nucleus (6, -1, 2), and posterior parietal cortex (PPC; 33, -61, 47).

Statistical threshold for the ROI analyses performed in SPSS was $p < .05$ (two-tailed). Significant interactions were followed up by extracting the mean signal across all voxels of significant clusters with MarsBar (Brett, Anton, Valabregue, & Poline, 2002) and analysing simple effects in SPSS using t-tests (with Bonferroni correction for multiple comparisons).

3.3 RESULTS

3.3.1 Behavioural results

3.3.1.1 Letter array working memory task

RT and accuracy data in the letter array working memory task were analysed with a 3 (Condition: Baseline, No reward, Reward) x 2 (Age group) mixed-design ANOVA. For *RT* data there was a main effect of Condition ($F(2,96) = 50.16$, $p < .001$, $\eta_p^2 = .51$, **Figure 3.2.A**): participants were faster in No reward trials than in Baseline trials and even faster for Reward trials ($M_{Baseline} = 779 \pm 12$ ms (SE), $M_{No\ reward} = 749 \pm 11$ ms, $M_{Reward} = 705 \pm 9$ ms; all *p's* < .001, Bonferroni corrected). Overall speed increased with age (**Table 3.1**). There was no significant interaction between Age group and Condition ($F(2,96) = 2.08$, $p = .15$).

For *accuracy* data there was a main effect of Condition ($F(2,96) = 4.19$, $p = .021$, $\eta_p^2 = .80$, **Figure 3.2.B**): participants were more accurate than in No reward trials than in Baseline trials ($M_{Baseline} = 84.8 \pm 1.5\%$ (SE), $M_{No\ reward} = 88.1 \pm 1.5\%$, $p = .017$), with similar, but not significant, increased accuracy in Reward trials ($M_{Reward} = 88.6 \pm 1.6\%$, $p = .069$). Overall accuracy increased with age (**Table 3.1**). There was no significant interaction between Age group and Condition ($F(2,96) = 2.05$, $p = .159$).

Table 3.1: Summary statistics of measures collected in adolescent and adult participants.

	Adolescents (Mean ± SE)	**Adults (Mean ± SE)**	**Age group comparisons**
Letter array WM task RT	769 ± 12 ms	719 ± 15 ms	$F(1,48) = 6.57$, $p = .014$, $\eta_p^2 = .12$
Letter array WM task accuracy	84.1 ± 1.7 %	90.3 ± 2.1%	$F(1,48) = 5.41$, $p = .024$, $\eta_p^2 = .10$
Reward sensitivity composite[a]	.21 ± .13	-.19 ± .21	$t(47) = 1.75$, $p = .087$
Reward sensitivity SPSRQ (Possible range: 0 - 16)[a]	8.4 ± .6	6.2 ± .7	$t(1,49) = 2.30$, $p = .026$
Reward sensitivity BIS/BAS (Possible range: 13 - 52)[a]	40.3 ± 1.3	39.9 ± 1.3	n.s. ($p = .862$)
Forward digit span total score (Possible range: 1 -22)	17.0 ± .6	18.1 ± .7	n.s. ($p = .244$)
Backward digit span total score (Possible range: 1 -22)	8.9 ± .6	11.8 ± .8	$t(48) = 3.23$, $p = .002$
No go accuracy	87.8 ± 1.7 %	91.7± 1.9 %	n.s ($p = .137$)
WEBEXEC (Possible range: 6 -24)[b]	13.3 ± 0.5	12.9 ± 0.7	n.s. ($p = .566$)

[a] Higher scores indicate more sensitivity to reward

[b] Higher scores indicate more EF failures

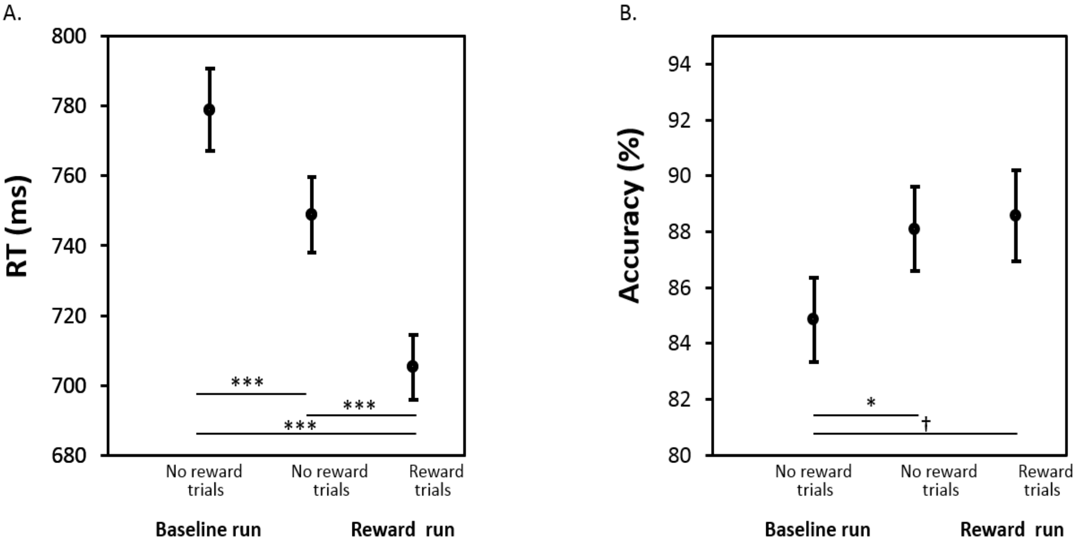


Figure 3.2. Mean RT (A) and accuracy (B) as a function of Condition. Error bars represent SE. † <.10, * $p < .05$, ** $p < .01$, *** $p < .001$ (Bonferroni corrected).

3.3.1.2 Individual differences in reward sensitivity

There was a trend for a decrease in Reward Sensitivity (z-score normalized composite index of the two self-report indices, SPSRQ and BIS/BAS) with age between adolescents and adults. A post hoc analysis revealed that adolescents were significantly more sensitive to rewards than adults when assessed with the SPSRQ (Torrubia et al., 2001). No difference was observed between adolescents and adults on the BIS/BAS (Carver & White, 1994). There was no correlation between individual Reward sensitivity and $RT_{\text{Reward – No reward}}$ improvement ($r(46)=-.17$, $p = .249$) or $RT_{\text{No reward - Baseline}}$ improvement (r(46)=-.005, r=.975) when controlling for age. Adolescents and adults earned comparable amounts of money ($M_{Adolescents}$ = 6.5, +- .24, M_{Adults}=6.67 +- .23, $p = .625$, possible range = 0 - 8), although adolescents reported finding money incentives more rewarding than adults ($M_{Adolescents}$ = 4.17 +- .14, M_{Adults} = 3.45 +- .30, $p = .036$, possible range = 1 – 5).

3.3.1.3 Individual differences in executive control

Adults had greater backwards digit span capacity than adolescents, but the two age groups did no differ on forward digit span capacity, accuracy in No go trials in the Go/No go task or on WEBEXEC scores (**Table 3.1**). When including backward digit span capacity as a covariate in the RM ANOVAs on letter-array working memory task, Accuracy becomes non- significant ($F(1,46) = 1.21$, $p = .277$). However, the main effect of age on RT remains ($F(1,46) = 5.82$, $p = .020$).

In summary, participants were faster and more accurate in No reward trials than in Baseline trials and fastest for Reward trials with no additional improvements in accuracy.

Adults were overall faster and more accurate than adolescents, with no interaction between Age group and Condition. This speed improvement with age (but not accuracy) is evident after covarying out working memory capacity. Results suggest that rewards impact behavioural indices of proactive and reactive control similarly for both adolescents and adults. However, this pattern of results might be also influenced by order effects (see Section 3.4.3 on Limitations).

3.3.2 Neuroimaging results

We first identified the network of brain regions generally associated with working memory in the letter array task in the absence of reward, to provide the context for assessing sustained and transient effects of reward within and outside of this network. In a second step, we assessed sustained difference between task blocks of the Reward and Baseline runs, and in a third step transient differences between Baseline, No reward and Reward trials.

3.3.2.1 Baseline working memory activation

3.3.2.1.1 Sustained working memory activation in the Baseline run (Baseline task blocks – fixation blocks)

A broad bilateral network of frontoparietal-temporal regions showed increased BOLD signal during letter array working memory task blocks compared to fixation blocks in the Baseline run (**Table 3.2** and **Figure 3.3.A**). In the frontal lobes, bilateral activation was observed in the superior frontal gyri and anterior part of the inferior frontal gyri, extending along the medial wall into the anterior aspect of the ACC. There was increased bilateral parietal activity in the left and right angular gyri, as well as in the left middle temporal gyri and medial and left inferior occipital gyri. Compared to adolescents, adults showed clusters of increased activation in the left superior frontal and superior medial gyri, extending into ACC, precentral gyrus and SMA, as well as activity in the lingual gyri (**Table 3.2** and **Figure 3.3.A**).

3.3.2.1.2 Transient working memory activation in the Baseline trials

Widespread increased BOLD activation was observed in frontal, parietal and temporal regions, during letter array working memory task events in the Baseline run (**Table 3.2** and **Figure 3.3.B**). In the frontal lobes, bilateral activation was observed in the superior frontal gyri and anterior part of the inferior frontal gyri, as well as orbitofrontal cortex, extending along the medial wall predominantly into the middle cingulate cortex. There was increased bilateral activity in the insulae, in the angular gyri in the parietal cortex, as well as in the middle temporal gyri and inferior occipital gyri. Increases in subcortical activation were observed in the caudate and putamen, as well as in bilateral thalami, and hippocampi. There was widespread bilateral activation in the cerebellum.

Compared to adolescents, adults showed increased activity in the precentral gyrus bilaterally, extending predominantly into the left postcentral gyrus (**Table 3.2** and **Figure 3.4.A**). Compared to adults, adolescents exhibited less deactivation in regions of the default mode network: MPFC and precuneus (**Table 3.2** and **Figure 3.4.B)**.

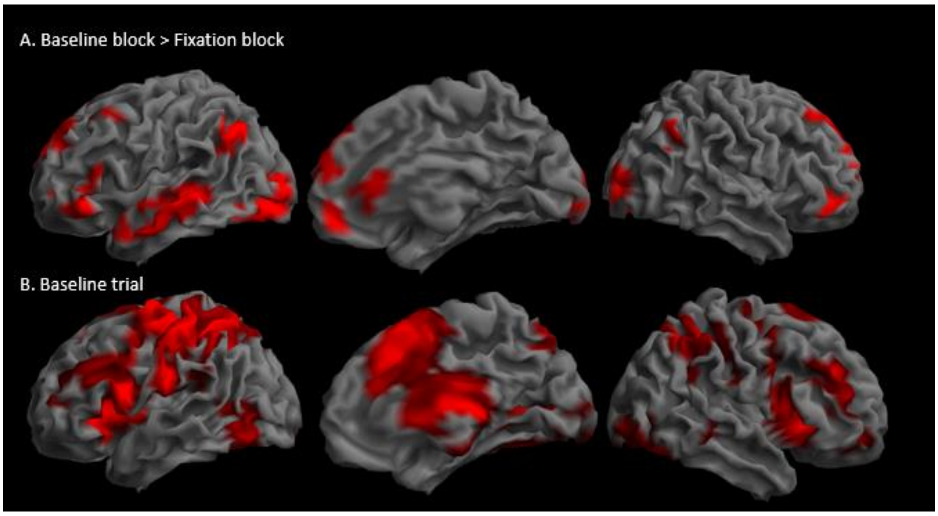


Figure 3.3 *Letter working memory task related activation in the absence of reward*. (A) Regions showing sustained increased BOLD signal in the Baseline task blocks vs. fixation blocks. (B) Regions showing transient increased BOLD signal in Baseline trials. Contrasts are rendered on the surface of the SPM12 MNI template. Threshold: $p_{\text{uncorr}} = .001$, cluster $p_{\text{FWE}} < .05$ (k =82).

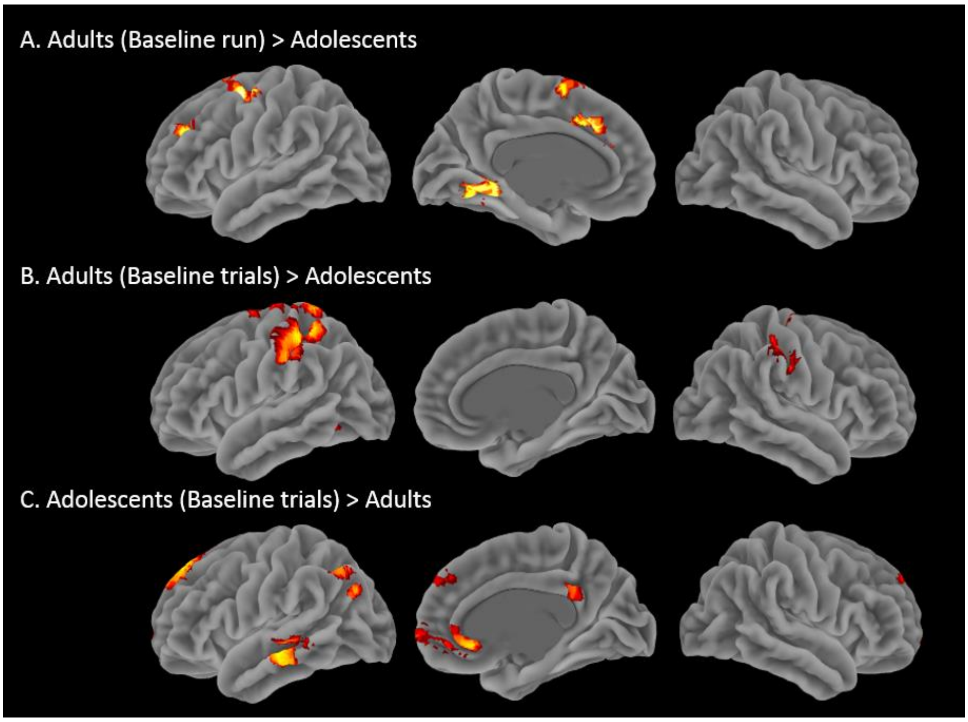


Figure 3.4 *Developmental effects on working-memory*. (A) Regions showing sustained increased BOLD signal for adults compared to adolescents in Baseline blocks vs fixation blocks. (B) Regions showing transient increased BOLD signal for adults compared to adolescents in Baseline trials. (C) Regions showing transient increased BOLD signal for adolescents compared to adults in Baseline trials. Contrasts are rendered on the surface of the bspmview MNI template. Threshold: p_{uncorr} = .001, cluster p_{FWE} < .05 (k =82).

Table 3.2: *Working memory neuroimaging results*. Coordinates and t-values are listed for regions showing a significant difference in BOLD signal in the whole brain analysis of block effects of working memory [(Baseline blocks – Fixation blocks)] and trial effects of working memory [(Baseline trials)]. x, y, and z = Montreal Neurological Institute (MNI) coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively. Regions labelling was done using Automatic Anatomic Labelling 2 (AAL2) (Tzourio-Mazoyer et al., 2002). Brodmann area labelling of peak of activations was done using MRIcron. ^{a} indicates voxels where p_{FWE} < .05 at the voxel-level, ^{b} indicates clusters where p_{FWE} < .05 at the cluster-level, with a cluster-defining threshold of p < .001 uncorrected at the voxel-level with a minimum extent of 82. BA = Brodmann area, L/R = Left/Right hemisphere.

Region	L/R	Extent	t-score	x	y	z	BA
Baseline task blocks > fixation blocks							
Inferior occipital cortex	L	630 ^{b}	10.09 ^{a}	-27	-88	-10	18
Inferior occipital cortex	L		6.01 ^{a}	-36	-67	-10	19
Fusiform gyrus	L		5.73 ^{a}	-36	-46	-19	37
Mid occipital cortex	R	334 ^{b}	8.63 ^{a}	27	-97	5	17
Mid temporal gyrus	L	895 ^{b}	6.90 ^{a}	-60	-28	-1	21
Mid temporal gyrus	L		6.89 ^{a}	-60	-10	-16	21
Mid temporal pole	L		4.33 ^{a}	-48	11	-31	20
Mid superior frontal gyrus	L	2650 ^{b}	6.82 ^{a}	-9	50	50	9
Superior frontal gyrus	L		6.19 ^{a}	-21	29	59	8
Inferior frontal gyrus	R		5.92 ^{a}	12	32	5	11
Putamen	L	176 ^{b}	5.97 ^{a}	-21	2	5	
Angular gyrus	L	323 ^{b}	5.64 ^{a}	-42	-58	29	39
Angular gyrus	L		5.57 ^{a}	-45	-67	47	39
Angular gyrus	R	125 ^{b}	5.50 ^{a}	51	-61	32	39
Adults (Baseline blocks – fixation blocks) > Adolescents							
Superior frontal gyrus	L	168 ^{b}	4.64	-18	2	56	6
Precentral gyrus	L		4.58	-39	-4	56	6
Supplementary Motor Area	L		3.49	-6	17	65	6

Medial superior frontal gyrus	L	102[b]	4.43	-9	17	41	32
Anterior cingulate cortex	L		3.76	-6	32	26	32
Lingual gyrus	L	160[b]	4.23	-18	-46	-7	30
Lingual gyrus	L		3.96	-21	-67	-13	18
Superior medial frontal gyrus	L	113[b]	4.21	-30	47	26	46
Superior frontal gyrus	L		4.05	-30	38	47	9
Baseline trials							
Precentral gyrus	L	18304	26.63	-36	-7	68	6
Insula	L		24.92	-30	20	5	48
Postcentral gyrus	L		23.83	-45	-37	53	2
Middle frontal gyrus	R	530	12.82	42	38	32	46
Middle frontal gyrus	R		9.14	39	56	14	46
Orbitofrontal cortex	R	97	7.07	21	44	-16	11
Adults (Baseline trials) > Adolescents							
Postcentral gyrus	L	695[b]	8.18[a]	-36	-43	62	2
Inferior parietal lobe	L		5.71[a]	-51	-28	50	2
Precuneus	L	339[b]	7.26[a]	-21	-46	8	37
Inferior temporal gyrus	L		5.80[a]	-39	-55	-7	37
Hippocampus	L		4.08	-36	-31	-10	37/20
Hippocampus	R	167[b]	6.23[a]	24	-40	8	37
Hippocampus	L		3.80	39	-37	-7	37
Superior frontal gyrus	R	364[b]	6.21[a]	33	-4	68	6
Paracentral lobule	R		6.09[a]	6	-19	80	6
Superior frontal gyrus	L		5.79[a]	-33	-4	68	6
Postcentral gyrus	R	148[b]	4.56	42	-31	50	3
Adolescents (Baseline trials) > Adults							
Medial orbitofrontal cortex		521[b]	7.41[a]	0	56	-4	10
Medial orbitofrontal cortex			6.70[a]	0	32	-10	11
Caudate			3.76	0	11	-13	25
Superior frontal gyrus	L	431[b]	7.05[a]	-9	47	47	9
Medial superior frontal gyrus			5.59[a]	0	44	20	32
Medial superior frontal gyrus	R		4.19	15	53	41	9

Mid temporal gyrus	L	250 [b]	6.23 [a]	-60	-25	-16	20
Posterior cingulate cortex	L	136 [b]	4.60	-3	-55	32	23

3.3.2.2 *Reward effects*

3.3.2.2.1 Sustained effect of reward: Proactive control (Reward block – fixation > Baseline block - fixation)

Regions of the frontal and parietal cortex as well as the subcortical regions and the insulae showed increased BOLD signal in task blocks of the Reward run versus the Baseline run (**Table 3.3** and **Figure 3.5.A**). Peaks of increased BOLD signal were observed in the left and right insulae. The cluster extended into left and right frontal cortex in ventral (BA 45/47) and only right dorsolateral (BA 6/48/44) regions, as well as into the caudate and putamen subcortically. There was an additional cluster in the right angular and supramarginal gyri. The pattern of activation did not largely overlap with the sustained Working memory effects (**Figure 3.5.A**). There were no significant differences in activation of this contrast between age groups. No increased activation was observed in the reverse contrast (Baseline blocks > Reward blocks).

3.3.2.2.2 Transient effects of reward: Reactive control (Reward block – fixation > Baseline block - fixation)

3.3.2.2.2.1 Comparison with Baseline trials

Reward trials were associated with less deactivation of precuneus, lingual gyrus and middle occipital cortex when compared to Baseline trials (**Table 3.3** and **Figure 3.5.D, where blue indicates hypoactivation compared to the implicit baseline**). No differences in activation were observed in the reverse contrast (Baseline trials > Reward trials). There was higher activation in bilateral insulae, medial frontal gyrus extending into middle cingulate gyrus, and left inferior cortex for Baseline trials than No reward trials (**Table 3.3** and **Figure 3.5.C, where red indicates hyperactivation compared to the implicit baseline**). No reward trials compared to Baseline trials were associated with higher activation in the superior frontal gyrus, precuneus and middle occipital cortex (**Table 3.3** and **Figure 3.5.E**).

3.3.2.2.2.2 Reward trials > No reward trials (Reactive control)

In the frontal lobes, increased BOLD signal in Reward trials compared to No reward trials within the Reward run was observed in right frontal cortex in ventral and dorsolateral regions. Increased medial activation was observed extending from medial frontal cortex into anterior and middle cingulate cortex. There was increased activity in bilateral insulae. Posterior activity was observed bilaterally in the superior and inferior parietal cortex. There was also increased BOLD activity in a large inferior and middle occipital cluster. Subcortical activity was observed bilaterally in caudate nucleus extending slightly into accumbens, pallidum, thalamus, and bilateral hippocampi. There was widespread activation of cerebellar regions. At the whole-brain level, no age differences between adolescents and adults were observed. No increased activation was observed in the reverse contrast (No reward trials > Reward trials) (**Table 3.3 and Figure 3.5.B)**.

In summary, a pattern of activation of Reward trials > Baseline trials > No reward trials was observed regions showing overall WM activation, mainly in the anterior insulae, ACC and caudate (see **Figure 3.5**). This suggests that Baseline levels of activation in these regions were maintained in the Reward run only for Reward trials but nor for No reward trials, where there was less activation compared to Baseline trials. In addition, both Reward and No reward trials were associated with less deactivation in the temporo-parietal junction (TPJ) and precuneus compared to the Baseline trials.

3.3.2.3 Comparison of sustained and transient changes to reward

Across the whole brain bilateral insulae (BA 47), right posterior parietal cortex (BA 40/7), and subcortical clusters including right caudate nucleus and thalamus, and left pallidum, exhibited context-related changes in both transient and sustained activity. No age differences between adolescents and adults were identified (**Table 3.3)**.

Across the whole brain the more anterior aspect of the ACC (BA 24) as well as some cerebellar and occipital areas exhibited transient changes exclusively in response to reward, when excluding the overlap with transient working memory regions. No age differences between adolescents and adults were identified. No regions exhibited an exclusively sustained pattern of activation.

Table 3.3: *Effects of reward on proactive and reactive neuroimaging results*. Coordinates and t-values are listed for regions showing a significant difference in BOLD signal for the whole brain analysis for block effects of reward [(Reward run – Fixation) > (Baseline run - Fixation)] and trial effect of reward [Reward trial > No reward] or [No reward trial > Reward trial]. x, y, and z = Montreal Neurological Institute (MNI) coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively. [a] indicates voxels where $p_{FWE} < .05$ at the voxel-level, [b] indicates clusters where $p_{FWE} < .05$ at the cluster-level, with a cluster-defining threshold of $p < .001$ uncorrected at the voxel-level with a minimum extent of 82. BA = Brodmann area, L/R = Left/Right hemisphere.

Region	L/R	Extent	t-score	x	y	z	BA
Proactive control **Reward block - fixation > Baseline run - fixation**							
Insula	R	1152 [b]	5.72 [a]	30	20	-4	47
Insula	L		5.47 [a]	-30	23	-4	47
Caudate	R		5.24 [a]	9	8	14	

Insula	R		4.94	45	20	-7	38
Precentral gyrus	R		4.82	45	5	47	6
Pallidum	R		4.66	6	-1	2	
Middle frontal gyrus	R		4.31	48	20	29	44
Angular gyrus	R	356[b]	4.98	33	-61	47	7
Reactive control **Reward trials > No reward trials**							
Inferior occipital cortex	L	11426[b]	11.54[a]	-21	-91	-7	18
Cerebellum	L		9.12[a]	-33	-58	-19	37
Cerebellum	R		8.44[a]	30	-58	-19	37
ACC	R		7.36[a]	6	35	20	24
Insula	R		6.95[a]	36	20	-7	47
Insula	L	332[b]	6.42[a]	-30	23	2	47
Precentral gyrus	R	97[b]	3.93	45	5	35	6
Middle frontal gyrus	R	94[b]	3.77	45	47	8	45
Reward trials > Baseline trials							
Lingual gyrus	L	819[b]	7.42[a]	-18	-94	-7	18
Precuneus	L	854[b]	5.85[a]	-6	-58	29	23
Middle occipital cortex	L	107[b]	4.14	-36	-70	26	39
No reward trials > Baseline trials							
Precuneus	L	601[b]	6.83[a]	-6	-58	29	23
Middle occipital cortex	L	202[b]	5.35[a]	-48	-73	35	39
Superior frontal gyrus	L	94[b]	4.56	-21	38	50	9
Baseline trials > No reward trials							
Inferior frontal gyrus (pars orbitalis)	L	239[b]	5.76[a]	-39	20	-4	47
Insula	R	120[b]	5.32[a]	36	23	-7	47
Precentral gyrus	L	346[b]	5.20[a]	-33	-10	62	6
Middle cingulate cortex	L	285[b]	5.15[a]	-9	20	38	32
SMA	L		4.97	-6	8	56	6
SMA	R		3.20	15	8	68	6
Caudate	R	182[b]	5.01[a]	3	5	2	

Inferior occipital gyrus	L	127[b]	4.73	-39	-67	-10	19
Middle occipital gyrus	R	202[b]	4.64	36	-85	-1	19
Fusiform gyrus	R		4.02	33	-61	-16	19
Mixed regions **(Reward block - fixation > Baseline run – fixation) + (Reward trials > No reward trials)**							
Insula	R	225[b]	5.72[a]	30	20	-4	47
Insula	L	156[b]	5.47[a]	-30	23	-4	47
Angular gyrus	R	187[b]	4.98	33	-61	47	7
Caudate	R	109[b]	4.66	6	-1	2	
Exclusively transient regions **(Reward trials > No reward trials)**							
Inferior occipital lobe	L	5371	11.54	-21	-91	-7	18
ACC	R	618	6.79	3	35	20	24
Inferior parietal lobule	L	112	4.87	-45	-40	50	40
Insula	L	92	4.82	42	11	-10	48

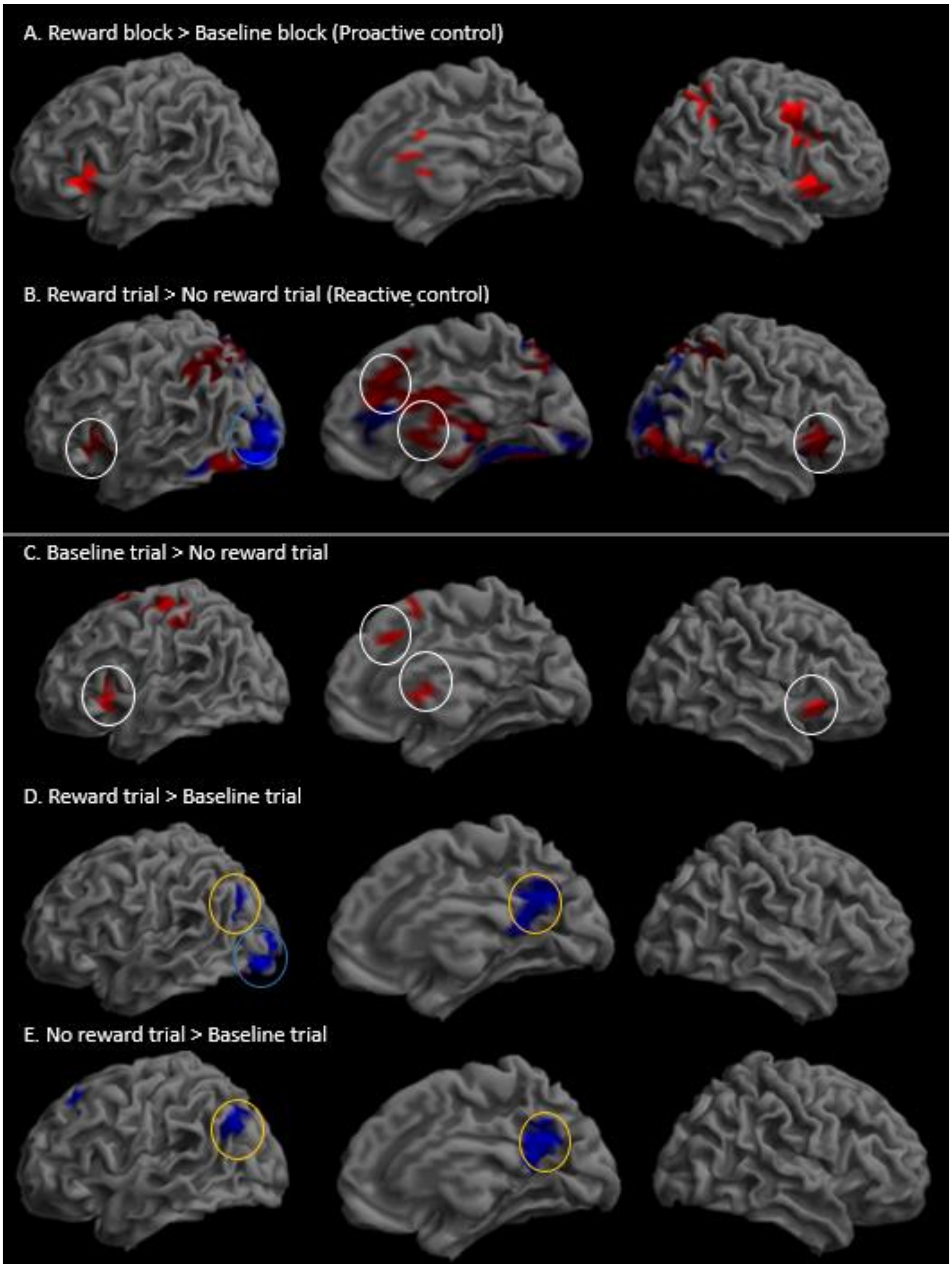


Figure 3.5. *Sustained and transient effects of reward.* Top panel depicts regions showing increased BOLD signal in the main contrasts of interest: (A) [Reward blocks – fixation blocks] > [Baseline blocks – fixation blocks] and (B) Reward trials > No reward trials. Bottom panel details the pattern of transient across contrasts for interpretation of activation and deactivation compared to Baseline. (C) Baseline trials compared to No reward trials, (D) No reward trial > Baseline trials and (E) No reward trial > Baseline trials. For B – E, red shows overall event-related activation versus the implicit baseline, while blue shows regions of overall event-related deactivation versus the implicit baseline, to indicate the different patterns of increased or decreased activation in different conditions. Different coloured circles depict overlap across different contrasts. Contrasts are rendered on the surface of the SPM template. Threshold: $p_{\text{uncorr}} = .001$, cluster $p_{\text{FWE}} < .05$ (k =82).

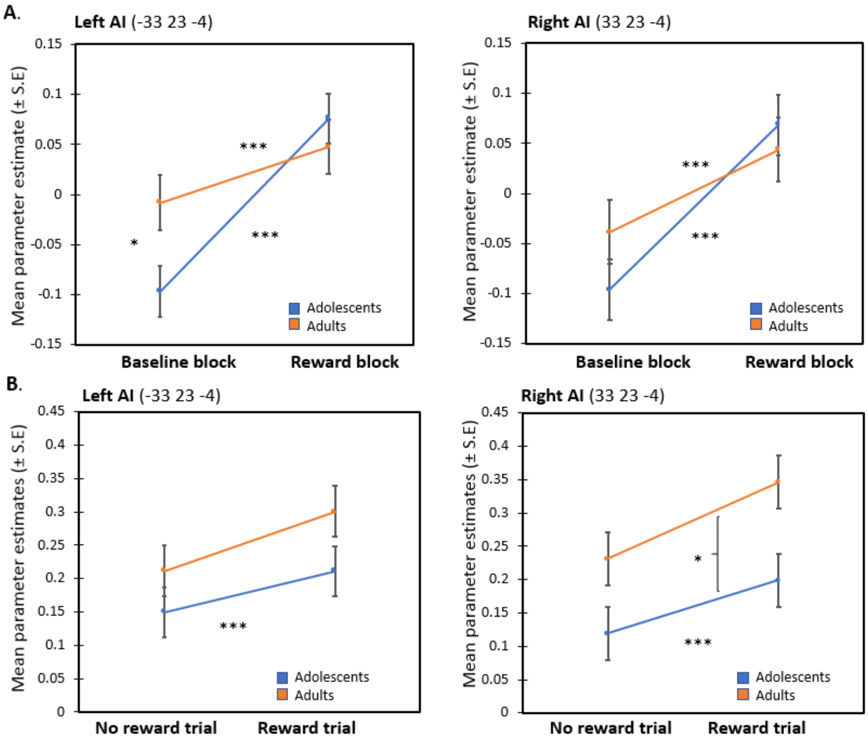


Figure 3.6. *Reward effects on AIns.* Parameter estimates extracted from the left and right AIns are plotted to illustrate interactions and main effect of age on (A) block and (B) trial effects. Error bars represent SE. * p < .05, ** p < .01, *** p < .001 (Bonferroni corrected).

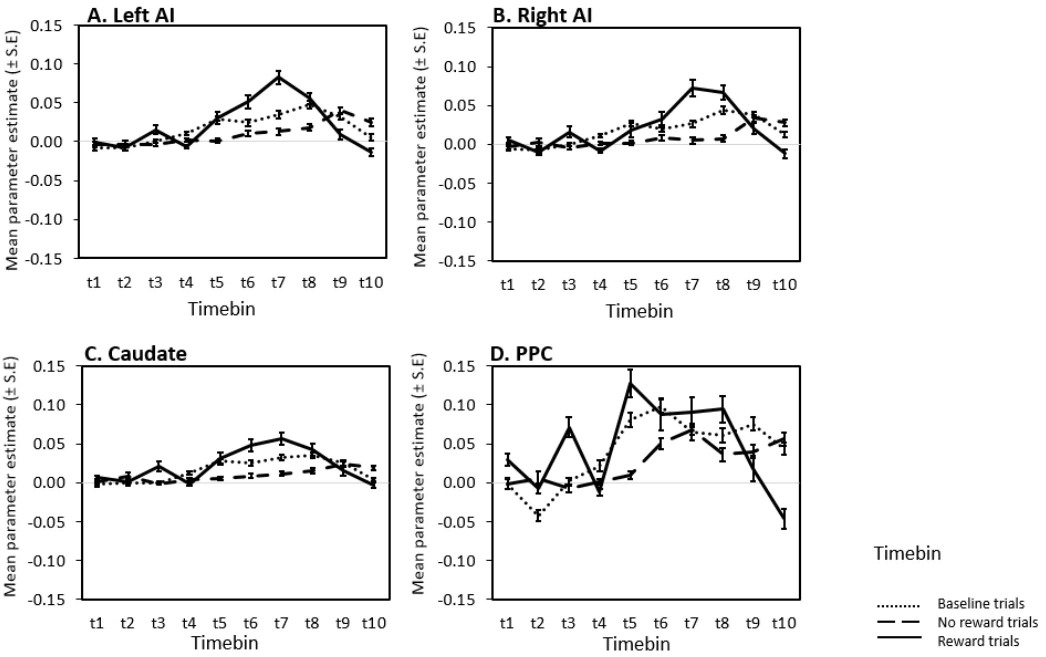


Figure 3.7 *Time course of transient activity in Baseline, No reward and Reward trials.* Time course was extracted from regions exhibiting a mixed response to reward with follow up FIR analyses (see **Methods, section 3.5.2.3** for details) in bilateral AIns, caudate and PPC. Error bars represent 1 S.E. Each timebin corresponds to 2s.

3.3.2.4 ROI analyses

We extracted mean parameter estimates in spherical 10 mm ROIs around the coordinates of clusters that exhibited a mixed pattern of activation (left and right insulae, PPC and caudate). We examined interactions and age effects (see **Figure 3.6**), the time course associated with trial activation (see **Figure 3.7**), and correlation with performance.

3.3.2.5 Developmental effects

Only the left AIns showed effects of age group on sustained activations. Within the left AIns, there was a significant interaction between Run and age: adolescents exhibited a greater increase in reward-dependent sustained activation than adults (*F*(1,48) = 6.62, *p* = .01). Within the right AIns, a similar, albeit not significant, pattern was observed (*F*(1,48) =3, *p* =.09) (**Figure 3.6)**. Analyses of transient activations showed that adults exhibited increased overall activity in the right AIns for Reward and No reward trials compared to adolescents (*F*(1,48) = 5.53, *p* = .02). No other age effects were identified.

3.3.2.6 Correlations with performance and reward sensitivity

No association was found between activity within these ROIs and indices of improved performance in RT or ACC (all *p*'s > .05). Reward sensitivity was positively correlated with the degree of sustained activation increase for the Reward run in the caudate (*r*(49) = .331, p =.021) and the ACC (*r*(49) = .307, *p* =.034).

3.4 DISCUSSION

This study examined the impact of reward expectation on sustained and transient engagement of cognitive control. It investigated whether differences exist between adulthood and adolescence, an age characterised by a shift towards reactive control and increased reward sensitivity. We employed an fMRI study using a letter array working memory task in which accurate and quick performance in some of the trials could be monetarily rewarded (Jimura et al., 2010). As has been previously described (Jimura et al., 2010), high accuracy rates can be achieved with a reactive control strategy. However, to produce accurate responses that are *fast enough*, the optimal strategy is to proactively sustain the task set and rule use across trials, in anticipation of the stimulus. Results showed behavioural and neural evidence for engagement of proactive and reactive strategies in both adolescents and adults, with high similarities across age groups.

3.4.1 Behavioural results

Reaction times and accuracy for No reward trials were better than Baseline, which is suggestive of sustained block improvement associated with a proactive strategy. These results are in line with RT improvements between these conditions reported by Jimura et al. (2010) in a similar paradigm with adult participants. In addition, in the current study, both adolescents and adults were fastest for Reward trials. This trial-by-trial improvement is suggestive of a motivational performance enhancement reflecting reactive control. However, Jimura et al. (2010) did not investigate differences between these types of trials, which prevent us from making a direct comparison. In addition, there might be an impact of order effects, given the nature of the task (see section 3.4.3 on Limitations).

In line with developmental studies of cognitive control (Humphrey & Dumontheil, 2016; Luna et al., 2015), adults had greater overall accuracy and faster reaction times than adolescents, as well as greater backwards digit span capacity (Karakas, Yalin, Irak, & Erzengin, 2002). However, since speed thresholds were determined individually to keep difficulty as homogenous as possible between the age groups, adolescents and adults earned comparable monetary rewards. Adolescents reported finding monetary incentives more rewarding than adults. These results are suggestive that the comparable performance between adolescents and adults might be driven by increased motivation to perform by the adolescents, perhaps associated with finding money more rewarding. The magnitude of control enhancement was not correlated with trait reward-sensitivity of participants, unlike previous accounts (Jimura et al., 2010).

Adolescents showed a trend for more reward sensitivity than adults in a composite self-report measure that was adapted from the adult study (Jimura et al. 2010). This is in line with the well described increase in reward sensitivity during adolescence (Galván, 2013; van Duijvenvoorde et al., 2016). In a post hoc analysis, we found adolescents had significantly greater reward sensitivity than adults on the SPSRQ (Torrubia et al., 2001), which assesses reward sensitivity *per se*, but not on the BIS/BAS (Carver & White, 1994), which measure approach motivations. We decided to employ these questionnaires to compare with previous findings by Jimura and colleagues, and due to the fact that we had both adolescents and adults. However, in future studies, reward sensitivity should be assessed with adolescent specific questionnaires.

In the absence of rewards, previous developmental work has suggested that adolescents employ a more reactive than proactive cognitive control strategy (Alahyane, et al., 2014; Andrews-Hanna et al., 2011; Velanova et al., 2009). In the present study we show that, similar to Strang and Pollack (2014), in the context of potential rewards, adolescents, like adults, can sustain cognitive control proactively. By also examining reactive control, in contrast to Strang and Pollack (2014), who only focused on proactive control), we provide evidence for additional improvements in a trial-by-trial fashion.

3.4.2 Neuroimaging results

We employed a mixed block/event-related fMRI design to dissociate sustained and transient responses associated with working memory in the varying reward contexts.

3.4.2.1 Working memory

In the absence of reward, performance of the letter array working memory task was associated with regions that exhibited sustained effects in areas distinct from sites of event-related responses. There was activation of a broad frontoparietal network which is associated with the WM network (see Wager and Smith, 2003 for a review). The Sternberg Item Recognition Paradigm measures the ability to maintain and search items in WM, and has been robustly related with activation of regions associated with storage (such as inferior frontal cortex and PPC), and DLPFC at higher load levels. Sustained-state effects were observed in regions that have been associated with sustained and transient activation in an n-back working memory paradigm (Marklund et al., 2007). The observed activity in the letter array working memory task in the absence of reward largely corresponds to previous reports of sustained and transient activity in regions implicated in domain general control processes as well as memory domains.

3.4.2.1.1 Developmental differences in working memory

For sustained activation, adults showed higher BOLD signal in the precentral gyrus and SMA (BA 6), a core region of the WM network in adults (Wager & Smith, 2003), which has however also been implicated in motor control (Seitz et al., 2009). Increased activation with age in these regions has been reported in a meta-analysis of WM fMRI studies in healthy adolescents and adults (Andre, Picchioni, Zhang, & Toulopoulou, 2015). Age effects were also observed for in the left superior frontal cortex (BA 46/9). These results are in line with reports of increased engagement of DLPFC with age in visuo-spatial working memory studies observed between children and adolescents (Klingberg et al., 2002)(Klingberg et al., 2002), children and emerging adults (Kwon et al., 2002), and adolescents and adults (Olesen et al., 2006). Adults also exhibited higher activity in superior medial gyri, extending into ACC (BA 24/32), as well as the lingual gyri in the occipital cortex.

For transient effects, adults exhibited higher BOLD signal in bilateral precentral gyri and the left postcentral gyri (BA 2) extending into inferior parietal lobule (BA 40/7), an area that has been implicated in WM updating (Wager & Smith, 2003). Developmental differences in the parietal cortex during working memory have been highlighted previously (Brahmbhatt et al., 2010; Crone et al., 2006; Klingberg et al., 2002). Adults showed more deactivation of the default mode network associated with accurate working memory trials than did adolescents, as has been previously observed in relation to successful memory encoding (Anticevic, Repovs, Shulman, & Barch, 2010; Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014).

We did not find evidence of instances where younger participants had higher greater WM activation than adults, in contrast with Brahmbhatt et al. (2010). Differences might be due to age differences of the samples (12-16 compared to 9-13 years old). Further studies examining a broader age range might help clarify developmental patterns.

Our results are consistent with the idea that sustained processes are subject to important developmental improvements with age. Beyond maintenance of WM, sustained activation may also reflect task control processes (Brahmbhatt et al., 2010; Dosenbach et al., 2007). Developmental changes in sustained aspects of cognitive control have also been observed in an inhibitory control task (Alahyane et al., 2014).

3.4.2.2 Proactive control (block effects)

Reward blocks were associated with sustained activity in cognitive control network areas: right LPFC clusters (BA 44/9, 6), bilateral AIns (BA 47) and right inferior parietal lobule (BA 40/7) for both adolescents and adults, perhaps playing a role in maintaining goal relevant information as well as more ventro-frontal regions (BA 45/47) that have been associated with working memory but also semantic memory and language comprehension. This sustained activation in the frontoparietal network did not overlap with the regions engaged during performance of the letter array WM task.

Sustained activity in the DLPFC and parietal cortex in task blocks of the Reward run might have enabled participants to maintain attention throughout a long and repetitive task, and earn rewards by making faster and more accurate responses. These results are in line with adult studies that examine sustained activity associated with proactive strategies: Jimura et al. (2010) describe a peak of activity in right LPFC (BA 46/9) and posterior parietal cortex (BA 40/7), while Locke and Braver (2008) found sustained activity in the right lateral RLPFC, right parietal cortex, and ACC in reward blocks of the AX-CPT task. In a similar developmental study, extended LPFC (including BA 44/48) activation in reward blocks of the AX-CPT was described in children, adolescents and adults by Strang and Pollack (2014).

Sustained activity was observed in bilateral AIns, which fits with previous accounts of its involvement in task-set maintenance (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; S. M. Nelson et al., 2010), and in tracking how stable cognitive control demands are in the environment (Jiang, Beck, Heller, & Egner, 2015). In addition, there was evidence for sustained activation in regions typically associated with reward: caudate, putamen and OFC

(BA 11). Further, sustained activity in the caudate positively tracked individual levels of reward sensitivity, with no age differences. While the role of the caudate in reward processing is well established (Silverman et al., 2015), it has recently been suggested by Jiang et al. (2015) that the caudate also plays a role in predicting forthcoming control demands. In this view, dorsal ACC and DLPFC would be involved in the implementation of proactive control in response to demands anticipated by the caudate. However, the design of the task, in which the Baseline run always preceded the Reward run, gives rise to potential order effects which limit the interpretation of the role of reward (see Section 3.4.3 for Limitations).

The pattern of results replicates previous findings in adults (Jiang et al., 2015; Jimura et al., 2010) and extends them to adolescents. Similarly to Strang and Pollack (2014), we did not find either behavioural or neuroimaging evidence for age-related differences in the shift to proactive control in sustained-only regions. Developmental findings by Alahyane and colleagues (2014) of reduced frontoparietal activity during saccade preparation, along with longer saccade RT and more errors, were driven by the youngest age group in their study (8-12 years old). Differences with age seemed to level off after age 13, which matches the early to mid-adolescent participants tested in the current study.

3.4.2.3 Reactive control (trial effects)

Across age groups, Reward trials were associated with increased transient activity in cortical regions related with letter-array working memory and cognitive control (AI, ACC and parietal cortex). In contrast, the block effects of reward were not observed in regions showing increased sustained activation during the working memory task. Perhaps, there is still scope for increased trial-by-trial recruitment with reward, on top of working memory transient activation, as transient activation is not as resource consuming.

Bilateral AIns showed transient activation. The AIns has been previously implicated in transient detection of salient stimuli and initiating attentional control signals which are then sustained by the ACC and the ventrolateral and dorsolateral PFC (Menon & Uddin, 2010). The ACC is usually engaged by conflict, in turn recruiting higher control order structures in the LPFC. Transient activity in the ACC might be related to increased monitoring in response to reward (Matthew M. Botvinick & Braver, 2015).

In addition, reward trials recruited regions typically implicated in reward processing: the right orbitofrontal cortex, as well as subcortically, the caudate and putamen (Silverman, Jedd, & Luciana, 2015). The caudate nucleus has been implicated in processing extrinsic reward related to monetary gains and losses (Haber & Knutson, 2010; Richards, Plate, &

Ernst, 2013). In line with these findings, we found that activity in the caudate nucleus tracked trial reward status as baseline activity was maintained for Reward trials only, while activation was lower for No reward trials. A speculative interpretation is that this pattern might suggest that once the explicit reward trials were introduced, the value of the No reward trials dropped compared to their starting level.

We did not find age differences in activation related to Reward trials compared to No reward trials. Although brain activation differences in adolescence are often described in the reward literature (Ernst et al., 2006; Galván, 2013) there are some discrepancies which have been explained in terms of the stage of reward processing (cue presentation, anticipation of reward and feedback) and type of reward task employed (Galván, 2010). The design of the current experiment was optimised for the investigation of cognitive control and not reward processing, as we could not capture the different stages of each trial, including the reward cue and feedback, which might explain the lack of age differences.

3.4.2.4 Mixed and exclusively transient regions

Bilateral insulae, the right posterior parietal cortex and the caudate nucleus exhibited a mixed pattern, with higher sustained activity for the Reward run compared to the Baseline run, as well as higher transient activity for Reward trials compared to No reward trials, and lower transient activation for No reward trials compared to Baseline rials. This pattern of activation would suggest that participants transiently decrease cognitive control for No reward trials and increase it for Reward trials. However, this is not reflected in behaviour, which might suggest that participants rely on heightened proactive control across the whole Reward run, as suggested by the block effect. In contrast, the anterior aspect of the ACC, and some cerebellar and occipital areas exhibited transient increases for the Reward trials exclusively.

Our results speak to the debate surrounding two underlying configurations which have been proposed for the DMC (Jiang et al., 2015). One of the accounts proposes that proactive and reactive control are implemented by different dynamics within the same region of the LPFC (Braver et al., 2009; G. C. Burgess & Braver, 2010; Jimura et al., 2010). Other accounts propose that different strategies are implemented by distinct brain regions (De Pisapia & Braver, 2006; Jiang et al., 2015). Here, we found evidence that both mechanisms might be at play. We show that there are both regions that are largely uniquely transient and sustained, but also regions with a mixed pattern of response.

In contrast to previous reports that point to the DLPFC, in our analyses, the AIns emerges as the key mixed region, while the DLPFC had a more sustained pattern of activation. These would be in line with the mixed role of the AIns which has been implicated in top-down control processes as well as bottom-up salience detection of more relevant, reward cues in this case (Menon & Uddin, 2010).

The AIns is part of the salience network and a key cognitive-emotional hub in the brain (Hauser et al., 2015; Menon & Uddin, 2010; A. R. Smith, Steinberg, & Chein, 2014). It is one of the most commonly activated areas in fMRI studies (Nelson et al., 2010) and has been implicated in controlling attention and task demands (see Nelson et al., 2010 for a review). In adults, activity in this region has been found to predict task switching in a cognitive flexibility task (Hampton & O'Doherty, 2007), and is involved when feedback is processes consciously (Nelson et al., 2010).

The AIns and inferior frontal gyrus (IFG) have been suggested to monitor current control demands, by encoding volatility in control demand and prediction error (Jiang et al., 2015). The AI/IFG tend to be more activated in higher demand tasks, and have been identified as part of the frontoparietal multiple demand cognitive control network (Duncan, 2010). Some authors argue that AI/IFG form a subnetwork involved in sustaining task control (Dosenbach et al., 2007; Nelson et al., 2010).

Further, the AIns has been associated with reward magnitude as well as expected value in a probabilistic decision task (Rolls, McCabe, & Redoute, 2008). It has recently been suggested that AIns might be an important area in the reward processing during the anticipation of rewards in adolescence and adulthood (A. R. Smith, Steinberg, & Chein, 2014). In follow-up ROI analyses, we found that without reward, adolescents had lower sustained and transient levels of activation than adults in left and right AIns. Transient increases for the Reward trials were similar for both age groups. However, adolescents showed a greater increase in sustained activation in task blocks of the Reward run compared to the Baseline run within the left AIns (with a similar, but not significant, increase in right AIns, "catching up" with adult levels of activation. This is suggestive that adolescents might be relying on an adaptive mechanism of sustained, but not transient, increase in AIns activation, compared to adults. This speaks to an immature proactive capacity in adolescents that is only engaged in the context of reward. However, one limitation of the study is that the mixed model employed might not fully dissociate block- from event-related activity (Petersen & Dubis, 2012).

Previous work in early and late childhood has shown that older children typically rely on reactive control but can be prompted to engage in proactive, preparatory processes, under different task conditions including labelling (Doebel, Dickerson, Hoover, & Munakata, 2017), goal activation (Barker & Munakata, 2015), and metacognitive processes associated with monitoring (Chevalier, Martis, Curran, & Munakata, 2015). Here, we suggest that reward might be another task feature that prompts adolescents into engaging effortful proactive control processes at the neural level that results in comparable behaviour to adults.

Developmental differences in AIns have been reported in studies of cognitive flexibility and attention (Christakou et al., 2009; Rubia et al., 2006; A. B. Smith et al., 2011) in other cognitive domains, such as relational reasoning (Dumontheil et al., 2010; Magis-Weinberg, Blakemore, & Dumontheil, 2017). The role of AIns in adolescent decision-making processes is increasingly recognised, suggesting that the relative immaturity of this cognitive-emotional hub may bias adolescents in affectively driven contexts (A. R. Smith et al., 2014). Smith et al. largely focus on the role this immaturity can play in negative risk-taking in adolescence. Our results, in contrast, suggest that a sensitivity to reward context in the AIns may support increased sustained engagement of cognitive control in some instances.

Further, the AIns is functionally connected with the ACC (Cauda et al., 2011) and together these regions are important for flexible adaptation in response to task demands (Sridharan, Levitin, & Menon, 2008). Exclusively transient activations were observed in anterior aspects of the ACC, which has been shown to be selectively involved in reactive control processes (Jiang et al., 2015). The authors have suggested that anterior ACC plays a role in improving resolution of residual conflict, consistent with the conflict-monitoring role of the ACC (Botvinick & Braver, 2015). In this case, it might be that the source of conflict comes from decisions related to necessary effort required to complete the task (Shenhav et al., 2013).

This complementary account to the proactive and reactive account contemplates the role of motivation on cognitive resource allocation. Impaired performance in tasks that require sustained attention can be explained by resource theories which posit there is a limited pool of cognitive resources for a given task that diminished with time, and assume that participants exert their maximal effort (Nicholls, Loveless, Thomas, Loetscher, & Churches, 2015). In a developmental context differences in performance in children and adolescents might be reflective of their limited resources compared to adults, as evidence by lower WM capacity. However, resource models have been revised to reflect that allocation of cognitive resources might not always be maximal but mediated by the magnitude of reward instead (Kurzban, Duckworth, Kable, & Myers, 2013)

Further, resource provision is subject to a cost-benefit analysis where cost of task performance is weighed against expect values of its outcome and necessary effort required

(Botvinick & Braver, 2015; Shenhav et al., 2013). Providing evidence for this, Massar et al. (2016) found that effort allocation in a sustained attention performance is affected by the motivational value of the task, and that the subjective value of reward is discounted by the effort required to receive the reward, assuming volitional control over resource allocation (Massar, Lim, Sasmita, & Chee, 2016). Although we did not do a cost-benefit analysis in the current experiment, our results align with the account of mobilization of resources in a proactive fashion in response to rewards. Interestingly, both adolescents and adults have “extra” resources available to be mobilized towards enhanced performance in the adequate context.

3.4.3 Limitations and future directions

Order effects might be a potential limitation of the current study. Counterbalancing the order of blocks was not possible to ensure participants were at first naïve regarding potential rewards to determine their baseline performance. All participants completed a Baseline run without any knowledge about potential rewards before the Reward run, which could result in practice or fatigue effects. To minimise order effects, we introduced a long practice period of 35 trials outside the scanner to ensure that participant’s performance stabilised before executing the task inside the scanner. However, our design does not allow us to fully differentiate reward from order effects. Although demanding, the task was not very difficult, as reflected by high accuracy rates. In addition, individual speed thresholds were established. Both were intentional features aimed at reducing confounds of age-related performance on brain activity. However, it might be that the balance between proactive and reactive strategies begins to emerge in more challenging cognitive control tasks, and future studies could investigate this. Finally, although few differences at the whole-brain level of analysis were found, further analysis could focus on whether age related differences exist in fronto-stratial connectivity (Vink et al., 2014).

3.5 CONCLUSION

Cognitive control can be sustained throughout a task (proactive control), or be recruited transiently at the trial level (reactive control), and this balance is sensitive to the reward context. Prior work has suggested that proactive and reactive control are supported both by separable neural circuitries, and by different dynamics within the same brain regions. This study investigated the development of cognitive control enhancement in the context of rewards, using fMRI with a mixed block-event-related design. The results show behavioural and neuroimaging evidence of modulation of both proactive and reactive control by reward in adults and in adolescents. In addition, the results suggest that proactive and reactive control are supported both by separable neural frontoparietal neural circuitries, as well as encoded by regions that can exhibit both sustained and transient temporal modulation that is sensitive to reward. In the face of incentives, both adolescents and adults can sustain cognitive control in a proactive fashion, with additional transient readjustments in response to the reward, and some evidence of adaptive higher activation by adolescents in the context of reward.

4 SOCIAL AND NON-SOCIAL RELATIONAL REASONING IN ADOLESCENCE AND ADULTHOOD

Abstract

Reasoning during social interactions requires the individual manipulation of mental representations of one's own traits and those of other people, as well as their joint consideration (relational integration). Research using non-social paradigms has linked relational integration to activity in the RLPFC. A recent study in a large developmental population found evidence for general development of social and non-social relational reasoning between the ages of 11 and 39. Here, we investigated whether social reasoning is supported by the same general system or whether it additionally relies on regions of the social brain network, such as the MPFC. We further assessed the development of social reasoning. In the social task, participants evaluated themselves or a friend, or compared themselves with their friend, on a series of traits. In the non-social task, participants evaluated their hometown or another town, or compared the two. Thirty-nine female participants (10-31 years) took part in a neuroimaging study. Activation of the relational integration network, including the RLPFC, was observed in the comparison condition of both the social and non-social tasks, while MPFC showed greater activation when participants processed social as opposed to non-social information across conditions. Developmentally, the right AIns showed greater activity in adolescents compared with adults during the comparison of non-social vs. social information. This study shows parallel recruitment of the social brain and the relational reasoning network during the relational integration of social information in adolescence and adulthood.

4.1 INTRODUCTION

Is London more expensive than Cambridge? Answering this question entails at least two levels of relational reasoning. At the first level, one needs to judge the prices in each city independently *(evaluation of single relations, e.g. how much do houses in London cost?*). At the second level, one needs to simultaneously consider mental representations of both cities, and to integrate the single judgements into a higher-order comparison *(relational integration,* in this case, comparing the house prices in London and Cambridge*)*. Relational integration has typically been studied in non-social contexts, in particular using the Raven's Progressive Matrices (Raven, 1998). However, relational integration also occurs in the social domain, for example, when comparing people on personality traits (*e.g. are you more patient than your friend?*). The neural processes supporting this kind of social reasoning, and the way it develops, are not well understood. Recently, a large behavioural study investigated the combination of domain-general and social domain-specific processes that support relational integration of social information between late childhood and adulthood (Magis-Weinberg et al., 2017). The current **Chapter**, expanded on these findings and investigated the development of these processes during adolescence, in a functional magnetic resonance (fMRI) study that employed a paradigm that permits the comparison of relational integration of social versus non-social information (Magis-Weinberg et al., 2017; Raposo, Vicens, Clithero, Dobbins, & Huettel, 2011).

As has been described in greater detail in the **Introduction** (see Section **1.3.2**), previous fMRI research has identified lateral PFC and lateral parietal cortex as involved in relational integration (Bunge, Helskog, & Wendelken, 2009; Dumontheil, 2014; Smith, Keramatian & Christoff, 2007; Wendelken, Nakhabenko, Donohue, Carter & Bunge, 2008), while medial PFC has been associated with the processing and manipulation of social information (Gilbert et al., 2006; Van Overwalle, 2009; Wood & Grafman, 2003). The current study aimed to bring together these separate strands of neuroimaging research to investigate domain-general and social domain-specific processes that support the relational integration of social information. Both relational reasoning and social cognition and their underlying neural substrates undergo significant reorganization during adolescence (Dumontheil, 2014; Kilford, Garrett & Blakemore, 2016). A previous behavioural study involving 325 participants (11-39 years), found that integrating relations compared to performing single relational judgements improves during adolescence, both for social and non-social information (Magis-Weinberg et al., 2017). Therefore, a second aim of the current study was to compare social reasoning in adolescents and adults.

We employed a paradigm that allows the investigation and comparison of relational integration of both social and non-social information (Magis-Weinberg et al., 2017; Raposo et al., 2011). We investigated the development of relational integration of social and non-social information from late childhood until adulthood and the neural correlates of these cognitive processes in adolescence and adulthood.

4.1.1 Neural bases of relational integration and social cognition

Relational reasoning research suggests a central role of the RLPFC, which corresponds to BA 10/46 and 10/47, in relational integration compared with processing single relations. Imaging studies using the Raven's Progressive Matrices in adults have shown RLPFC involvement in the joint manipulation of visuospatial patterns (Christoff et al., 2001; Kroger et al., 2002), as well as in the integration of relations in analogical reasoning tasks (Bunge, Wendelken, Badre, & Wagner, 2005; Wendelken, at al., 2008) and in the integration of multiple relations to reach a logical conclusion (Wendelken & Bunge, 2009). A study comparing visuospatial and semantic variants of a relational matching task found considerable activation overlap within left RLPFC, suggesting a domain-general role for RLPFC in relational integration (Wendelken, Chung, & Bunge, 2012).

As described in the **Introduction**, RLPFC is the key region at the top of the cognitive control hierarchy and is broadly engaged in cognitive functions such as prospective memory (see **Chapter 2**), episodic memory retrieval and attentional set-shifting (Hyafil et al., 2009; Mansouri et al., 2017). As such, it has been proposed that the function of RLPFC is to relate to the control of attention towards self-generated thoughts and the manipulation of self-generated thoughts (Burgess, Dumontheil, & Gilbert, 2007; Christoff, Ream, Geddes, & Gabrieli, 2003), and the cognitive control of abstract or temporally extended information (Badre, 2008) (see **Introduction**, Section **1.3.2**). A computational model of human RLPFC (or more specifically, BA 10) function suggests the underlying cognitive process supported by RLPFC is branching, whereby a task (A) is maintained in a pending state while another task (B) is executed, allowing a return to task A when task B is completed (Hyafil & Koechlin, 2016; Koechlin, Ody, & Kouneiher, 2003). In the context of relational integration, cognitive branching may allow the sequential processing, and maintenance, of single relations, and in turn their integration (see Section **1.3.2**).

Social cognitive research suggests a role of the MPFC, which corresponds to BA 8/9/10, in the processing of social information (see Van Overwalle, 2009 for a meta-analysis). Studies with adults have shown that this region is involved in considering one's thoughts and feelings (Gusnard, 2005; Rameson, Satpute, & Lieberman, 2010; Zysset, Huber, Samson, Ferstl, & von Cramon, 2003) and in perspective taking (Aichhorn, Perner, Kronbichler, Staffen, & Ladurner, 2006; D'Argembeau et al., 2007; David et al., 2008; David et al., 2006; Ruby & Decety, 2001, 2004; Vogeley et al., 2004). The MPFC is also recruited during tasks that require mentalising, that is, the consideration of other people’s mental states (Amodio & Frith, 2006; Decety & Sommerville, 2003; Frith & Frith, 2003).

4.1.2 Development during adolescence

Both relational integration and social cognition show protracted development in terms of improved performance and associated brain activity between adolescence and adulthood (Blakemore, 2012; Crone et al., 2009; Crone & Dahl, 2012; Dumontheil & Blakemore, 2012; Dumontheil, Burgess, & Blakemore, 2008, Dumontheil, Hillebrandt, Apperly, & Blakemore, 2012). The RLPFC undergoes structural and functional development with age, with evidence that its activity during relational integration tasks becomes increasingly specialised with age (Crone et al., 2009; Dumontheil, 2014; Dumontheil et al., 2008; Dumontheil, Houlton, Christoff, & Blakemore, 2010; Ferrer, O'Hare, & Bunge, 2009; Wendelken, O'Hare, Whitaker, Ferrer, & Bunge, 2011). In addition, a complex pattern of developmental changes in functional connectivity related to reasoning ability has been identified, including changes in connectivity between the RLPFC and the parietal cortex (Bazargani, Hillebrandt, Christoff, & Dumontheil, 2014; Wendelken, Ferrer, Whitaker, & Bunge, 2015). Bazargani et al. (2014) observed a decrease in short-range (fronto-insular) connectivity with stable long-range connectivity (frontoparietal) and an increase of modulatory connections with age. Wendelken et al. (2015) found a pattern of developmental changes suggestive of increasing communication between prefrontal regions and specific targets.

Key regions of the social brain, including the MPFC, undergo structural and functional changes during adolescence. Cortical thickness and grey matter volume in the MPFC decrease between late childhood and the early twenties (Mills, Lalonde, Clasen, Giedd and Blakemore, 2014). In parallel, several fMRI studies have shown that MPFC activity during mentalising tasks decreases between early adolescence and adulthood (Burnett et al., 2011; Blakemore, 2008, 2012). In a previous study investigating the development of the neural correlates of mentalising, participants were required either to take someone else’s perspective or to use symbolic cues to select an appropriate action in a communicative context. We found that adolescents showed hypoactivation of domain-general cognitive control regions in the parietal cortex and PFC, and hyperactivation of parts of the social brain network (Dumontheil, et al., 2012). This study thus demonstrated the engagement of cognitive control and social brain regions within a single paradigm, and that the engagement of these regions changes as a function of age.

Relational integration within the social domain has previously been investigated in adults using a task that combined both mentalising and relational integration (Raposo et al., 2011). Participants judged how pleasant they found a certain word, how pleasant a friend would find the word, and how their rating of pleasantness would compare to that of their friend. Behaviourally, reaction times were higher when participants were comparing themselves to their friend relative to the two single relations conditions. MPFC activation was higher during the friend judgement compared with the self judgement, while dorsolateral frontal cortex activation was higher when contrasting the relational integration comparison and the self judgement conditions. The study did not include a non-social relational reasoning condition, preventing the conclusion that the activation patterns are specific to relational integration of social information per se, or reflective of relational integration more generally.

4.1.3 The present study

Here, we adapted the paradigm designed by Raposo et al. (2011) and employed by Magis-Weinberg, et al. (2017) to investigate both the behavioural and neural development of relational reasoning between adolescence and adulthood. We compared first-order judgements (1-REL) of traits associated with oneself or with another individual (e.g. How patient are you? (Self condition); How patient is your friend? (Other condition)), with second-order judgements (2-REL) about how these judgements related to each other (How much more patient are you than your friend? (Comparison condition)). Our paradigm also included a control non-social task, in which participants were asked to rate characteristics of towns. Our aim was to assess: (1) how performance on a task requiring relational integration of social or non-social traits develops between late childhood and adulthood; (2) how neural activity underlying these processes develops between early adolescence and adulthood; and (3) whether there is domain-specific activation for the relational integration of social vs non-social information.

In terms of behaviour, we predicted improvements in relational integration with age, both in terms of reaction time and the consistency of participants' responses between 1-REL and 2-REL judgements (Magis-Weinberg et al., 2017). In terms of blood-oxygen level dependent (BOLD) signal, we expected domain-general activations associated with relational integration in RLPFC, dorsolateral PFC and parietal cortex. We also predicted there would be additional domain-specific activations in parts of the social brain network associated with the People task, specifically regions involved in processing social information and mentalising (Dumontheil & Blakemore, 2012; Meyer, Spunt, Berkman, Taylor, & Lieberman, 2012; Meyer, Taylor, Lieberman, 2015; Raposo et al., 2011). Finally, we predicted that the

RLPFC would show increased specificity of activation for REL-2 vs. REL-1 judgements in adults compared to adolescents (Dumontheil, 2014), and that MPFC would show greater activation in adolescents than adults in the social vs. non-social task (Blakemore, 2008; Blakemore & Robbins, 2012; Burnett et al., 2011).

4.2 METHODS

4.2.1 Participants

Thirty-nine female participants took part in the study: 19 adolescents between 10 and 16 years old (*M* = 14.1 ± 1.9 (*SD*)) and 20 adults between 22 and 31 years old (*M* = 25.9 ± 2.8). Seven adolescents and two adults had previously taken part in the large behavioural study (Magis-Weinberg et al., 2017), with an interval of between 4 and 10 months between the testing sessions. Only female participants were included to reduce variability in the sample due to sex differences in brain development (Herting, Maxwell, Irvine, & Nagel, 2012; Raznahan et al., 2011). Gender differences were not found in the large behavioural study or in a previous behavioural and neuroimaging study of visuospatial relational reasoning development (Wendelken et al., 2011). However, other behavioural studies have reported gender differences in mentalising (e.g. Charman, Ruffman & Clements, 2002) and in relational reasoning (Lynn & Irwing, 2004). Since we were unable to collect a sample large enough to investigate gender differences, we chose to maximize the homogeneity of our sample by only including female participants.

Participants were reimbursed £20 and their travel expenses for taking part in the study. The study was approved by the UCL Research Ethics Committee. Participants were divided into two groups, adolescents and adults. Adolescents were combined into a single group because of the sample size, with a focus on investigating the development of the neural correlates of relational reasoning. Adolescent (*M* = 116.8 ± 11.4 (*SD*)) and adult (*M* = 119.9 ± 6.7) The two groups were matched on estimated IQ (*t*(36) = 1.02, *p* = .314), which was assessed using the Vocabulary and Matrices subtests of the WASI (Wechsler, 1999). WASI data were missing for one participant.

4.2.2 Design and stimulus material

The fMRI task had two within-subjects factors (Task: People, Town; Condition: Self, Other, Comparison, Vowels) and one between-subjects factor (Age group: adults, adolescents), resulting in a 2 x 4 x 2 mixed design. Participants were first trained on the task outside the scanner. After going through the four types of question for each Task, participants performed one block of three trials for each Task and Condition. Participants then performed four scanning runs as well as a structural scan between the second and third task runs. After scanning, participants completed the Interpersonal Reactivity Index (IRI; Davis, 1980), which provides measures of four components of empathy (empathic concern, fantasy, personal distress and perspective taking), and were assessed on the WASI. The IRI was included as it has been used in previous neuroimaging studies as a measure of individual differences in social cognition in everyday life (Meyer, et al., 2012; Raposo et al., 2011). Meyer et al. (2012) found an association between memory load-dependent activity within mentalising regions and scores on the Perspective Taking scale. We therefore aimed to relate activity within mentalising regions with this everyday life measure of perspective taking.

4.2.3 Relational reasoning task

The experimenter started by asking participants to think of someone that they knew quite well but who was quite different from them, and to give his/her name. If participants did not respond, the experimenter suggested they consider a close friend or a sibling who was quite different from them. Second, participants were asked to name the town where they lived (typically London) and then pick a town that they knew quite well but which was quite different from London. Again, if participants did not respond, the experimenter suggested they consider a town where they go on holiday or where their grandparents live. Instructions were then presented on the screen and read aloud to the participants, explaining the different types of judgement they would make during the task, and the rating scale. Participants used the index, middle and ring fingers of both hands to respond. The task was programmed in Cogent (http://www.vislab.ucl.ac.uk/cogent_graphics.php) running in MatLab (MathWorks) on a DELL 12 inch laptop or similar.

Judgements were blocked according to Task and Condition and the order of the blocks was counterbalanced within and between participants. Each block started with an instruction screen indicating to participants what type of judgement they should make during that block. On each trial, this information was repeated at the top (e.g. “You”), an adjective was presented in the middle of the screen, and a rating scale from 1 to 6 was provided at the bottom of the scale (**See 1**).

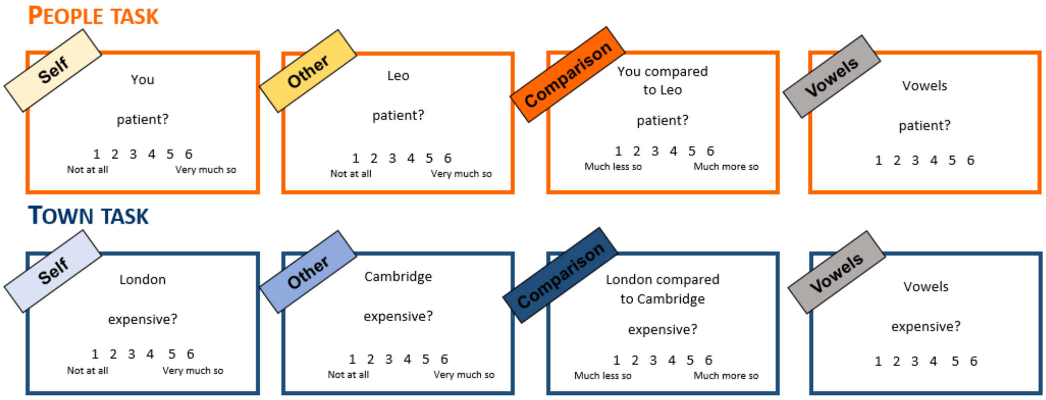


Figure 4.1: Example of stimuli for each task and condition. In the People task, participants were asked: “How much do you think the following words apply to you/your friend?” (Self/Other), or “How much do you think the following words apply to you compared to your friend?” (Comparison). On the rating scale, 1 indicated not at all and 6 indicated very much so in the Self and Other conditions, while 1 indicated much less so and 6 indicated much more so in the Comparison condition. In the Vowels condition, participants had to indicate the number of vowels in the adjective. All text was presented in white on a black background. (Figure originally in Magis-Weinberg et al. 2017, reproduced under a CC BY-NC-ND 3.0 license).

The task included a Vowels condition in which participants were required to count the number of vowels in the adjective presented on the screen. This condition matched visual and verbal processing and motor execution demands while minimising relational reasoning demands and, as such, was used as a baseline in the fMRI analyses. Regions of the social brain often show high activation at rest or during fixation phases, as part of the default mode network. Using an active baseline allowed the identification of activation of these brain regions, which was important for the People task. In addition, the words presented in the People and Town tasks differed, and using the Vowels condition as a baseline allowed us to control for BOLD signal differences elicited by the presentation of these words. The paradigm was similar to the task described by Raposo et al. (2011), with two differences. First, traits were different for the People and Town tasks in an attempt to make them more relevant to each category. Second, a fixed inter-stimulus-interval (ISI) of 100 ms was used.

Participants performed two scanning runs of the People and Town task, alternating in an ABAB or BABA order, counterbalanced across participants. Each run comprised five blocks of each condition (Self, Other, Comparison and Vowels). The order of the conditions was fixed within a run, and counterbalanced across runs and participants. After every Vowels block, there was a fixation block. Task blocks were preceded by a 1 s instruction that specified the condition of the next block (e.g. “You”, “Leo”, “You compared to Leo”, “Vowels”, “London”, “Cambridge”, “London compared to Cambridge”) and comprised three trials each.

Participants had a maximum of 6.05 s to input their response on each trial, during which time the stimulus remained on the screen. When participants responded, the number they pressed turned red and the stimulus remained on the screen until 6.1s after the onset of the trial presentation. A blank screen was displayed during the ISI. Stimuli consisted of lists of 30 adjectives in each task, which were matched for number of letters, number of vowels, frequency and familiarity (see **Table 4.1**). Each adjective was presented once in each of the four conditions. Half of the adjectives were presented in the first scanning run of a task, half in the second run.

Table 4.*1* *List of stimuli for each task*. In the People task, participants were asked: "How much do you think the following words apply to you/your friend?", or "How much do you think the following words apply to you compared to your friend?". In the Town task, participants were asked: "How much do you think the following words apply to your town/other town?", or "How much do you think the following words apply to your town compared to the other town?". Familiarity and frequency measures were included to ensure that all adjectives were commonly used English words, and that their occurrence was comparable between Tasks.

	People	**Town**	
Adjectives	arrogant, jealous, timid, selfish, careless, witty, cheerful, thoughtful, stubborn, ambitious, confident, aggressive, clever, smart, bold, brave, generous, helpful, mature, wise, tough, funny, curious, honest, sensitive, friendly, fair, patient, bright, happy	run-down, shabby, boring, rainy, noisy, sleepy, vibrant, picturesque, polluted, quaint, historic, lively, dull, exciting, romantic, dirty, urban, expensive, dangerous, rural, cultural, safe, unusual, clean, quiet, traditional, famous, amazing, flat, ancient	
Number of letters	*M* = 6.7, *SD* = 1.8,	*M* = 6.6, *SD* = 1.9	*t*(58) = 0.14, *p* = .89
Number of vowels	*M* = 2.5, *SD* = 1.1	*M* = 2.6, *SD* = 1.1	*t(*58) = 0.36, *p* = .73
Familiarity	*M* = 541.6*, SD* = 48.6	*M* = 561.6, *SD* = 53.6	*t(*40*)* = 1.2, *p* =.23
Brown frequency	*M* = 9.26, *SD* = 10.6	*M* = 7.70, *SD* = 11.0	*t*(41) = 0.47, *p* = .64
Kucera-Francis frequency	*M* = 32.0, *SD* = 26.9	*M* = 35.3, *SD* = 27.2	*t*(58) = 0.47, *p* = .64

4.2.4 FMRI acquisition

Multi-slice T2-weighted echo-planar volumes with BOLD contrast (35 axial slices with a voxel resolution of 3 × 3 × 3 mm covering most of the cerebrum; TR = 2.975 s; TE = 50 ms; TA = 2.925 s) were obtained using a 1.5 T MRI scanner (Siemens TIM Avanto, Erlangen, Germany). Functional images were acquired in four scanning runs lasting approximately 8 min 40 s each in which 174 volumes were obtained. The first four volumes of each run were discarded to allow for T1 equilibrium effects. A 3D T1-weighted fast-field echo anatomical image lasting 5 min 30 s was acquired after the first two functional runs for each participant.

4.2.5 Data Analysis

4.2.5.1 Behavioural data

A 2 (Task) x 4 (Condition) x 2 (Age group) mixed rmANOVA was performed on median RT data. A 2 (Task) x 2 (Age group) mixed rmANOVA was employed to analyse mean consistency, which was calculated as the Fisher *z*-transformed Spearman correlation between participants' answers in the Comparison condition and the difference between their answers in the Self and Other conditions.

4.2.5.2 MRI data

MRI data were preprocessed and analysed using SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Images were realigned to the first analysed volume with a second-degree B-spline interpolation to correct for movement during the session. The bias-field corrected structural image was coregistered to the mean, realigned functional image and segmented on the basis of Montreal Neurological Institute (MNI)-registered International Consortium for Brain Mapping (ICBM) tissue probability maps. Resulting spatial normalisation parameters were applied to the realigned images to obtain normalised functional images with a voxel size of 3 x 3 x 3 mm, which were smoothed with an 8-mm full width at half maximum Gaussian kernel.

Realignment estimates were used to calculated framewise displacement (FD) for each volume, which is a composite, scalar measure of head motion across the six realignment estimates (Siegel et al., 2014)**.** Volumes with an FD > 0.9 mm were censored and excluded from general linear model (GLM) estimation by including a regressor of no interest for each censored volume. Scanning sessions with more than 10 % of volumes censored or a root mean square (RMS) movement over the whole session greater than 1.5 mm (1 session for three participants, 2 sessions for one participant) were excluded from the analysis. Adolescent and adult participants significantly differed in the number of overall censored volumes ($M_{\text{adolescents}}$ = 3.39 ± 3.61 (SD), M_{adults} = 0.19 ± 0.38; $p < .001$), mean RMS translational movement ($M_{\text{adolescents}}$ = 0.32 mm ± 0.11, M_{adults} = 0.24 mm ± 0.07; $p = .005$), and mean FD ($M_{\text{adolescents}}$ = 0.18 mm ± 0.08, M_{adults} = 0.10 mm ± 0.02; $p < .001$). There was a no difference between groups in terms of mean RMS rotational movement ($M_{\text{adolescents}}$ = 0.23 mm ± 0.12, M_{adults} = 0.17 mm ± 0.08; $p = .088$).

Scanning runs were treated as separate time series and each series was modelled by a set of regressors in the GLM. Runs of the People or Town Task were each modelled by six box-car regressors: four regressors corresponding to each Condition (Self, Other, Comparison, Vowels), with a duration of 18.6 s; Instructions, with a duration of 1 s; and Fixation blocks, with a duration of 18.6 s except for the last block which had a duration of 39 s. All regressors were convolved with a canonical haemodynamic response function and, together with the separate regressors representing each censored volume and the mean over scans, comprised the full model for each session. The data and model were high-pass filtered to a cut-off of 1/128 Hz.

The second-level whole-brain analysis focused on relational integration, i.e. the main effect of Comparison (2-REL) versus Self and Other (1-REL) conditions, and on differences between social and non-social tasks. The 1-REL conditions, Self and Other, were thus combined within each task. Four first level contrasts were calculated using the Vowels condition as a baseline within each task: People [Self, Other] – People Vowels (*People SO*), People Comparison – People Vowels (*People Comp*), Town [Self, Other] – Town Vowels (*Town SO*), Town Comparison – Town Vowels (*Town Comp)*. These contrasts were then entered into a random-effects analysis using a Subject x Age group (2) x Block type (4) flexible factorial design, modelling Subject as a main effect (to account for the repeated-measure nature of the data) and the Age group x Block type interaction.

Main effects of Condition (Comparison > SO) and Task (People > Town and Town > People) and the interaction between the two factors and with Age group were determined using the t statistic on a voxel-by-voxel basis. Statistical contrasts were used to create SPM maps thresholded at $p < .001$ at the voxel level and at family-wise error (FWE)-corrected $p < .05$ at the cluster-level (corresponding to a minimum cluster size of 77 voxels determined with SPM8). Activations that survived whole-brain FWE correction at $p < .05$ at the voxel-level are indicated. All coordinates are given in MNI space. Significant interactions were followed up by extracting the mean signal across all voxels of significant clusters with MarsBar (Brett et al., 2002) and analysing simple effects in SPSS using t-tests (with Bonferroni correction for multiple comparisons).

We performed exploratory correlation analyses between consistency in ratings and individual differences in activation in the tasks. Relevant task contrasts were entered in a two-sample t-test design modelling the two age groups separately, with the behavioural measure as a single covariate of interest. Correlations were run between the contrasts [Comparison > SO] and [Comparison/Self/Other > Vowels] and the mean consistency across tasks; between the contrast [People Comparison > SO] and consistency in the People task; and between the contrast [Town Comparison > SO] and consistency in the Town task. In the same manner, we explored correlations between individual differences in the [People > Town] and [People Comparison > SO] contrasts and the perspective-taking scale of the IRI (see Meyer, Taylor, & Lieberman, 2015, for a similar approach).

4.3 RESULTS

4.3.1 Behavioural results

4.3.1.1 Reaction times

There was a main effect of Task ($F(1, 37) = 13.51$, $p = .001$, $\eta_p^2 = .27$). Participants were slower in the Town ($M = 2419 \pm 69$ ms (SE)) relative to the People task ($M = 2282 \pm 63$ ms). There was a main effect of Condition ($F(1.8, 66.8) = 29.17$, $p < .001$, $\eta_p^2 = .44$) (**Table 4.2, Figure 4.2.A**). Pairwise comparisons with Bonferroni correction revealed that participants were slowest in the Comparison condition relative to all other conditions ($M_{Comparison} = 2638 \pm 79$ ms, $M_{Self} = 2180 \pm 67$ ms, $M_{Other} = 2195 \pm 62$ ms, $M_{Vowels} = 2388 \pm 77$ ms, all p's < .005). The Vowels condition was the next slowest (all p's < .05). Self and Other conditions did not differ significantly from one another ($p > .05$). There was no main effect of Age group ($F(1,37) = 2.21$).

Table 4.2: Mean median RT and SE (ms) for each Task (People, Town) and Condition (Self, Other, Comparison, Vowels).

	People		**Town**	
	Adolescents Mean (SE)	*Adults* Mean (SE)	*Adolescents* Mean (SE)	*Adults* Mean (SE)
Self	2215 (110)	2057 (107)	2333 (100)	2115 (98)
Other	2123 (94)	2112 (92)	2378 (96)	2171 (94)
Comparison	2570 (108)	2460 (106)	2904 (136)	2618 (133)
Vowels	2503 (112)	2212 (109)	2529 (120)	2309 (117)

There was a significant interaction between Task and Condition ($F(3, 111) = 3.14$, $p = .028$, $\eta_p^2 = .08$). This was followed up by analysing the data in the People and Town tasks separately. In both the People and Town tasks, participants were slower in Comparison than Self and Other trials (all p's < .001). In the People task, participants were slower in Vowels than Self and Other trials (all p's < .05). The two-way interaction is driven by a greater difference between Comparison and Vowels trials in the Town ($M_{Comp\text{-}Vowels} = 342$ ms) than in the People task ($M_{Comp\text{-}Vowels} = 157$ ms, $p = .008$) while the difference between

Comparison and Self and Other trials did not differ between tasks (*p*'s > .05). There was no significant interactions between Condition and Age group (*F*(1.8, 66.8) = 0.55). There were no significant interactions between Task and Age group (*F*(1,37) = 1.43, *p* = .24, $\eta_p{}^2$ = .04) or amongst Condition, Task and Age group (*F*(2.7, 98.8) = 1.76).

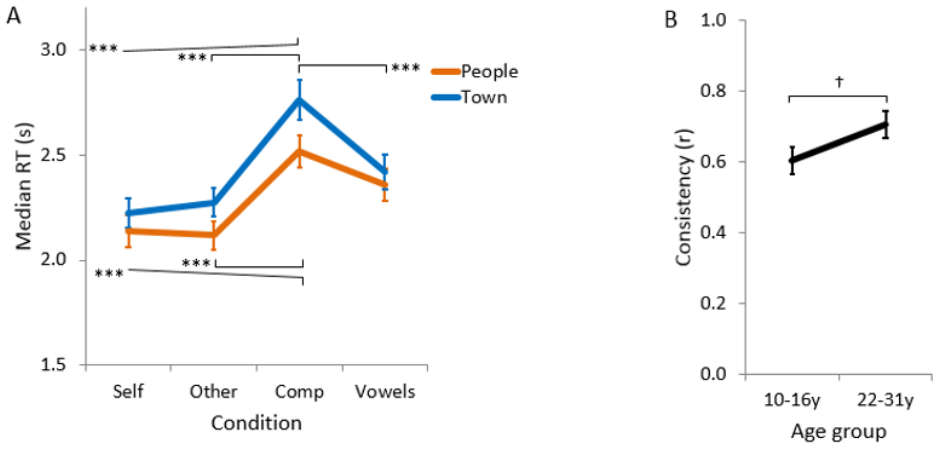


Figure 4.2: Mean RT and consistency scores as a function of task and condition or age group. **(A)** Mean RTs a function of Task and Condition. **(B)** Mean consistency scores as a function of Age group. Error bars represent SE. * $p < .05$, ** $p < .01$, *** $p < .001$ (Bonferroni corrected). (Figure originally in Magis-Weinberg et al. 2017, reproduced under a CC BY-NC-ND 3.0 license)

4.3.1.2 Consistency

Participants were consistent overall, with positive correlations between the 1-REL and 2-REL ratings**.** There was a trend effect of Age group (*F*(1, 37) = 3. 46, *p* = .071, $\eta_p{}^2$ = .09, **Figure 4.2.B**), with lower consistency in adolescents than adults. There was also a main effect of Task (*F*(1, 37) = 18.04, *p* < .001, $\eta_p{}^2$ = .33): consistency was lower for People than for Town (M_{People} = .74± .05, M_{Town} = .96 ± .07). The interaction between Task and Age group was not significant (*F*(1,37) = 0.67).

4.3.1.3 IRI

Analyses of the subscales of the IRI revealed significantly higher Perspective Taking (PT) and Empathic Concern (EC) scores for adults (M_{PT} = 19.5 ± .91 (*SE*); M_{EC} = 20.9 ± 1.1) than for adolescents (M_{PT} = 14.1 ± .94; M_{EC} = 16.8 ± 1.1; all *p*'s < .05). Pearson correlation coefficients were computed to assess the relationship between PT and performance in the task. There was no correlation between PT and Consistency in the People task (*r* = -.187, *p* = .255). There was also no correlation between PT and mean median RT for the Self (*r* = -.021, *p* = .897), Other (*r* = .006, *p* = .973), or Comparison (*r* = .068, *p* = .680) conditions in the People task.

4.3.2 FMRI Results

Whole-brain analyses contrasted the Comparison condition to the combined Self and Other (SO) conditions in the People and Town tasks. The Vowels condition served as an active baseline.

Table 4.3: *Summary of neuroimaging results*. Coordinates and Z-scores are listed for regions showing a significant difference in BOLD signal for the main effect of Condition [Comparison > SO], the main effect of Task [People > Town] or [Town > People], and the interaction between Condition, Task and Age Group [(Adolescents > Adults [(Town Comparison > SO) > [People (Comparison > SO)]]. Regions labelling was done using Automatic Anatomic Labelling (AAL) (Tzourio-Mazoyer et al., 2002). BA labelling of peak of activations was done using MRIcron. [a] indicates voxels where $p_{FWE} < .05$ at the voxel-level, [b] indicates clusters where $p_{FWE} < .05$ at the cluster-level, with a cluster-defining threshold of $p < .001$ uncorrected at the voxel-level. BA = Brodmann area, L/R = Left/Right hemisphere, Pre-SMA = pre-supplementary motor area.

Region	L/R	Extent	Z-score	x	y	z	BA
Main effect of Condition (Comparison > SO)							
Lingual gyrus	L	4959[b]	>8[a]	-9	-85	-14	12
Calcarine gyrus			>8[a]	0	-85	1	17
Lingual gyrus	L		>8[a]	-21	-79	-14	18
Lingual gyrus	R		>8[a]	18	-79	-14	18
Precuneus	R		>8[a]	3	-61	46	7
Middle occipital gyrus	R		7.31[a]	30	-79	19	19
Middle occipital gyrus	L		6.53[a]	-30	-76	22	19
Middle temporal gyrus	L		6.22[a]	-48	-46	10	21
Inferior parietal gyrus	L		6.13[a]	-45	-46	43	40
Fusiform	R		5.90[a]	27	-64	-5	19
Inferior frontal gyrus	L	1351[b]	6.59[a]	-48	14	25	48
Precentral and middle frontal gyri	L		5.78[a]	-39	-1	55	6
Middle cingulate cortex and pre-SMA	R		5.77[a]	9	20	46	32
Inferior frontal gyrus	L		5.68[a]	-36	20	22	48
Middle frontal gyrus	R	819[b]	5.55[a]	30	14	43	44
Inferior frontal gyrus	R		5.32[a]	48	26	31	44
Middle frontal gyrus	R		5.03[a]	30	23	52	8
Middle and superior frontal gyri	R		4.56[a]	30	59	7	10
Precentral gyrus	R		4.44	30	-4	46	6

Inferior and middle frontal gyri	L	95[b]	4.91 [a]	-39	47	-2	47
Main Effect of Task (People > Town)							
Medial prefrontal cortex	R	1649[b]	7.22[a]	6	53	13	10
Anterior cingulate cortex	L		7.11[a]	-3	53	13	32
Anterior cingulate cortex	L		5.95[a]	-6	44	1	10
Anterior insula	R	69	5.74[a]	30	17	-17	48
Precuneus and posterior cingulate cortex	R	132[b]	5.26[a]	6	-52	28	23
Main Effect of Task (Town>People)							
Lingual gyrus	R	2164[b]	>8[a]		-49	4	30
Calcarine gyrus	R		7.65[a]	15	-52	13	30
Calcarine gyrus	L		7.17[a]	-12	-55	10	30
Middle occipital gyrus	L		6.08[a]	-33	-76	28	19
Middle occipital gyrus	R		5.90[a]	36	-70	37	19
Superior occipital gyrus	L		5.25[a]	-21	-64	28	23
Superior occipital gyrus	R		4.62[a]	24	-76	46	7
Fusiform and parahippocampal gyri	L	192[b]	>8 [a]	-30	-37	-14	37
Fusiform gyrus	R	302[b]	6.97[a]	30	-31	-17	37
Inferior temporal gyrus	R		4.13	54	-46	-11	20
Parahippocampal gyrus	R		3.73	21	-13	-20	35
Middle cingulate cortex	R	60	4.78[a]	9	-34	34	23
Precentral gyrus and inferior frontal operculum	L	181[b]	4.58[a]	-42	8	28	44
Postcentral and precentral gyri	R	108 [b]	3.93	60	-10	31	43
Interaction Adolescents > Adults [(Town Comparison > SO) > [People (Comparison > SO)]							
Anterior insula	R	178[b]	4.26	33	17	-8	48
Anterior insula	R		3.71	39	26	4	47
Temporal pole	R		3.59	45	14	-20	38

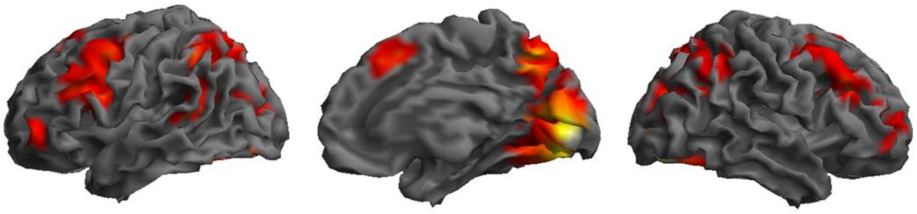
4.3.2.1 Relational integration

A broad bilateral network of fronto-parietal, temporal and occipital regions, including bilateral RLPFC, showed increased BOLD signal in Comparison vs SO conditions, (**Table 4.3** and **Figure 4.3.A**), that is, in 2-REL as opposed to 1-REL processing. Increases in BOLD signal were observed in a large posterior cluster extending into bilateral occipital and lingual gyri, calcarine sulcus, inferior parietal lobule, and in anterior clusters in the precentral gyrus, pre-supplementary motor area (pre-SMA), and inferior and middle frontal gyri.

4.3.2.2 Social information processing

When comparing the People task to the Town task, that is, when the information to be processed was of social (traits of participant or a friend) versus non-social nature (characteristics of towns), increased BOLD signal was observed in clusters in the MPFC, insula, and precuneus (**Table 4.3** and **Figure 4.3.B**). The reverse contrast revealed increased BOLD signal in a large cluster extending into bilateral calcarine gyri, middle and superior occipital gyri, as well as bilateral clusters in the fusiform and parahippocampal gyri extending into the medial temporal gyri, in the middle cingulate cortex, bilateral pre- and postcentral gyri and left inferior frontal cortex (**Table 4.3**).

A **Comparison > Self & Other**



B **People > Town**

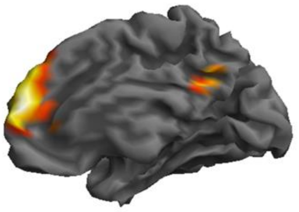


Figure 4.3: *FMRI results across age groups*. (**A**) Main effect of Condition. Regions showing increased BOLD signal in Comparison (2-REL) compared to Self and Other (1-REL) conditions are rendered on the SPM8 surface mesh template. From left to right: lateral view of the left hemisphere, medial and lateral views of the right hemisphere. (**B**) Main effect of Task. Regions showing increased BOLD signal in the People compared to the Town task are rendered on the SPM8 surface mesh template (medial view of the right hemisphere). (Figure originally in Magis-Weinberg et al. 2017, reproduced under a CC BY-NC-ND 3.0 license).

4.3.3 Age group differences

There was no two-way interaction between Task and Age group nor between Condition and Age group, however whole-brain analyses showed a significant three-way interaction between Task, Condition and Age group in BOLD signal in the right insula (see **Table 4.3** and **Figure 4.4**). The mean parameter estimates in this cluster were calculated and the interaction was followed up by running 2 (Condition) x 2 (Age group) mixed rmANOVAs in each Task separately. There was an interaction between Condition and Age group in the People task ($F(1, 37) = 7.20$, $p = 0.011$, $\eta_p^2 = .16$), and in the Town task ($F(1, 37) = 8.64$, $p = .006$, $\eta_p^2 = .19$).

These interactions were further explored by comparing SO and Comparison conditions within each age group. In the People task, adolescents showed greater activation in the SO than the Comparison condition (*p* = .026), while the conditions did not differ in adults (*p* = .132). In the Town task, adolescents reversely showed greater activation in the Comparison than the SO condition (*p* = .018), while again there was no difference in adults (*p* = .176).

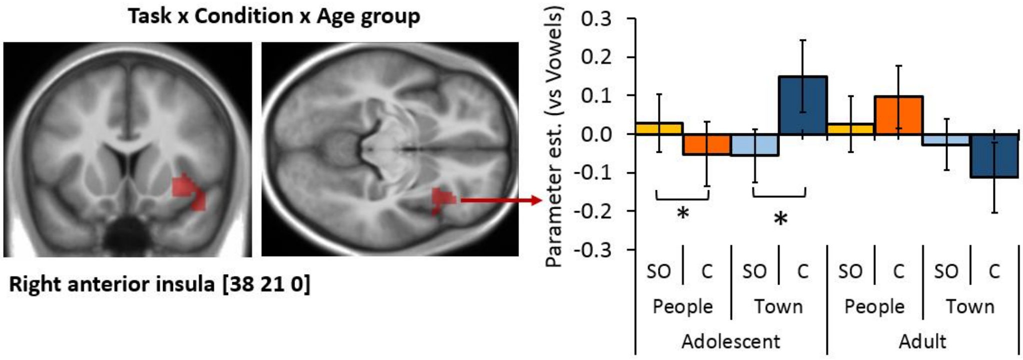


Figure 4.4: *FMRI results of the interaction between Task, Condition and Age group*. On the left, the right anterior insula cluster showing a three-way interaction between Task, Condition and Age group is shown on an average structural scan of all participants in the study (left y = 21; right: z = 0). The contrast was thresholded at $p < .001$ uncorrected at the voxel level, $p_{FWE} < .05$ at the cluster level. On the right, parameter estimates extracted from this cluster are plotted in a bar chart to illustrate the three-way interaction. Error bars represent SE. † $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$. (Figure originally in Magis-Weinberg et al. ,2017, reproduced under a CC BY-NC-ND 3.0 license).

4.3.4 Covariate analyses

Whole-brain analyses were performed to investigate correlations between the behavioural measure of Consistency and BOLD signal during the task. No correlation between Consistency scores and individual differences in BOLD signal in the contrasts [Comparison > SO], [Comparison/Self/Other > Vowels], [People Comparison > People SO], [Town Comparison > Town SO]) was observed. Further whole-brain analyses showed that BOLD signal in the [People > Town] and [People Comparison > People SO] contrasts was not significantly related to the perspective-taking scale of the IRI.

4.4 DISCUSSION

We performed an fMRI study aiming to disentangle general and specific processes underlying relational integration of social information between adolescence and adulthood. We did not find strong behavioural evidence for general development of social and non-social relational reasoning. We discovered similar patterns of neural activity for adolescents and adults showing domain general involvement of the fronto-parietal cortex areas associated with relational integration for both social and non-social relations, and domain specific involvement of the social brain for the manipulation of social information.

4.4.1 Behavioural findings

4.4.1.1 Relational integration

RTs were slower in the Comparison than in the Self and Other conditions. There was a trend for poorer consistency in the adolescents, but no developmental effects on RTs. These results should be considered in the light of findings from a large behavioural study which employed this task to test 11– 39 years old. Magis-Weinberg et al. (2017) found that there was a considerable difference in RT between 2-REL and 1-REL judgments, which decreased between 11–12 and 13–14 years old. Consistency was also higher in the Town than in the People task and improved between 13–14 and 15–17 years old. There was no interaction between Task and Age group, suggesting no evidence of a developmental difference in relational integration between the social and non-social tasks (Magis-Weinberg et al., 2017). The results from the present investigation are in line with findings of development on consistency of the large behavioural study. However, the less robust behavioural results and lack of RT effects in this study were likely due to the smaller sample size in the imaging study (n= 39 versus n = 325).

The lack of developmental effects on relational integration are at odds with previous findings from visuospatial relational integration tasks, which indicate poorer relational integration accuracy in 8-12 yo than in adults (Crone et al., 2009), improvements in accuracy between 9 and 19 yo (Rosso, Young, Femia, & Yurgelun-Todd, 2004) and poorer combined accuracy and RT in 7-9 yo than in 14-17 yo (Dumontheil, Houlton, et al., 2010, reanalysed in Dumontheil, 2014). Our results are not consistent with a previous investigation of the development of the integration of semantic information using an analogical reasoning task, which demonstrated poorer performance in 6-13-year-olds than in adults (Wright, Matlen, Baym, Ferrer, & Bunge, 2008). Instead, these results align with Wendelken et al. (2011) who did not find age differences in 7-18-year-olds (see Dumontheil, 2014, for review).

4.4.1.2 Social information processing

RTs were faster overall for the People task regardless of level of relational processing, which is in line with previous findings of benefits in performance when stimuli are social rather than symbolic (den Ouden, Frith, Frith, & Blakemore, 2005; Dumontheil, Hassan, Gilbert, & Blakemore, 2010). Both adolescents and adults showed increased speed for social information. Similarly, although consistency was overall greater in the non-social task, domain general, not social specific, a trend for developmental change was observed. This is at odds with studies showing increased sensitivity to social stimuli during adolescence (Foulkes & Blakemore, 2016). This might be due to the low arousal and/or affective demands of the current task, and should be explored in further studies. Furthermore, poorer overall consistency in the social task may be due to the greater complexity and variability of people's traits compared with towns' characteristics; this difference would apply to both adolescents and adults. For example, my friend Leo may be funny sometimes, but at other times he is quite grumpy, while London is always busy.

Our behavioural findings provide some evidence for differential performance for social information, regardless of relational level, for both adolescents and adults. Furthermore, we provide some evidence for domain general development of consistency in relational integration of simple relations which does not differ as a function of the social or non-social nature of the semantic information being processed.

4.4.2 Neuroimaging findings

4.4.2.1 Relational integration

Relational integration was associated with greater activation in a large bilateral fronto-parietal network including the RLPFC in both the People and Town tasks. A similar pattern of activation was observed by Raposo et al. (2011) in the Compare vs Other contrast. These results further support the involvement of RLPFC and the inferior parietal cortex in relational integration (Crone et al., 2009; Wendelken et al., 2012). By adapting the task by Raposo et al. we were able to directly compare manipulation of social and non-social information and provide evidence for domain-general recruitment of the RLPFC through adolescence and adulthood across social and non-social domains.

Overall, we did not find evidence of an interaction between relational integration and social vs non-social task: both networks were recruited in parallel for relational integration and social demands. This parallel recruitment of the two networks is similar to that observed by Meyer et al. (2012, 2015) in their social working memory task. However, these studies showed that the MPFC activation associated with social working memory was modulated by working memory load (Meyer et al., 2012, 2015), while in the present study, MPFC activation was not modulated by the number of relations participants had to consider. Similarly, although Meyer et al. (2012) found that perspective taking on the IRI scale was positively associated with social-working memory load-dependent activity within the MPFC and posterior cingulate cortex in adults, we found no association between self-reported perspective taking on this questionnaire and behaviour or brain activity in our task. A possible source of this difference in findings is that social cognitive load in the Meyer et al. (2012) study was higher than in the present study, with the requirement to compare two, three or four individuals, whose names were maintained in working memory, on given personality traits. In the present study, our participants only compared two individuals and the relevant information remained on the screen over the duration of the trial. These differences may have contributed to both the lack of observed association between performance and MPFC activation and as well as with self-reported real-life perspective taking.

We did not observe developmental differences in activation in the RLPFC during relational integration across tasks in whole-brain analyses. Developmental differences have been previously reported in this brain region (e.g. Crone et al. 2009; Dumontheil, Houlton, et al., 2010). However, in the study by Crone et al., the age effects were mainly due to differences in time course of activations evident in their event-related design, which our block design did not allow us to test. In our previous study, age group effects were observed in ROI, vs whole brain, analyses (Dumontheil, Houlton, et al., 2010). Relational reasoning studies have traditionally involved demanding visuospatial reasoning tasks, such as the Raven Progressive Matrices. It might be that semantic reasoning about traits of people and towns is not demanding enough to tax adolescents in the same way.

Our results suggest domain-general recruitment of the RLPFC through adolescence and adulthood, independent of whether the information being manipulated is social or non-social. These results are therefore in line with the finding that the integration of visuospatial or semantic relations elicits similar activation of the relational integration network (Wendelken et al., 2012).

4.4.2.2 Social vs non-social information processing

Social information was associated with greater activation in the precuneus and MPFC in both adolescents and adults. These results are in line with a large body of literature that documents the involvement of these regions when processing social information (e.g. see Van Overwalle, 2009, for meta-analysis). Note that, although towns can be considered social to some extent, as one can imagine the population of individuals living there, characteristics of towns were considered to be less social than traits of people.

Similar to the present study, the investigation of social relational reasoning in adults by Raposo and colleagues (2011) reported greater MPFC activation in Self, Other, and Relational conditions when contrasted to a vowel judgement condition. However, in contrast to our findings, Raposo et al. (2011) observed activation across ventral and dorsal MPFC in the Other vs Self contrast, and no activation in the Self > Other contrast. This difference between the two studies may be due to the precise question participants were asked to answer. In the present study, participants simply rated how funny (or other adjectives) they were, or their friend was, while in the Raposo et al. (2011) study participants always rated how *pleasant* or *unpleasant* they found a concept (e.g. tower), or how *pleasant* or *unpleasant* they thought their friend would find this concept. It is possible that this latter question elicited greater mentalising by asking participants to put themselves in their friend's shoes rather than asking their own opinion. Overall, our results suggest social-specific recruitment of the MPFC during adolescence and adulthood for social information, whether simple relations or integration across levels.

4.4.2.3 Interaction between Task, Condition and Age group

One neural difference between age groups was observed. At the cluster-corrected level, the right anterior insula showed a significant three-way interaction between Condition, Task and Age group, driven by differential recruitment according to the domain (social vs. non-social) and the relational integration requirements with age. Although these results were not significant with an FWE-corrected threshold at the voxel level, they replicate the decreased activation with age in the anterior insula observed in a visuospatial relational reasoning task (Dumontheil, Houlton, et al., 2010). Functional changes in the anterior insula might reflect the maturation of neurocognitive strategies, which possibly include changes in task-specific connectivity between brain regions (e.g. see Bazargani et al., 2014; Dumontheil et al., 2010; and Dumontheil, 2014 for discussion). This neuroimaging finding does not directly map onto behavioural differences between the age groups. In a previous study, we similarly observed that developmental changes in anterior insula activation during relational reasoning were not accounted for by individual differences in performance on the task (Dumontheil, Houlton, et al., 2010). Beyond differences in the sensitivity of behavioural and brain imaging measures (e.g. evidenced by greater sensitivity of neuroimaging data than behavioural data to genetic differences; Dumontheil, Roggeman, Ziermans, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2010), differences may be due to the fact that behaviour reflects a large combination of factors beyond the block-related activations measured in the current fMRI paradigm, such as event-related activations, which may have had compensatory effects on performance.

4.5 CONCLUSION

We aimed to investigate the development of performance in social and non-social relational reasoning and their associated neural substrates. The paradigm required participants to make first and second order relational judgements about social and non-social information. We did not find evidence of differential development of relational integration of social vs non-social information in our behavioural studies. Similarly, the fMRI data showed that in both adolescents and adults, relational integration of social and non-social information recruited a similar fronto-parietal network. The processing of social information additionally engaged MPFC and precuneus regions of the social brain, regardless of the order of reasoning. These findings provide further evidence that relational integration is a domain-general process (Wendelken et al., 2012).

5 GENERAL DISCUSSION

Adolescence is characterised as a period where the ability to exert cognitive control is particularly sensitive to context as a result of a maturational imbalance between an earlier developing socio-affective processing limbic system and a later developing regulatory cognitive control system (van Duijvenvoorde et al., 2016). The dominating line of research that results from this framing has focused on maladaptive instances of increased sensation seeking and antisocial risk taking (Boyer, 2006; Eaton et al., 2010; Steinberg, 2008), and increased sensitivity to peer influence (Brown, 2004; Gardner & Steinberg, 2005; Steinberg & Monahan, 2007).

However, finer aspects of cognitive control in varying contexts have been less explored. The focus of this dissertation was to characterise other aspects of cognitive control beyond its regulatory aspect of risk-associated behaviours. I have presented results from three developmental neuroimaging experiments that investigated: (1) prospective memory and its sensitivity to cue salience, (2) the effect of reward in proactive and reactive control of working memory, and (3) relational reasoning about social and non-social information. In the following sections, experimental evidence regarding these questions will be summarised and integrated with some of the current models of cognitive control and adolescent development. Methodological considerations that limit interpretation of the current findings will be discussed. Finally, I will briefly outline future directions for this line of research.

5.1 SUMMARY OF FINDINGS

5.1.1 Prospective memory in adolescence and adulthood: impact of cue salience

The neural correlates of PM development in adolescence remain an under-studied area of research (Dumontheil, 2014). The RLPFC, which is one of the key regions implicated in PM, usually exhibits prolonged changes during adolescence in functional imaging studies (Dumontheil, Burgess, & Blakemore, 2008). The first aim of the study described in **Chapter 2** was to characterise the fMRI neural correlates of event-based PM in adolescence.

The behavioural results showed that event-based PM continues to develop during adolescence. Interestingly, the salience of the cue did not affect developmental differences in performance. There were preliminary findings that the most considerable improvements occur between early and mid-adolescence. No age differences in fMRI activation patterns in the frontoparietal network were identified between the group of adolescents aged 12 -16 and the adults aged 22 – 30, but there is some initial evidence for higher activation in occipital regions in the youngest adolescents in this sample (12 – 14 years old) compared to the adults.

PM maps onto a general DMC framework, where both proactive monitoring for cues and additional reactive adjustments are needed for adequate performance. Mixed block/event related fMRI has proven to be a useful methodological tool for the DMC approach (Chiew & Braver, 2017). Thus, the second aim of the study was to determine whether cue salience would modulate behavioural performance or sustained/transient associated brain activation associated with increased demands for strategic monitoring. Behaviourally, non-salient cues had larger interference effects on OT suggestive of increased monitoring demands as well as less efficient PM execution. Cue salience did not interact with age. Sustained frontoparietal activation was observed in PM-related regions, including RLPFC and parietal cortex, and cognitive control regions, including DLPFC and AIns. Regions that had transient activation included the RLPFC, VLPFC and DLPFC.

The results from **Chapter 2**, provide evidence that PM relies on multiple dissociable transient and sustained cognitive processes which are supported by a distinct set of frontoparietal brain regions, and that adolescents and adults exhibited similar patterns of hemodynamic brain changes.

5.1.2 Proactive and reactive control of working memory in adolescence and adulthood: impact of reward context

This line of research is inscribed in the rejuvenated interest in the interaction between motivation and cognition that has been sparked in part by the recently emerging developmental approach that draws upon the social psychology and cognitive neuroscience operationalisation of motivation (Braver et al., 2014). In adolescence, cognitive control is particularly modulated by incentive-related motivational influences. A focus on developmental changes during this age group, alongside exploration of candidate neural mechanisms, provides a unique opportunity to integrate cognitive and socio-affective components of motivational influence.

Developmental studies suggest that adolescents rely more on a reactive strategy (recruiting resources transiently in response to a cue) than a proactive strategy (sustaining these resources in anticipation of the cue). The balance between these strategies usually shifts towards a more proactive strategy in adulthood, but is sensitive to contextual manipulations including reward (Andrews-Hanna et al., 2011; Jimura et al., 2010; Locke & Braver, 2008). Motivated by the reports of increased sensitivity to reward in adolescence (Galván, 2013; Silverman et al., 2015), **Chapter 3** investigated how proactive and reactive control of working memory as a function of reward context developed between 12 – 16 years and 22 – 31 years.

Throughout the run where some reward trials could be expected, participants' accuracy for both rewarded and non-rewarded trials increased with age. Across age groups, participants were faster for the non-reward trials of the Reward run compared to the Baseline run (where none of the trials were rewarded), indicating engagement of proactive control. Participants were fastest for reward trials, suggesting an additional reactive engagement of cognitive control.

Chapter 3, fMRI results showed that proactive control is associated with activity in the DLPFC, AIns and PPC, while reactive control is associated with the ACC, LPFC and AIns. The AIns, caudate and PPC emerge as regions that can exhibit both sustained and transient temporal modulation that is sensitive to reward, with some evidence of developmental differences in AIns recruitment for sustained reward.

5.1.3 Relational reasoning in adolescence and adulthood: impact of type of information

Extensive behavioural evidence has shown the development of non-social relational reasoning in adolescence and identifies it as key building block for advanced cognition with age (Crone et al., 2009; Dumontheil et al., 2010). An important aspect of relational reasoning is the joint consideration of simple relations or judgments (relational integration). In addition, relational reasoning and integration are also key elements of social interactions (Raposo et al., 2011). In a behavioural study that was not included in this dissertation, a relational reasoning task was adapted to test the manipulation of social versus non-social information, and showed domain-general improvements in early adolescence (Magis-Weinberg et al., 2017). In cognitive neuroscience studies, relational reasoning has been associated with lateral (relational reasoning) and medial (social processing) aspects of the rostral frontal cortex, which in turn exhibits protracted structural and functional development in adolescence (Dumontheil et al., 2008). Motivated by this background, the experiment described in **Chapter 4** aimed to integrate across these ideas and investigated how social and non-social relational reasoning develop in adolescence in relation to activity in RLPFC and MPFC.

In contrast to the previous findings, in our smaller sample, we did not find strong evidence for the development of relational reasoning and integration. **Chapter 4** found that social information facilitated relational reasoning for both age groups. Our results provide evidence for domain-general recruitment of the frontoparietal network, including the RLPFC, for relational integration, and social-specific recruitment of the social brain network, including the MPFC for social information processing. Contrary to the study predictions, no developmental effects in these regions were observed. Developmentally, the right anterior insula showed greater activity in adolescents compared with adults during the comparison of non-social vs. social information. This study shows parallel recruitment of the social brain and the relational reasoning network during the processing of social information across adolescence and adulthood.

5.2 DISCUSSION OF FINDINGS IN RELATION TO THEORIES OF COGNITIVE CONTROL

5.2.1 Cognitive branching

The studies described in **Chapter 2** and **Chapter 4** involved manipulations related to the hierarchical model of control (Badre, 2008; Koechlin, 2011; Koechlin et al., 2003). **Chapter 2** investigated PM, which requires integration of temporally extended information, as opposed to information that can be directly perceptually derived. **Chapter 4** investigated relational integration, a capacity at the top of the processing hierarchy which requires to abstract relations between categories in different levels. Both PM and relational integration can be considered instances of cognitive branching or goal-subgoal integration (Mansouri et al., 2017). In these tasks, participants had to sustain an overarching goal while they engaged in a subordinate task, tapping into a capacity to hierarchically organise goals.

Chapter 2 showed that in the PM task, participants had to keep the main task goal of identifying the position of the triangle, while branching to execute the delayed intention as prompted, sporadically, by PM cues of varying salience. Results showed RT and accuracy costs when the ongoing trial was contaminated with a delayed intention, which might be conceived as an alternative subgoal. In the relational integration task, reported in **Chapter 4**, cognitive branching may allow the sequential processing, and maintenance, of single relations, and in turn their integration. Results from this study showed that participants were slower when making comparisons than when making simple judgements. This pattern of performance points toward cognitive branching, with participants needing extra resources to disengage from the main goal and switch to the alternative.

Neuroimaging findings from both studies provide further support for cognitive branching in the context of hierarchical control models. RLPFC had relatively low domain-selectivity, as it was recruited by maintenance of a delayed intention (**Chapter 2**) and relational integration (**Chapter 4**). This lack of task domain specificity, can be suggestive of its involvement in abstract, integrative processes (Christoff et al., 2001, 2009; Christoff & Owen, 2006; Dumontheil, 2014). This abstract role is further supported in PM by findings of Gilbert (2011) of content-independent engagement of RLPFC in PM storage. On the other hand, the

RLPFC had relative increased selectivity when considering a shared aspect across tasks: cognitive complexity. As discussed in the **Introduction,** cognitive complexity can be defined as goal–subgoal hierarchy (Badre & D'Esposito, 2009), the number of relations (Christoff et al., 2001; Dumontheil et al., 2010), or the number of items held in working memory (J. D. Cohen, 1997).

In the PM task, complexity was related to the number of goals that had to be kept in mind. The main goal was to identify the position of a shape and press left or right, and the subgoal was to react to a particular environmental cue and press a different key. Sustained frontal activity extending into the RLPFC was observed for instances in which a subgoal had to be maintained while executing a goal, with additional transient activity in the RLPFC for PM trials, which were arguably more complex and abstract. In the relational integration task, complexity was related to the number of relations that needed to be maintained. For simple relations, trait judgements were made for either self or other. The Comparison condition, in contrast, required integration across single relations. Certainly, we observed frontoparietal activity, including the RLPFC, in the integration condition relative to self and other conditions. Our results align with evidence of robust RLPFC activation when cognitive processing complexity is high across multiple domains (Christoff & Owen, 2006), as relational integration (**Chapter 4**), subgoal processing and manipulation of self-generated information (in the form of internal representations of intention) are theorised to have the highest levels of cognitive complexity.

5.2.2 Sustained and transient cognitive control

In the DMC framework, the studies described in **Chapter 2** and **Chapter 3** investigated whether adolescents exhibit developmental changes in sustained and transient cognitive control capacities in the context of prospective and (retrospective) working memory. While there are a handful of studies investigating these processes in other tasks in adolescence such as Stroop (Andrews-Hanna et al., 2011; Vijayakumar et al., 2014), and antisaccade task (Alahyane et al., 2014; Velanova et al., 2009), here we present the first fMRI study to investigate prospective memory in this age group, and one of the few to examine proactive and reactive control in varying contexts of reward (Strang & Pollak, 2014). The DMC has proved to be a useful framework to understand sources of cognitive control variability in many paradigms, including cued working memory and prospective memory (Chiew & Braver, 2017). Since studies in adults have suggested that the temporal dynamics of each strategy might be separable (Braver, 2012), both studies incorporated a mixed block/event related design to dissociate block and event-related neural activity in PM and how this is influenced by cue salience (**Chapter 2**) and the impact of reward in working memory (**Chapter 3**) in adolescence and adulthood.

Chapter 2 investigated the impact of cue salience in an event-based PM task, which allowed the manipulation of monitoring demands. It has been recently noted that the multi-process account of PM, which postulates a key distinction between sustained attentional monitoring and spontaneous retrieval processes, aligns well to distinctions between proactive and reactive control (McDaniel, Lamontagne, Beck, Scullin, & Braver, 2013). Non-salient cues required sustained anticipatory processes to be detected, tapping into proactive control mechanisms. In contrast, detection of salient cues could have relied more on late occurring, "corrective", reactive control. It was shown that varying the degree of cue salience of the PM targets had a strong influence on both task performance and the dynamics and strength of prefrontal control regions activation. The extent to which PM requires sustained versus transient control may also help to inform more general issues of goal-driven behaviour (McDaniel et al., 2013). The study described in **Chapter 3** employed a working memory paradigm in which potential payoffs were manipulated at the block and trial levels. In adults, this manipulation has been shown to bias participants towards proactive control (Jimura et al., 2010). Participants of both age groups showed behavioural improvements for the rewarded trials as expected, but also had enhanced performance non-rewarded trials. This pattern is consistent with increased engagement of preparatory processes, triggered by tasks cues, which might have led to improved encoding and maintenance of the stimuli set throughout the delay (Chiew & Braver, 2017; Friedman & Miyake, 2017).

Across tasks, similar domain general activation was observed in bilateral insula, right superior parietal lobule, DLPFC and precentral gyri and FEF, as well as middle aspect of ACC with sustained and transient changes in BOLD signal. These regions have been previously implicated as neural correlates of the DMC (Braver, 2012; Jiang et al., 2015), where the temporal dynamics within some regions, in addition of activation of distinct brain networks, would enable the shift between modes of cognitive control. Both studies demonstrate the utility of the DMC as a framework to pinpoint development and stability in cognitive control strategies between adolescence and adulthood. In this view, differences and similarities in cognitive control reflect a fluid shift in strategy, and not simply differences in trait cognitive control capacity. As we have demonstrated here, flexible engagement of control is sensitive to task factors and cost-benefit analysis (Chiew & Braver, 2017).

The conceptualisation of proactive control in the dual mechanisms framework shares many similarities with the Common EF factor from the Unity/Diversity model (Miyake &

Friedman, 2012). Although Braver (2012) notes that the balance between proactive and reactive control is dependent on context to an extent, he recognises there might also be stable individual cognitive abilities that bias the tendency towards proactive control (Braver, 2012), namely working memory capacity and fluid intelligence. In this sense, the Common EF factor might relate to stable biases between proactive and reactive strategies (Friedman & Miyake, 2017).

5.2.3 Contextual effects

Contextual factors have been show to influence flexible engagement of control (Chiew & Braver, 2017). Also, it has been suggested that adolescent cognition might be particularly sensitive to context (Hartley & Somerville, 2015), and potentially impaired in hot affective contexts. Thus, one aim of this dissertation was to explore how complex cognitive tasks interact with variations in context. Manipulations were done at varying stages and had, arguably, mild arousal effects (in contrast to studies of peer observation in adolescence, for example). The main manipulations were: PM cue salience (**Chapter 2**), reward context at block and trial level (**Chapter 3**) and type of information being manipulated (social vs. non-social) (**Chapter 4**).

5.2.3.1 Cue – target manipulations

Variability in context processing tasks, in which cues indicate how to optimally respond to target items has been extensively investigated in the DMC framework (Chiew & Braver, 2017). As such, framing of our tasks in the DMC framework is particularly suited for the purpose of this dissertation, in which we aimed to investigate how context interacts with cognitive control. **Chapter 3** is an example of a more classical DMC framework task, where manipulations are done at the level of cues preceding each trial which inform participants about reward and allow them to engage in preparatory processes if deemed necessary. In contrast, in **Chapter 2**, the manipulation of salience was done not as a preparatory cue but at the PM target. Participants were also instructed at the beginning of each block about upcoming type of PM targets.

In both cases, the balance between proactive and reactive control was sensitive to context and shifted towards more sustained set maintenance in the case of the reward blocks or sustained monitoring for non-salient cues. Behaviourally, participants improved performance not only for the rewarded trials, but also for the non-rewarded trials in the context of the Reward run, which suggests more sustained strategies in addition to transient trial-by-trial correction. In the PM task, behavioural evidence for proactive control is not as clear. However, participants did show RT costs for contaminated trials but constant levels of accuracy which might suggest participants were using the same criteria of confidence to arrive at a response, and could indicate a proactive bias.

The shift toward proactive control was further supported by the neuroimaging findings in which our approach of mixed block/event related fMRI allowed for separation of sustained and transient activations. It has been suggested that reward might affect the strength of goal representation and hence influence task switching capacities (Friedman & Miyake, 2017), which is also consistent with the gating model in the DMC (Braver & Cohen, 1999). Across tasks, there was evidence for sustained activation in the DLPFC and PPC, regions implicated in a variety of cognitive control tasks, suggestive of general mechanisms of task set maintenance. In addition, there was transient recruitment of a more widespread set of frontoparietal regions including DLPFC, and RLPFC, pre-SMA and ACC, as well as posterior parietal cortex for both the prospective and working memory task. The bilateral AIns emerged as a key mixed region that exhibited both sustained and transient changes.

There was also evidence of contextual influences on task-specific activations. In the PM task, the RLPFC was sensitive to degree of cue salience. PM execution on non-salient trials was associated with higher activation in RLPFC than salient PM trials. In the working memory task, various regions were sensitive to context, including subcortical regions typically engaged in reward processing, and inferior occipital regions, as well as cognitive control regions: AIns and PPC. There was evidence that contextual manipulations of PM targets and reward cues had an impact on the dynamics and location of prefrontal control regions in two different tasks investigating proactive and reactive cognitive control. This is in line with previous reports of studies in adult populations which manipulated cue focality in PM (McDaniel, Lamontagne, Beck, Scullin, & Braver, 2013), cued task switching and context processing paradigms (Ruge, Goschke, & Braver, 2009), and encoding/retention versus probe periods in working memory paradigms (Jimura et al., 2010).

5.2.3.2 Type of information

Motivated by the relevance of social interaction in adolescence (Blakemore & Mills, 2014), in **Chapter 4** we investigated whether type of information would impact relational reasoning. In separate blocks, participants had to make trait judgments about self and other, or compare across the two either for social or non-social contexts. Our task was adapted from an adult study (Raposo et al., 2011), and added a non-social task as a comparison to make stronger conclusions about domain general vs specific relational reasoning. Behaviourally, there was evidence for facilitation of information processing when information is social. However, these results should be interpreted with caution as they are in contrast with a larger behavioural only study (Magis-Weinberg et al., 2017) where there was no evidence for differential processing of social and non-social information.

FMRI results showed domain general involvement of the frontoparietal network for relational integration with additional recruitment of social brain regions for processing social information. This suggests that both reasoning and social brain regions underlie the capacity to make social comparisons between self and other. In this study, the focus was placed on relational reasoning, just one of the many abilities required to navigate the complexities of the social world.

5.3 DISCUSSION OF FINDINGS IN RELATION TO THEORIES OF ADOLESCENT DEVELOPMENT

5.3.1 Developmental changes

Across tasks, there was behavioural evidence for general improvements in performance. Overall, adults had faster and more accurate responses. Age interacted with the type of task only in the PM study. There was no strong evidence of an interaction of age with tasks or conditions in the other studies.

In **Chapter 2**, we observed that PM performance improved with age. Adults made fewer errors and were faster to respond to the PM targets than adolescents. Further, the study showed that age improvements were not due to general processing and instead were specific to PM processes, as there were no age differences in OT performance. There have been only a handful of PM studies in adolescence, with inconclusive evidence about developmental improvements after age 13. In our study, we found improvement between ages 12 and 17. However, post-hoc exploratory analyses suggest that the effects were driven by the youngest participants in our sample (12 -14 years old). Future studies should explore a broader age range and sample across the whole range of adolescence to allow for a finer characterisation of the developmental pattern. To our knowledge, ours was the first fMRI study of PM in adolescence. Although there were no age-related differences when comparing the two age groups, preliminary findings suggest that early adolescence might be associated with increased precentral and occipital activation during PM trials in the non-salient condition compared to adults. This result could guide future studies which have an adequately powered sample of early, mid and older adolescents to investigate developmental trajectories (see **Section 5.4** for Methodological considerations).

In **Chapter 3**, we observed improved general working memory RT and accuracy with age. In contrast to our prediction of a bias towards reactive control in adolescence, we found a similar pattern of improvements for adolescents and adults. The majority of developmental studies of proactive and reactive control have been conducted in neutral contexts, and find that adolescents exhibit a more reactive pattern of response (Alahyane, et al., 2014; Andrews-Hanna et al., 2011; Vijayakumar et al., 2014). It is interesting that in the context of reward, adolescents exhibit similar responses to adults, and had comparable general earnings. These results highlight the role of motivation in mobilising cognitive control resources, and could be conceptually conceived to sit at the intersection of the DMC (Braver, 2012) and cost-benefit analysis framework (Shenhav et al., 2013). In this sense, the subjective cost of exerting control relates directly to proactive control demands (Westbrook, Kester, & Braver, 2013). Further, it has been suggested that individual difference factors such as sensitivity to reward and age (Westbrook et al., 2013) may impact subjective costs of exerting cognitive control. An extension of the current study could explicitly test how adolescence impacts cost-benefit analyses. Variability in the proactive/reactive balance with age might be framed in terms of subjective value and costs (Botvinick & Braver, 2015).

In **Chapter 4**, there was no evidence for impaired relational integration in the adolescents, aged 12 -16, who took part in the fMRI study. These results are in contrast with the findings of a large behavioural study that used a similar task (Magis-Weinberg, et al., 2017), which found that difference between RTs for the comparison and single judgments was largest for the 11 – 12 yo compared to other age groups. It is possible that the smaller fMRI study sample did not have enough power to detect developmental differences (see **Section 5.4** on limitations). We did find a trend for increased consistency with age, which is similar to the results from the large behavioural study, which found increased consistency between 11 – 14 yo and 15-39 yo. Contrary to predictions of age differences in RLPFC (Crone et al., 2009; Dumontheil et al., 2010) and MPFC fMRI results (Burnett et al., 2011; Mills et al., 2012), the only region which showed and interaction with task and condition was the AIns. The results showed decreased involvement of the AIns for relational integration of non-social information with age.

5.3.2 Models of adolescent development

The studies reported here did not find evidence for many of the predictions of developmental changes between adolescence and adulthood, particularly in relation to patterns of fMRI activation (see **Section 5.4** for methodological considerations). The prevailing dual-system models approach to adolescence have suggested that affective hot contexts impair adolescent performance as a result of maturational imbalance between an earlier maturing reward processing unrestrained by the protracted maturation of regulatory systems (see **Section 1.2**, **Introduction**). Although adolescents approach adult-like levels in tasks requiring cognitive control in neutral contexts, their performance can be readily disrupted by social and reward related contexts (Cauffman et al., 2010;Cohen et al., 2016; Crone & Dahl, 2012).

Two of the presented experiments could be characterised as cognition in a hot context. **Chapter 3** involved a manipulation of reward while **Chapter 4** involved social information. Neither of these manipulations showed a negative impact of hot contexts on adolescent performance. In fact, **Chapter 3**, found evidence for an enhancement effect, which is in line with previous results from related paradigms (Paulsen et al., 2015; Strang & Pollak, 2014). In **Chapter 4**, there was no difference in the way in which adolescents manipulated social information.

Much focus has been placed on the regulatory aspect of cognitive control systems in restraining reward sensitivity systems, where social influence has a negative impact. In contrast, less is known of the development during adolescence of situations where reward sensitivity fosters cognitive control (Strang & Pollak, 2014) or instances where there might be conserved abilities between adolescence and adults. Our results challenge the somewhat simplistic dual-system models and invite towards revised models which also consider positive motivational and adaptive effects of adolescents' sensitivity to context (Crone & Dahl, 2012).

Dominated by research on the maturational imbalance, the field of adolescent cognitive neuroscience has focused mostly on regions such as the PFC and VS. Particularly in earlier studies, there was a bias towards studying certain ROIs, which might neglect the role of other regions and networks (Pfeifer & Allen, 2016). Recently, there has been increased recognition of the role other regions might play, and how they should be incorporated into the current models of adolescent development (Casey, 2014; Luna, Paulsen, Padmanabhan, & Geier, 2013).

Current results support that considering other regions might enrich our understanding of development in adolescence. In our studies, for example, a whole-brain approach consistently identified a key role played by the anterior insula in proactive and reactive control as well as some developmental effects in this region for relational integration. However, the developmental relevance of the anterior insula has largely been overlooked (Hauser et al., 2015). In **Chapter** 3, we showed that adolescents ramped up sustained activation in the left AIns in the context of reward. A highly speculative idea is that the AIns can play a particularly important role at the intersection of motivation and cognition. This notion seems to be in line with Hauser and colleagues who suggested that increased insular activity shows that that adolescents adapt faster to negative feedback as they give a bigger weight to affective information (Hauser et al., 2015). Further, Smith et al. (2014) have also proposed that the AIns might be a cognitive-emotional hub, important in adolescent-decision making.

These studies contribute findings from mixed blocked/event-related designs, which might shed further light on sustained vs transient activity in development. This design allows the assessment of sustained response states which might be key in understanding the basis of development of cognitive control (Luna, 2009). Improvements in adolescence are not due to the emergence of new cognitive abilities, but are related instead to the capacity to efficiently engage existing abilities in a flexible and consistent fashion. In this view, the capacity to maintain goals and establish a response state to coordinate lower level abilities emerges as a crucial developmental hallmark (Luna et al., 2004; Velanova et al., 2009). Results from this dissertation speak directly to the relevance of response states and goal maintenance and contribute evidence of developmental continuity between adolescence and adulthood in the balance between proactive and reactive control. Further, it has been shown that adolescents and adults responded similarly to different manipulations with preserved abilities to maintain goals in a sustained fashion. At least in the experimental tasks reported here, there are no marked differences between adolescents (12 – 16 years old) and adults.

In summary, our results challenge the prevailing conception of cognitive control as a restraining mechanism of overactive affective-limbic processes, delineating other (perhaps more positive) alternatives of interaction between motivation and cognition. I posit that the consideration of sustained-state effects as well as trial-related effects is a useful approach in explaining age-related variability in the capacity to flexibly exert cognitive control in adolescence. Finally, these studies add to the existing literature on models of adolescent development by suggesting a broader consideration of the role in maturation of other brain regions (namely the AIns). However, there certainly may be important methodological considerations underlying the lack of differences, such as the limited sample size and interpretation of fMRI results (see **Section 5.4** for and extensive discussion of the limitations).

5.4 METHODOLOGICAL CONSIDERATIONS

A number of limiting factors need to be taken into consideration when interpreting the results reported here. Robust evidence of developmental functional changes in key brain regions involved in the cognitive processes of interest motivated my selection of fMRI studies as the main research instrument for my PhD. However, related to practicalities and constraints of running fMRI studies, the results presented here are derived from cross-sectional studies with a limited sample size. This section will address some of the main limitations that resulted from these constraints.

5.4.1 MRI neuroimaging studies

5.4.1.1 Reverse inference

The neural inference specificity that can be drawn from the presented fMRI result should be limited to the extent that neuroimaging studies may encourage reverse inference (Pfeifer & Allen, 2016; Poldrack, 2006). Reverse inference occurs when we infer the engagement of a specific mental process from observed patterns in activation (Poldrack, 2006). This process relies on one-to-one mapping between the construct and the physiological process being measured and is certainly not limited to the BOLD signal (Cacioppo & Tassinary, 1990). This problem has been highlighted in the context of dual-system models (see **Section 1.1.2** in the **Introduction**) in developmental cognitive neuroscience by Pfeifer and Allen (2012) and Casey (2015). In relation to the problem of one-to-many and many-to-one mapping in neuropsychological inference Casey notes: “new findings have moved the field away from simplistic one-to-one mappings of the ventral striatum and amygdala to reward and avoidant behaviours, toward the recognition of distinct computational roles they each play in learning that influence adaptive action in response to both positive and negative outcomes” (p. 299).

Poldrack shows that the usefulness of reverse inference depends on the selectivity of activation in the region of interest (2006). In response, Christoff and Owen (2006) highlighted how the usefulness of reverse inference also depends on other relevant task characteristics, such as domain and complexity. This is particularly relevant for a region such as the RLPFC (see **Section 5.2.1**) which has been implicated in a variety of cognitive processes, including prospective memory, and relational integration in this dissertation. Consequently, reverse inference will only provide very limited evidence that a cognitive process might be involved when a region with low selectivity is activated (Poldrack, 2006). Results presented here should be interpreted with this caveat.

5.4.1.2 Developmental interpretations of BOLD changes

The interpretation of developmental increases and decreases in brain function is an area of the literature still in need of clarification. In developmental neuroimaging studies, where adults are considered the model system, any deviation could be interpreted as immaturity (Luna et al., 2010). Higher activation in younger subjects compared to adults is typically taken as a signature of increased “effort” (Luna et al., 2004; Tamm et al., 2002)based on load dependent higher activation in adults (Keller, Carpenter, & Just, 2001). In contrast, results of lower activation have been interpreted as the inability to access mature regions. In both cases, brain circuitry might be available but immature, with changes in processing efficiency (Luna et al., 2010). In addition, it is unclear which neural patterns constitute immaturity as few studies have systematically investigated links between neural correlates and its impact on behaviour (Pfeifer & Allen, 2016).

Further, it remains unclear whether age-related changes in BOLD response reflect brain processing, or differences in strategy use at a psychological or neural level. Changes in BOLD might not be related to changes in brain processes, but instead associated with differences in psychological processes (e.g., using verbal strategies to support working memory) (Luna et al., 2010). We have tried to address this point by considering whether our samples are matched in terms of IQ, and in the case of **Chapter 3**, by adjusting difficulty at an individual level. However, our current methods and designs limit our ability to distinguish between these two alternatives.

5.4.2 Research on adolescence

Specificity is also necessary in the definition of adolescence, including understanding transition periods in adolescence, such as the onset of puberty and the changes in social maturity. Adolescence is a long phase of development and still an emerging field of research. As a result, there is a lack of consensus on how to define relevant distinct stages: research sometimes operationalises adolescence as a single, homogenous period, but often times can also split participants somewhat arbitrarily into early, middle, or late phases (see **Figure 5.1**). This limitation can impact interpretation of results and comparisons across studies (Pfeifer & Allen, 2016; van Duijvenvoorde et al., 2016).

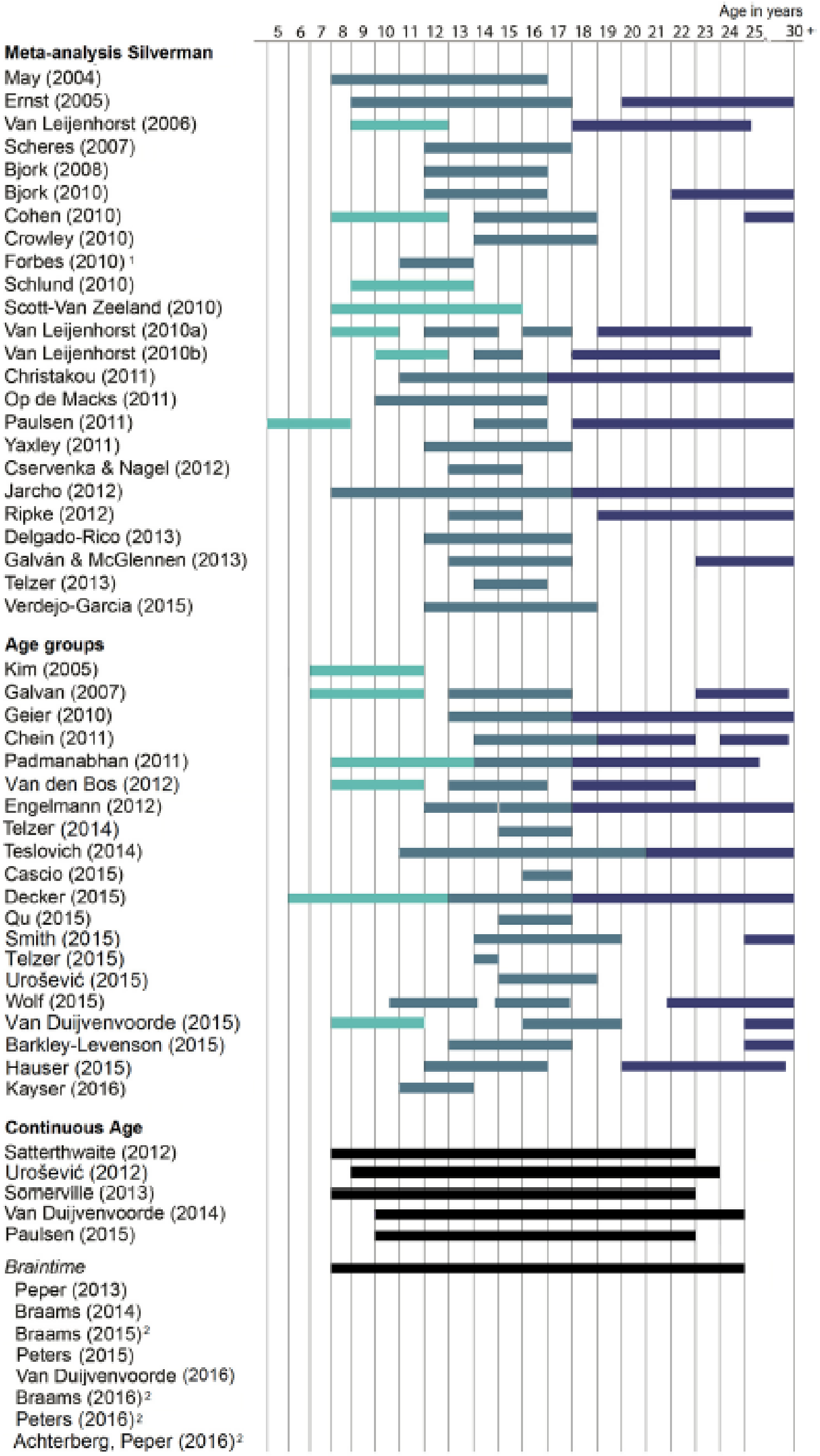


Figure 5.1 *Overview of the definition of childhood, adolescence and adulthood*. Light blue = children (as defined in the original studies), blue: adolescents, dark blue: adults. (Figure from van Duijvenvoorde, Peters, Braams, & Crone, 2016b, reproduced by permission of Elsevier)

Another methodological consideration is that developmental stages are often defined in terms of chronological age (Blakemore, Burnett, & Dahl, 2010; Pfeifer & Allen, 2016). However, age is an imperfect measure of development (Wohlwill, 1970). In adolescence, pubertal status and bodily changes can vary noticeably between individuals of the same chronological age (Ellis, 2004; Mirwald, Baxter-Jones, Bailey, & Beunen, 2002). In addition, there is wide variation in timing and rate of puberty (Palmert & Boepple, 2001; Parent et al., 2003). As a result, adolescence may be difficult to fully characterise only using cross-sectional designs (McCormick, Qu, & Telzer, 2017). Discrepant results in the literature regarding age-related changes may also be due to methodological limitations of cross-sectional designs. These types of designs are not able to detect cases when individuals experience change at different rates. McCormick and colleagues (2017) have recently shown differential conclusions on cognitive control related neural activity from cross-sectional and longitudinal studies. They found that higher VLPFC activation at wave 1 was associated with lower risk taking, while increases in VLPFC as well as hyperactivation at wave 2 were associated with greater risk taking (McCormick et al., 2017).

Here, we ran cross-sectional studies on a relatively small sample of adolescents. For **Chapter 2** and **Chapter 3**, we tested the same sample of 30 adolescents between the ages of 12 and 16. For **Chapter 4**, we tested 19 girls between 11 and 17 years old. These decisions were informed by previous similar studies to maximise the possibility of finding differences between age groups. However, this does not allow for a full characterisation of developmental trajectories, and we can only offer preliminary findings that changes might be driven by the youngest participants in our samples. Future studies should also take into account measurements of pubertal stage, which might impact, above and beyond age, differences between individuals in brain and behaviour. Measuring puberty allows to directly investigate its effects, but also control for possible confounds on socio-affective/cognitive development (Blakemore et al., 2010).

5.5 FUTURE DIRECTIONS

In light of these limitations, several next steps can help to extend our knowledge concerning neural maturation and its consequences for behaviour in terms of the cognitive processes investigated here. These considerations address common limitations in developmental studies that result from trade-offs regarding feasibility and practicalities of running neuroimaging studies.

The first, as mentioned previously, is to extend the age range under examination. While constraining the age range of adolescence in our studies aimed to maximise difference between age groups, it limited our capacity to pick up effects that might be driven by the youngest participants or to identify nuances in the transition from late adolescence to adulthood. This is particularly relevant for **Chapter 2,** which presented preliminary findings suggesting that PM performance and associate neural correlates change the most between 12 – 14 years old. These results are limited given the sample size and their exploratory nature. Future studies could investigate a much broader age range, extending into childhood, to fully characterise the developmental trajectory of PM.

Furthermore, a finer characterisation could include pubertal measures to explore whether puberty, age or a combination of the two underlie the maturation in these processes. As discussed, longitudinal studies might sometime uncover developmental patterns that cross-sectional studies fail to identify. It would be interesting to employ longitudinal designs with the tasks presented here to elucidate developmental trajectories (McCormick et al., 2017).

Chapter 2 presents, to our knowledge, the first fMRI investigation of PM in adolescence. The study employed a non-focal event-based PM task in which cue salience was manipulated. Many questions remain regarding developmental trajectories of other aspects and associated neural correlates in PM. For example, future studies should systematically investigate in adolescent samples: different types of PM tasks (e.g. time or activity based), focality vs non focality of PM task, or cognitive load of ongoing and PM tasks. In line with results from enhanced proactive performance with reward (**Chapter 3**), and reports or incentive-contingent strategic monitoring in adults (Walter & Meier, 2014), it could be interesting to explore the effects of associating reward with PM targets in adolescence.

Results from **Chapter 3**, suggest that the pattern of reactive cognitive control observed in adolescence might be related to more to motivational than capacity factors. To address this outstanding question, the cost-benefit framework (Shenhav et al., 2013), could guide a systematic investigation in how increasing levels of task complexity/demands interact with varying levels of reward. It would also be interesting to explore whether other types of rewards (such as social) can have an impact on the balance between both control strategies (Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009).

Development of proactive/reactive control has been studied in a fragmented approach, with many studies focusing on childhood, and fewer in adolescence, but none spanning the whole age range (Munakata, Snyder, & Chatham, 2012). Understanding the developmental transition across childhood and adolescence in domain general dynamics of proactive and reactive control is critical to gaining insight into developmental mechanisms, especially as it has recently been suggested as a useful tool in informing cognitive control interventions (Doebelet al., 2017).

Results from **Chapter 4** provide evidence regarding brain mechanisms that support social behaviour at the level of processing information. The results point to several avenues of future research on the role of medial and lateral PFC in different aspects of social cognition and interactions. Here, we explored just one minimal social component related to making judgements about traits and comparisons. Our results suggest that lateral PFC and other frontoparietal regions, which are typically associated with complex cognitive tasks, also play a role in social cognition. Although our results indicated parallel recruitment of areas typically implicated in reasoning and in social cognition, it might be that interactions emerge at different levels of complexity. Future studies could explore if interactions between medial and lateral PFC are needed to facilitate more complex social skills.

6 OVERALL SUMMARY

The aim of this dissertation was to examine the development of complex cognitive control in adolescence in relation to different contexts at the behavioural and neural level. I sought to explore capacities that span across different theoretical models of cognitive control, including prospective memory, proactive and reactive control of working memory, and relational reasoning. I explored the effects of prospective memory cue salience, motivational contexts and type of information.

Two studies of proactive and reactive control provided evidence of dissociable sustained and transient activation in frontoparietal regions, including lateral and medial aspects of the prefrontal cortex. In addition, the results showed that some regions exhibit a mixed pattern of haemodynamic changes, principally the anterior insula. These neural changes support the sustained and anticipatory maintenance of task sets across blocks, and transient trial-level corrections and underlie performance in prospective and working memory tasks. Finally, the results suggested that manipulation of cue salience and reward context can bias control strategy towards proactive control.

The RLPFC, a key region at the top of the cognitive control hierarchy, was recruited alongside other regions of the frontoparietal network for prospective memory and relational integration, two example processes of cognitive branching. Cognitive branching was sensitive to contextual changes, such as cue salience or type of information being manipulated. Behaviourally, the results showed that social information facilitated relational reasoning, compared to non-social information. Overall, the frontoparietal network exhibited domain general recruitment, with social-specific recruitment of social brain regions. In the prospective memory task, high cue salience limited monitoring costs. The RLPFC was sensitive to prospective memory cue salience.

Across studies, there was some evidence for general improvements of performance with age. There were few differences in task-driven haemodynamic brain changes between adolescence and adulthood. Developmentally, we showed that prospective memory continues to develop in adolescence. With the first fMRI investigation in this age group, we contribute preliminary findings of increased recruitment of precentral and occipital regions in the youngest adolescents. There were no strong developmental effects in a relational integration task that draws upon cognitive branching. Contrary to our predictions, there were no developmental differences in RLPFC engagement in either prospective memory or relational integration. However, there were age-related changes in AIns engagement in the relational integration of social and non-social information.

No impact of age in the strategy used to maintain control across blocks and recruit additional transient resources on a trial-by-trial basis was found. This is suggestive that motivated adolescents can shift to proactive control similarly to adults to optimise incentive contingent-performance. Results suggest that this might be related to strength of activation in the AIns.

Overall, these studies contribute to the field of cognitive control by characterising behavioural and neural changes and stabilities in adolescence regarding prospective memory, proactive and reactive control and relational integration. I believe the topic of contextual influences exposes flexibilities in cognitive control engagement that might be particularly relevant in an everyday life setting, where social interactions are predominant and various types of reward interact with our capacity to regulate behaviour.

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