FMRI OF A VISUAL-PATTERNS N-BACK WORKING MEMORY TASK IN TYPICAL DEVELOPMENT

by

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Abstract

The term working memory (WM) refers to a set of cognitive processes that allows for the temporary storage and manipulation of information. Neural correlates of the N-back task, a well-established WM measure used in neuroimaging, have been studied extensively in adults but less so in developmental populations. This thesis determines the effect of age on brain activations that mediate cognitive processes for remembering non-verbal/visual stimuli. Block-design fMRI was used to record activity in 84 subjects (6-35 years) during a visual-patterns 0- and 1-back task. Regions activated during the 1-back condition were largely common to all age groups, with adults displaying the largest extent of activations. Children and adolescents showed similar 0-back activations (distinct from 1-back) while adults engaged an analogous 1-back activation pattern during 0-back, suggesting that brain mechanisms underlying memory and attentional processes required for this task in children and adolescents are not yet mature and that strategy usage is varied.

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List of Abbreviations

Abbreviation	Regions
ACC	anterior cingulate cortex
AG	angular gyrus
CingG	cingulate gyrus
FG	fusiform gyrus
IFG	inferior frontal gyrus
IOG	inferior occipital gyrus
IPL	inferior parietal lobule
LG	lingual gyrus
MeFG	medial frontal gyrus
MFG	middle frontal gyrus
MOG	middle occipital gyrus
MTG	middle temporal gyrus
PCC	posterior cingulate cortex
PostCG	postcentral gyrus (sensory cortex)
PreCG	precentral gyrus (motor cortex)
SFG	superior frontal gyrus
SMG	supramarginal gyrus
SOG	superior occipital gyrus
SPL	superior parietal lobule
STG	superior temporal gyrus

Note. Other abbreviations used in tables include L., R. and Bil. which stand for left, right and bilateral respectively.

CHAPTER 1: INTRODUCTION

The assembly of the basic architecture of the brain begins within weeks of conception and its development occurs throughout childhood and adolescence. Age-specific heterochronous changes that occur over the lifespan reflect an extensive developmental course of sculpting and fine-tuning, that vary with brain region. Over the last decade, advances in non-invasive brain-mapping techniques such as functional magnetic resonance image (fMRI), have offered new approaches to investigate the development of cognitive processes and their neural correlates. The basic aim of developmental cognitive neuroscience is to link brain structure with cognitive functions in development. This thesis focuses on typical development of working memory (WM) and its neural correlates.

WM, the ability to temporarily hold and manipulate information for a short period of time, is a central construct in cognitive psychology (e.g., Baddeley, 1992). It consists of a fundamental set of processes and it is an integral component of many cognitive operations, from complex decision making to selective attention. WM is an important ability for much of human higher cognitive activity and behaviour; its intact function is essential for coping with everyday activities and is essential for learning. WM has been related to academic performance (Alloway et al., 2005; Alloway, Gathercole, Willis and Adams, 2004; Aronen et al., 2005; Biederman et al., 2004; Gathercole, Brown and Pickering, 2003; Gathercole, Pickering, Knight and Stegmann, 2004) and been found to predict intelligence (Swanson, 2008) – thereby underlying the emergence of many abilities that are hallmarks of mature, higher level cognitive functions. Although

rudimentary forms of WM are present relatively early in life, WM goes through protracted development throughout preschool and early school years (e.g. Carlson, 2004; Davidson, Amso, Anderson and Diamond, 2006; Zelazo and Müller, 2002) into young adulthood, and this occurs along with the concurrent changes in underlying brain maturation (Giedd et al., 1999; Paus et al., 2001). Perturbations in this development have profound practical consequences for children (Cowan and Alloway, 2009; Gathercole, Lamont and Alloway, 2006). Past research found that deficits in WM, especially in executive functions, may contribute to a range of neuropsychological and neurodevelopmental disorders (Aronen et al., 2005; Hambrick, Wilhelm, Engle, 2002; Engle, Tuholski, Laughlin and Conway, 1999). Thus, understanding how WM works and functions during development is important as it can help establish a basis for a normative framework that will not only improve our understanding of cognitive development but also inform future work on children with atypical development.

A variety of experimental paradigms purported to measure WM have been used to study diverse populations; some examples include the Digit Span task, the Sternberg task, the N-back task and delayed match-to-sample. The N-back task is, however, likely the most a popular measure of WM used in fMRI studies. In this task, participants are presented with a series of stimuli and are asked to indicate whether the current stimulus matches the stimulus presented *N* stimuli back in the series. The majority of fMRI studies using N-back paradigm examined effects of task load or type of material (e.g., verbal vs. spatial) in adults (see Owen et al., 2005, for a meta-analysis) and found the well-established frontoparietal network of activations. In addition, this task has been used in many clinical studies to delineate differences and similarities between typical and

atypical adult populations, such as schizophrenia (Glahn et al., 2005; Schneider et al., 2007) and depression (Fitzgerald, Laird, Maller and Daskalakis, 2008; Mannie et al., 2010). Although many adult studies used the N-back task, only a handful of studies examined the neural correlates of this task over the course of development. Some of these developmental studies have shown that regions found during visuospatial WM in adults are increasingly engaged with advancing age (Klingberg et al., 2002; Kwon et al., 2002). Others found that children recruited core WM regions in the prefrontal cortex (PFC), but to a lesser extent than adults or adolescents (Crone et al., 2006; Olesen et al., 2007; Scherf et al., 2006). Review of these studies revealed that patterns of activation depend on the task employed, the age groups defined, the selected regions of interest and the chosen contrast (Bunge and Wright, 2007). There are still gaps in our knowledge on the neural changes subsuming WM and how they relate to changes in behaviour across development. To this end, the current thesis examined the neural correlates of a visual-pattern N-back WM task from childhood and adolescence to early adulthood.

In the present study, we conducted an fMRI experiment that used a simple visual WM paradigm (traditionally known as the "N-back") to probe the effects of age on brain activations in a large developmental sample (6 – 35 years). The objectives were (1) to delineate regional activation that was similar and different across age groups and (2) to delineate the age effects on brain activations. Chapter 2 presents literature background for this study. The terminology and definition of WM, overview of WM tasks and the N-back task will be described; and a summary of neuroimaging findings of WM from the adult literature will be provided. A review of what is currently known about anatomical brain development will be given along with a survey of the behavioural and

neuroimaging findings of WM development. Finally, a brief review of the BOLD-fMRI technique will be provided. Chapter 3 presents the aims and hypotheses for this study. Chapter 4 and Chapter 5 detail the methods and results of this work, respectively. Discussion, limitations and future directions of this work are offered in the last chapter, Chapter 6.

Chapter 2: LITERATURE REVIEW

2.1 Working memory (WM)

Working memory (WM) is an important resource for maintaining and manipulating small sets of information online for a brief period of time, a critical ability that supports general learning. Functionally, WM acts as a link between perception, attention, and long-term memory processing (Baddeley, 1996). In this section, WM is first defined in the context of this thesis. Tasks that are typically used in WM experiments are then described, with the focus on the N-back task employed in the present study. Finally, fMRI studies of WM in healthy adults are reviewed.

2.1.1 Definition of WM

Memory researchers have traditionally classified human memory systems into two distinct types: short-term memory and long-term memory (James, 1890; Hebb, 1949; Peterson and Petersen, 1959) – a distinction that still guides some contemporary memory research. In short-term memory, the memory trace for information that is held decays quickly within seconds, but if reinforced by active rehearsal, this information may be transferred into long-term memory where it can be retained for much longer periods (Baddeley, 1996). Research has also focused on different sensory modalities of short-term memory. For visual short-term memory, object representations are created/encoded rapidly, are maintained by means of an active mechanism and are terminated when active maintenance ends; this ability has a limited storage capacity of just a few simple objects

(Conway, Cowan and Bunting, 2001) and contains a limited amount of information (Simons and Rensink, 2005).

The concept of WM is often used interchangeably with short-term memory in memory research. Some investigators consider them as different constructs, while others view WM as the successor to the concept of short-term memory. The influential model of WM by Baddeley has set the context for much of the research on visual short-term memory (Baddeley and Hitch, 1974). The WM model proposed by Baddeley (1996) does not serve to replace the concept of short-term memory but instead shifts the emphasis to the role of short-term memory as buffers that are used in the service of cognitive tasks. Our view for the thesis aligns with Baddeley and we see no conflict between research on short-term memory and on WM as short-term memory is viewed as the visual storage component of the WM model. It is the temporary storage buffer used by visual processes, and the visual storage component of a broader, more complex WM system. The term WM has been used in many of the studies in cognitive psychology, using a range of tasks, and we will use the term visual WM throughout the thesis.

WM is generally defined as the temporary maintenance and manipulation of goal-relevant information in mind or the ability to concurrently remember and process information over brief periods of time (Baddeley, 1992). WM plays an important role in many forms of complex cognitive functions such as learning, reasoning, problem-solving and language comprehension. In the Baddeley model, WM includes a central executive that monitors two modality-dependent independent subsystems, the visuospatial sketchpad, and the phonological loop. The central executive is an attentional control system. The visuospatial sketchpad is comprised of an active rehearsal and a passive

storage component, while the phonological loop consists of an active articulated rehearsal process and passive phonological storage. A recent extension to the model is the addition of the "episodic buffer", which stores information in a multidimensional code and serves to integrate phonological and visuospatial information, and information stored in long-term memory (Baddeley, 2003).

2.1.2 WM tasks and the N-back task

Tasks that engage WM typically require observers to hold information in mind for a brief duration and to manipulate that temporary information. An example of a simple span WM task is digit span, where participants are asked to repeat a series of digits in the same order (forward condition) or in the reversed order (backwards condition). Length of digit series typically increases up to a maximum of 9 digits (and 8 for backwards; Wechsler, 1987). More complex WM tasks include the Sternberg task (Sternberg et al., 1966), mental attentional capacity tasks (Arsalidou et al., 2010; Pascual-Leone and Baillargeon, 1994), the N-back task (Owen et al., 2005; Ragland et al., 2002), dual tasks (Cowan et al., 2005; Siegel, 1994), and the delayed match-to-sample task (Schon, Tinaz, Somers and Stern, 2008). For instance, in the Sternberg task, participants view the presentation of a set of stimuli followed by a delay and then a single probe stimulus, and have to decide whether the probe was part of the set. The Sternberg task manipulated cognitive load by the number of items in the display that needed to be processed. While for the delayed match-to-sample tasks, participants view the presentation of a single stimulus and have to recognize it among a set of stimuli afterwards. For the N-back task,

participants are presented with a continuous stream of stimuli and have to respond when they detect a repetition at a specified delay.

There are several dimensions to a task that purports to measure WM, for example, the material/content type (e.g., verbal, visual), the length of the inter-stimulus delay (e.g., interval between target and probe in the Sternberg task), the target stimulus feature (i.e., identity or the location of stimulus), the amount of cognitive load, and interval of retention or distraction/interference (i.e., interval between criterion and target stimuli in the N-back). Non-verbal stimuli such as abstract objects or faces and verbal stimuli such as letters, words, digits or nameable objects are common material types tested in human studies.

Choosing and/or designing age-appropriate tasks is a necessary step in brain imaging studies of cognitive development. These tasks must not only be straightforward to explain, and relatively easy to complete, but they must also engage a child's attention for long enough to collect fMRI data without head motion or loss of motivation. Although many adult behavioural tasks are usable in the paediatric settings, most require alterations for appropriate use with children. Adult tasks for which performance has already been linked to neural correlates are recommended for modifications for paediatric use (Luna, 2010). This allows for ready comparisons across literatures and can also enhance the ability to understand brain-behaviour relations. For the present study, we have chosen the N-back paradigm, a common measure in neuroimaging studies for assessing WM capacities in adults (for reviews, see Owen et al., 2005; Rottschy et al., 2012). In this task, participants are presented with a continuous stream of stimuli and

must determine whether the currently displayed stimulus matches the one presented *N* trials previously. We have utilized the 0-back and 1-back data for the present study.

The N-back task, first described by Wayne K. Kirchner in 1958, involves the presentation of "rapidly, continuously changing information" and measures very short-term retention. It was originally created to examine age-related changes in reaction time and performance between young and old adults (Kirchner, 1958) and since has been employed widely in the experimental literature as a measure of WM ability, to the point that it has been referred to as the gold-standard WM assessment technique in cognitive neuroscience (Kane and Engle, 2002; Kane et al., 2007).

In the N-back task, individuals are presented with a continuous sequence of stimuli and are required to recall if a stimulus was presented a specified number back in the sequence (N represents how far back in the sequence the individual needs to remember). For example, at an N of one, the target would be the stimulus that was presented immediately prior to the current stimulus. At an N of two, the correct response is to a repeat of the stimulus that was presented two prior to the current stimulus. Task difficulty/load increases correspond with the value of N. This task has high face validity as a measure of WM due to the attentional and memory requirement to maintain the target stimulus and to continuously update the stimuli being held on-line.

There are several cognitive sub-processes at play in N-back performance. At all values of N in N-back, the task requires that participants (i) encode each incoming stimulus in the presented series, (ii) monitor the sequence of stimuli one at a time, (iii) maintain a representation of the target stimulus in memory and update this representation, if necessary; (iv) match each new item-representation against this stored representation of

the target, and (v) respond to a target by pressing a button. Some additional cognitive operations such as decision-making, selection, behavioural inhibition and interference resolution are also crucial for the updating function and for keeping track of item order (Jonides et al., 1997; D'Esposito et al., 1999; Badre and Wagner, 2005). The sequential nature of the task requires execution of several cognitive operations simultaneously, especially simultaneous storage and processing of material (Jaeggi et al., 2010). Adult neuroimaging studies using the N-back task usually vary load between 1-back and 3-back, with 0-back typically serving as a control condition (Owen et al., 2005). Experimenters studying children often find that higher loads (e.g., 2- and 3-back) are harder to attain consistently satisfactory performance, particularly in younger children. Even after pre-scan training and considering the age-appropriateness of a task, children can still fail at performing. For example, Casey et al. (1995) compared 1-back child data and 2-back adult data, as children could not achieve satisfactory performance on 2-back. Our behavioural findings echo such difficulties from previous studies, as only a small subset of our entire developmental sample was able to achieve the accuracy criteria of 75% on the 2-back task. As a result, for the analyses of this thesis, our efforts were concentrated on data from the 0-back and 1-back task conditions, as younger children reliably completed these tasks.

2.1.3 Neural correlates of WM: findings from adult neuroimaging studies

Past neuroimaging studies in healthy adults demonstrated that neural substrates subserving WM have primarily been associated with activation in frontal and parietal cortices (Braver et al., 1997; Cohen et al., 1997; Courtney et al., 1996; Fiez et al., 1996;

Jonides et al., 1993; McCarthy et al., 1994; Petrides et al., 1993; Swartz et al., 1995; Owen et al., 2005), with particular focus on the prefrontal cortex (PFC).

The PFC plays an indisputably important role in WM, as the central executive region, as evidenced by early observations on patients with PFC lesions (Milner, 1982; Stuss et al., 1994), in selective lesion and electrophysiological recordings work with non-human primates (Fuster and Alexander, 1971; Goldman-Rakic, 1987; Levy and Goldman-Rakic, 1999) and further confirmed by modern neuroimaging methods (Owen et al., 2005). Subdivisions within the frontal cortex have been extensively studied, on the grounds of whether they are related to cognitive operations, material specificity or other dimensions of a typical WM task. For example, some studies indicated that the dorsolateral PFC presides over the processes of manipulative functions in WM (Fletcher and Henson, 2001) while the ventrolateral PFC is involved in encoding, maintenance and inhibition (Postle et al., 2000; D'Esposito et al., 1999; Sala and Courtney, 2007); other studies indicated that while dorsolateral PFC is associated with object location, ventrolateral PFC is associated with object recognition, in accordance to the ventral and dorsal visual stream theories.

It has also been suggested that activity in the PFC may be load-dependent, i.e., activation is related to the amount of information that has to be memorized (Cowan, 2001). Previous studies have reported a general increase in neural activation in the PFC in response to an increased WM load (Cappell et al., 2010; Gould et al., 2003; Linden et al., 2003; Wolf et al., 2010). However, other studies have reported a non-linear brain response to loading the WM capacity (Johnson et al., 2006; Jaeggi et al., 2003; Callicott et al., 1999). Neural response to medium loads is greater than that to low and/or high

loads (Manoach, 2003; Callicott et al., 2003; Johnson et al., 2006), leading some to suggest that there might be an inverted U-shape function that reflects the relation between WM capacity and PFC activation (Rypma et al., 1999; Kirschen et al., 2005), where a brain region is increasingly recruited as task demands increase (from low to medium WM loads), but then drops out when task demands become overly difficult (from medium to high WM loads). In the case of the N-back task, a number of previous studies have reported that frontoparietal activity increases during 2-back relative to 1-back task performance as well as parametric variations of N (Braver et al., 1997; Cohen et al., 1997; Jonides et al., 1997; Ragland et al., 2002), which possibly reflects the increase in load on control processes devoted to holding items and temporal information, and updating of maintained representations in WM (Smith and Jonides, 1999).

Other distinct cortical brain areas underlying proposed components of Baddeley's multi-component WM model have also been identified (Gathercole et al., 1999; Baddeley, 2003). Central executive processes are implicated in the left or bilateral dorsolateral PFC, the phonological loop is associated with the Broca's area (BA 6/44; Muller and Knight, 2006), left inferior parietal cortex (BA 40; Smith and Jonides, 1997; 1998), the left premotor cortex (BA 6) and the right inferior frontal cortex (BA 47), and the visuospatial sketchpad is linked with analogous regions as the phonological loop, but that are primarily localized to the right hemisphere (Smith and Jonides, 1997; 1998) with the addition of the right anterior extrastriate occipital cortex (BA 19), that is proposed to be associated with visual imagery (Kosslyn et al., 1993). Additionally, the network for visual WM involves other areas in temporal and occipital cortices. A cluster-analysis based meta-analysis by Wager and Smith (2003) found that updating processes in WM

activated right dorsolateral PFC (BA 9) and bilateral premotor cortices (BA 6/8), while manipulation demands and selective attention activated the right ventral frontal cortex (BA 10 and 47) and medial prefrontal cortex (BA 32), respectively. Posterior parietal areas (BA 7) are more involved in all WM process of updating, temporal ordering and manipulation and storage.

Owen et al. (2005) used Activation Likelihood Estimates (ALE) to examine 24 studies of N-back WM tasks manipulating either processes required for task performance (i.e., location/spatial- vs. identity/non-spatial-monitoring) or stimulus material (i.e., verbal or non-verbal). Some broadly consistent areas of activations that emerged across all of these studies included: medial and lateral posterior parietal cortices including precuneus and inferior parietal lobules (BA7/40), premotor cortex (BA6/8), dorsal cingulate and medial premotor cortices - including supplementary motor area (BA32/6), rostral PFC/frontal pole (BA10), dorsolateral PFC (BA9/46), mid-ventrolateral PFC/frontal operculum (BA45/47), and medial cerebellum. Owen et al. (2005) also found activation that varied in sub-regions of the PFC and/or hemispheric lateralization that was associated with experimental manipulations in WM process or content. For example, dorsal frontal is more involved in processing spatial information while ventral frontal is more involved in processing objects and faces – providing evidence for material specificity (Owen et al., 2005). Verbal identity monitoring (relative to non-verbal identity monitoring) was associated with enhanced activation in left ventrolateral PFC (a region known to be important for inner speech), medial and bilateral premotor cortex, bilateral medial posterior parietal cortex, and thalamus, while non-verbal tasks engaged frontal pole and dorsal cingulate regions (Owen et al., 2005). Non-verbal location

monitoring (relative to non-verbal identity monitoring) was associated with enhanced activation in right dorsolateral PFC, lateral premotor and posterior parietal cortices – a set of regions that have been described as a spatial attention network (Corbetta, Patel and Shulman, 2008; Schotten et al., 2011).

The most comprehensive ALE meta-analysis to date examined a total of 189 adult WM experiments that employed a variety of WM tasks, including the Sternberg task, a delayed match-to-sample task, and the N-back task (Rottschy et al., 2012). The authors reported a highly consistent activation of a widespread frontoparietal network and the existence of a core WM network that was common across WM task variants, with some differentiations between stimuli types, contrasts, and cognitive processes. This core WM network included bilateral inferior and posterior medial frontal gyrus, anterior insula, intraparietal sulcus, and pre-supplementary motor area – demonstrating congruent findings with Owen et al. (2005). While WM task effects (i.e., performing a WM task relative to a non-WM task or condition) were more prominent in left rostral PFC, superior parietal lobule, and anterior insula, load effects (i.e., demands on WM storage capacity) were more consistently seen in bilateral inferior frontal areas. Investigation of stimulus material revealed that verbal WM tasks elicited consistent activation in left Broca's area, whereas non-verbal tasks more consistently engaged dorsal and medial premotor areas. Memory for stimulus identity relied more on the posterior inferior frontal gyrus, while remembering location of stimuli recruited the posterior superior frontal gyrus. Some differences between the Sternberg and N-back tasks were also observed, where there was a stronger convergence for N-back tasks than the Sternberg tasks in the dorsolateral PFC. The authors suggested that this difference presumably

reflects the stronger demands on manipulation posed by N-back task than Sternberg tasks, which reflect more passive storage-retrieval processes. Taken together, research to date has observed a well-established set of literature investigating WM processes and its associated neural correlates in adults. In comparison, there are only a few studies investigating such effects in developmental populations.

2.2 WM development and brain maturation

The brain undergoes massive transformation over a very protracted period beginning shortly after conception. This development continues after birth through childhood and adolescence, and well into early adulthood. Early childhood development involves the establishment of basic visual, motor and sensory functions, subserved by the early developing primary motor and sensory cortices. More complex cognitive processes, such as reasoning, and abstract thinking, that rely on higher-order association cortices, gradually evolve over time during adolescence and young adulthood (Gogtay et al., 2004; Casey et al., 2005). As the brain grows and matures through neuroanatomical and neurophysiological changes (Giedd, 1999; Paus, 1999), we see parallel changes in behavioural and cognitive maturation (Casey et al., 2005). More recently, researchers have also found that measures of brain connectivity also undergo changes along with the improved cognitive abilities (Fair et al., 2009; Klingberg et al., 2006; Hagmann et al., 2010).

From childhood to adolescence, there is an increased ability to plan and organize, improved ability to problem solve, as well as increased abilities in the realms of attentional control and WM. In this section, principle findings from previous

developmental studies (behavioural and neuroimaging) will be briefly reviewed along with the neuroanatomical coupling of development.

2.2.1 Brain maturation

Neuroanatomical changes in the developing brain are reflective of the dynamic interplay of concurrent progressive and regressive neural processes. The construction of the human nervous system starts prenatally with a systematic sequence of events, including neurogenesis (Bharwag et al., 2006), neuron migration and maturation, and formation of the six-layered cortex (Marin-Padilla, 1978). Postnatally, processes such as axonal growth and synaptogenesis, pruning and myelination take precedence, leading to dynamic changes in gray and white matter that continue into late adolescence and young adulthood. A common theme running through all brain maturation processes is its heterochronous nature – the time-course of any neuroanatomical changes varies enormously by brain region.

Overall brain volume increases rapidly from birth until school age and continues to increase through childhood, albeit at a slower rate. The majority of brain volume growth occurs during infancy and toddlerhood. At term birth, the brain is approximately one quarter of the adult volume (Toga, Thompson and Sowell, 2006). By 6 years of age, the brain is approximately 90-95% of adult volume (Giedd, 2004; Reiss, Abrams, Singer, Ross and Denckla, 1996), which it reaches by about 10 years of age (Pfefferbaum et al., 1994). Despite comparable brain volumes between children and adults, gray and white matter continues to undergo dynamic changes into late adolescence and young adulthood (Casey et al., 2000; 2005). Change in gray matter volume/density is generally characterized by an inverted U-shaped pattern across lifespan development, i.e., gray

matter increases in early childhood, and then reduces after puberty, while white matter volume shows an almost linear increase that continues into adulthood (Jernigan et al., 1991; Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2003).

In the first years of life, massive overproduction of synaptic connections (synaptogenesis) is distributed across broad regions of the brain (Webb, Monk and Nelson, 2001). Synaptogenesis eventually reaches a plateau phase – redundant axonal processes that do not make synaptic contacts are selectively eliminated and synapses are pruned. Pruning is thought to result in more fine-tuned and efficient information processing (Holtmaat and Svoboda, 2009), and appears to follow the "*Hebbian synapse*" principle of use and disuse – more active synapses tend to be strengthened and less active synapses tend to be weakened or eliminated (Chechik, Meilijson and Ruppin, 1999).

Synaptogenesis and pruning vary greatly by brain regions (Huttenlocher, 1990; 2002; Huttenlocher and Dabholkar, 1997). Synaptic density peaks between 4 and 8 months of age in the visual cortex and at around the third postnatal month in the auditory cortex (Huttenlocher, 1979; 1982; 1983; 1990; 2002; Huttenlocher and Dabholkar, 1997); and is reduced to adult numbers by 4 to 6 years of age (Huttenlocher and de Courten, 1982; 1987). In contrast, in the PFC, the exuberant overgrowth of synapses occurs between three to four years of age and is not pruned to adult numbers until late adolescence and young adulthood (Huttenlocher, 1979; 1990; 1994; Huttenlocher and Dabholkar, 1997; Bourgeois et al., 1994), coinciding with the continued development of cognitive capacities.

Myelin, the lipid-protein sheathing around axons that increases neural conduction velocity, progresses in a similar heterochronous manner. Myelination of the primary

sensory and motor cortices takes place at earlier ages, in the first years of life, followed by temporal and parietal association cortices, and ending with higher association areas in PFC and lateral temporal regions that continue until the third decade (Durston et al., 2001; Yakovlev and Lecours, 1967; Gogtay et al., 2004).

Gray matter volumes peaks at around 4-8 years of age in the primary sensorimotor cortices, then at 11-13 years of age in the frontal and parietal cortices, and lastly at around 16 years of age into late adolescence in the PFC and temporal association areas (Giedd et al., 1999; Gogtay et al., 2004). More refined changes have been reported in the PFC, where gray matter loss is completed first in the orbitofrontal cortex, followed by ventrolateral PFC, and then dorsolateral PFC (Gogtay et al., 2004). Developmental changes in gray matter density also proceed in subcortical regions, such as the basal ganglia (Gogtay et al., 2004; Thompson et al., 2005) and the hippocampi (Gogtay et al., 2006). White matter volume, on the other hand, follows a posterior (caudal) to anterior (rostral) maturation with the most dramatic changes occurring in the frontal lobes through the adolescent period (Durston et al., 2001). Several longitudinal DTI studies have shown progressive maturation of white matter from early childhood to adulthood (Giedd et al., 1996; Giedd et al., 1996; Jernigan, Trauner, Hesselink and Tallal, 1991; Klingberg et al., 1999; Paus et al., 1999; Snook et al., 2005; Sowell, Thompson, Holmes, Jernigan and Toga, 1999). More recent studies of connectivity also linked myelination with the weakening of short-range and strengthening of long-range structural and functional connections with age (Fair et al., 2009; Hagmann et al., 2010).

In summary, neuroanatomical development is marked by a number of regressive (synapse elimination, cell death) and progressive (increase in brain volumes,

neurogenesis, myelination, synaptogenesis) events that occur first in phylogenetically older brain regions (i.e., sensorimotor systems), then in parietal and temporal association areas implicated in spatial attention and rudimentary language skills (Gogtay et al., 2004; Sowell et al., 2004), and finally in higher-order association areas like the PFC and lateral temporal cortices that are involved in higher cognition functions, such as attentional modulation and more complex language processes.

2.2.2 Behavioural findings of WM development

Although WM is evident in infancy (Diamond and Goldman-Rakic, 1989, Diamond, 1990), its maturation continues throughout childhood and adolescence (Conklin et al., 2007; Geier et al., 2009), with considerable increases even into young adulthood (Kwon et al., 2002; Zald et al., 1998). Early behavioural studies in infants and toddlers have shown that 6-month-olds can hold in WM the spatial location of a cued target for as long as 4 seconds (Gilmore and Johnson, 1995), and 8- to 12-month-olds are capable of correctly retaining objects in a delayed match-to-sample task with short delays but lack the ability to accurately reach to the target object (Diamond, 1990). Results from such studies suggest that the PFC-WM circuitry supporting simple response demands in encoding, maintenance and retrieval are detectable very early in development, but the neural substrates subserving more complex storage and processing abilities, i.e., the executive WM, are not yet sufficiently developed (Nelson, 1995). Neuroanatomical evidence also suggests that these changes coincide with the maturation timing of dorsal frontal and parietal cortices (Gogtay et al., 2004; Sowell et al., 1999). We now know that although the emergence of WM is relatively early, its key neural

correlate, the PFC, is amongst the last brain regions to reach adult-level functional maturity.

Cognitive or executive control is comprised of WM, attention, and inhibitory mechanisms, although whether these functions are of a single construct with a common underlying neural circuitry (Smith and Jonides, 1999; Casey et al. 2000; Miller and Cohen, 2001) or separable constructs (Miyake et al., 2000; Davidson et al., 2006; Huizinga et al., 2006) is still under debate in the literature. Regardless, the developmental maturation of all components of executive processes is characterized by a gradual improvement from preschool years into young adulthood. This age-related improvement is reflected by enhanced levels of task performance and is attributed to many factors. These include storage and processing capacity (Halford, Wilson and Phillips, 1998), attentional capacity (Arsalidou et al., 2010; Pascual-Leone and Baillargeon, 1994), a faster processing speed (Dempster, 1981; Hale et al., 1990; van den Wildenberg and van der Molen, 2004), strategy use and phonological coding (Pickering, 2001) and a better executive control over information held in WM storage (Gathercole, 1999).

Several studies using visuospatial and verbal WM tasks have demonstrated age-related improvements in task performance, however at different rates with varying task processing demands (Hale et al., 1997; Swanson, 1999; Gathercole and Alloway, 2004). More specifically, tasks that require simple maintenance of information, such as those tapping phonological or visuospatial stores, show a steep improvement up to 8 years of age and a more gradual increase until 11-12 years of age (Gathercole, 1999). In contrast, tasks that tap more complex memory systems including executive WM undergo a more

prolonged period of development (Gathercole, 1999). Additionally, the ability to recode visual information into verbal form is associated with age-related improvements in WM (Kemps et al., 2000; Pickering, 2001). Younger children tend to rely on visual information to remember pictorial stimuli due to immaturities in recoding visual information into verbal form. At around 7-8 years of age, children gradually become capable of complementing such visual coding with phonological coding, and thereby are able to devise more efficient and effective strategies that would encompass more dimensions of the presented stimuli (Hitch et al., 1988, 1989; Kemps et al., 2000; Pickering et al., 2001).

Several neuropsychological studies have found a marked improvement in WM from a very young age into adolescence and young adulthood. Luciana and Nelson (1998) found that at 4-7 years of age, children failed to employ both mnemonic and executive functions on a spatial WM task, whereas 8-year-old children were able to engage executive functions. With tasks that required increasing levels of executive control, Luciana and Nelson (2002) found that 12-year-old children perform better than their younger counterparts but still did not reach adult-like performance level. Conklin et al. (2007) reported that maintenance and manipulation processing for verbal WM is stable after 13-15 years of age, but additional manipulation skills continue to develop until 16-17 years of age. Similarly, several developmental neuropsychological studies have shown that WM continues to improve into young adulthood; a mature level of simple storage function is reached approximately at 11-13 years of age and that of more complex WM only after 15-19 years of age (Luna et al., 2004; Luciana et al., 2005; Huizinga et al., 2006; Vuontela et al., 2009; Zald et al., 1998). Behavioural work using

the Baddeley WM model also demonstrated that all WM model components are present from 6 years of age onwards but individual components increase in their capacity until early adolescence (Gathercole et al., 2004a). Taken together, these studies suggest that WM development starts with fine-tuning of basic perceptual and sensorimotor functions at early stages of development, and at subsequent stages of development, with the maturation of brain circuitry, more complex WM processes emerge.

2.2.3 Neuroimaging studies of WM development

Many studies have used fMRI to investigate the developmental changes associated with various components of executive function, including attentional processes (Konrad et al., 2005), WM (Klingberg et al., 2002; Vuontela et al., 2009), response inhibition (Luna and Sweeney, 2004), cognitive control (Luna, 2009), and set-shifting (Bunge and Wright, 2007). The PFC, viewed as the seat of executive functions, has been the exclusive focus in most of these studies. The overall finding, across tasks that tap into executive control and WM functions, is that activation in sub-regions of the PFC, such as BA 45 and 46, increases with age until the late 20s (see Luna et al., 2010 for a review).

More specifically for WM, several developmental neuroimaging studies have shown that children and adolescents appear to recruit similar frontoparietal circuitry as young adults while performing WM tasks (Casey et al., 1995; Ciesielski et al., 2006; Crone et al., 2006; Klingberg et al., 2002; Kwon et al., 2002; Olesen et al. 2003). However, differences in findings across studies do exist – specifically, between older and

newer studies. FMRI studies investigating the development of WM are summarized in Table 2.1.

Most of the older neuroimaging studies found that children and adults activate similar brain areas during the performance of verbal and spatial WM tasks (Cohen et al., 1994; Casey et al., 1995; Thomas et al., 1999; Nelson et al., 2000; Klingberg et al., 2002; Kwon et al., 2002). Areas activated during visuospatial WM processing include superior frontal gyrus, dorsolateral PFC, superior parietal lobule, and inferior parietal lobule (Thomas et al., 1999; Nelson et al., 2000; Klingberg et al., 2002; Kwon et al., 2002; Vuontela et al., 2009). Object WM in children has been shown to involve premotor cortex, dorsolateral and ventrolateral PFC, superior and inferior parietal lobules, cingulate gyrus, caudate/putamen, and cerebellum (Ciesielski et al., 2006; Crone et al., 2006). Similar activation between groups may reflect the recruitment of comparable cognitive processes such as those subserving WM and selective attention (Collette et al.,

Table 2.1.

List of fMRI studies investigating the development of WM

Author/Year	WM task	Stimuli type	Monitoring type	Sample size (N); age range or mean age
Casey et al., 1995	0-back, 1-back, 2-back	Letters	Identity	N=6: [9-11] years
Thomas et al., 1999	1-back, 2-back	Shape – coloured dot	Location	N=6: [8-10] years N=6: [19-26] years
Nelson et al., 2000	1-back, 2-back	Shape – coloured dot	Location	N=9: [8-11] years
Klingberg et al., 2002	Sternberg task	Shape	Location	N=13: [9-18] years
Kwon et al., 2002	2-back Location of letter O	Letter O	Location	N=8: [7-12] years N=8: [13-17] years N=7: [18-22] years
Schweinsburg et al., 2005	2-back	Abstract lines	Location	N=49: [12-17] years
Ciesielski et al., 2006	2-back	Colourful drawings of people, objects and animals	Identity (category)	N=9: [5.11-6.6] years N=8: [9.1-10.5] years N=10: [20-28] years
Crone et al., 2006	Verbal object naming WM task	Colourful drawings of objects	Identity (object), order/sequence	N=14: [8-12] years N=12: [13-17] years N=18: [18-25] years
Scherf et al., 2006	Oculomotor delayed response task	Dot	Location, reproduction by saccade	N=9: [10-13] years N=13: [14-17] years N=18: [18-47] years
Olesen et al., 2007	Sternberg, modified with distraction (one load level)	Dot	Location	N=13: 13.1 years N=11: 22.8 years
Brahmbhatt et al., 2008	2-back	Words, faces	Identity	N=15: [14-17] years N=15: [24-27] years
O'Hare et al., 2008	Sternberg (3 load levels)	Letters	Identity	N=14: [7-10] years N=10: [11-15] years N=8: [20-28] years
Thomason et al., 2008	Sternberg (3 load levels)	Letters and dots	Both location and identity verification	N=16: [7-12] years N=16: [20-29] years
Geier et al., 2009	Oculomotor delayed response task	Dot	Location, reproduction by saccade	N=13: [8-12] years N=13: [13-17] years N=17: [18-30] years
Libertus et al. 2009	2-back	Letters, numbers, faces	Identity	N=15: [8-9] years N=15: [20-35] years
Vuontela et al., 2009	0-back, 2-back	Coloured squares	Both location and identity	N=9: [11-13] years
Brahmbhatt et al., 2010	0-back, 1-back & 2-back	Letters	Identity	N=17: [9-13] years N=18: [18-23] years
Jolles et al., 2010	Verbal object naming WM task	Colourful drawings of objects	Identity (object), order/sequence	N=15: [11-13] years N=15: [19-25] years

2006) or similar cognitive strategies used for WM performance (Berl et al., 2006; Henson, 2005; Kirchhoff and Buckner, 2006; Rypma, 2006).

Some studies have not found such similarities in activations between age groups (Ciesielski et al., 2006; Crone et al., 2006; Scherf et al., 2006). Children were found to either recruit limited areas of the WM network compared to adolescents and adults or engage partially different neural networks during WM tasks (Ciesielski et al., 2006; Crone et al., 2006). For example, in an N-back task that required mnemonic processing of objects, children did not engage the frontal cortices, even those who performed similarly to adults (Ciesielski et al., 2006). Rather, children activated regions within the dorsal visual stream, suggesting the use of a different cognitive strategy for task performance (Ciesielski et al., 2006). In a visuospatial memory guided saccade task, children were found to activate only limited areas in the core frontoparietal WM regions and relied much more on the caudate nucleus and anterior insula (Scherf et al., 2006). Brahmbhatt et al. (2007) found group differences in frontal activations between adolescents (14 to 17 years) and adults in WM tasks, even in the absence of performance differences, underlining the continuation of functional development in the frontal lobes through adolescence. In a subsequent study that included children from 9 to 13 years of age, Brahmbhatt et al. (2010) found that children showed greater overall transient but less sustained activity in comparison to adults, suggesting that they had more difficulty with maintenance processes.

Studies that examined age-related changes in brain activity during WM performance have generally observed an increase in brain activity with age from childhood into adolescence (Crone et al., 2006; Klingberg et al., 2002; Olesen et al.

2003). However, other studies that included a wider age range from childhood to adulthood have found that age-related activity in the dorsolateral PFC associated with spatial WM tasks was non-linear – it follows an inverted U-shaped curve, peaking in adolescence until the late 20s (Scherf et al., 2006; Geier et al., 2009).

Additionally, while some studies have reported a developmental change from more diffuse, widespread, and higher magnitude of activation in children to focal activations in adults (Casey et al., 1995; Thomas et al., 1999; Nelson et al., 2000), others have observed both an increase in signal change as well as activation extent with advancing age (Klingberg et al., 2002; Kwon et al., 2002). Findings that support the "diffuse to focal" age-related changes in activity possibly reflect the fine-tuning of relevant neural systems (Durston et al., 2004; Berl et al., 2006; Johnson and Munakata, 2005). In contrast, more distributed activity across brain regions with age could suggest that cognitive function may be more evenly distributed across the brain, or efficiently specialized, therefore leading to decreased reliance on PFC systems (Luna et al., 2010). Furthermore, some other studies have found increases in activation with age for some cortical regions but also decreases in activation with age for other cortical regions (Booth et al., 2000; Brown et al., 2005; Schlaggar et al., 2002), suggesting that developmental change is reflected in the degree of engagement of each region within a distributed network of areas.

Some structural imaging studies have examined the relation between behavioural WM development and general intellectual functioning, with white matter and cortical gray matter. Early studies by Casey and colleagues (Casey et al., 1997; Casey et al., 1997) have shown that the size of prefrontal brain regions in children correlates with

performance on WM and inhibition tasks. Sowell et al. (2001) found an association between structural maturation of the PFC and improved memory function using neuropsychological measures, while Nagy et al. (2004) observed that white matter maturation in the PFC and in an area between the PFC and posterior parietal cortex were related to the development of visuospatial WM. Moreover, age-related joint maturation of white and gray matter in the PFC and posterior parietal cortex have been observed (Olesen et al., 2003), further highlighting the tight coupling of processes subserving the network of regions supporting WM.

Differences between study findings may be related to several aspects of methodological differences: age range, varying maturational status of participants, task difficulty, task performance differences, or differences in ability to devise and implement strategies (Berl et al., 2006). Some early studies had small sample sizes that cover a large age range (e.g., 13 participants between 9 and 18 years of age, Klingberg 2002), while other studies have more participants to examine children versus adolescents versus adults, but again the participant numbers within each group are frequently small. Thus, to create a broad normative base, it is critical to recruit participants at each year of age, to more clearly capture the full developmental trajectory.

2.3 MR physics and the BOLD-fMRI response

Since its discovery in the 1970s, magnetic resonance imaging (MRI) has become a versatile tool for various clinical and research applications. Arising from the local precession of protons, MRI provides a number of different contrast mechanisms through the manipulation of the precession using different magnetic field combinations. These include different relaxation factors (T1/T2), susceptibility differences, magnetization transfer contrast, flow, contrast agent, and diffusion.

This section reviews fMRI principles underlying the blood oxygenation level dependent (BOLD) signal. Particularly, the basic principles of MR signal detection and the underpinnings of the techniques are reviewed to provide necessary technical background for the subsequent sections.

2.3.1 How is the MR signal generated? MR physics and principles

The MR signal originates from the nuclei of atoms with unpaired protons and relies on the interaction of a nuclear spin with an external magnetic field (B0). Given the natural abundance of hydrogen atoms in water in tissues, its proton is typically used in MR imaging. The nuclei of the hydrogen atom act like small precessing magnets with a magnetic dipole moment, often called a spin. Precession refers to the circular motion of the axis of a spinning body about another fixed axis caused by the presence of an external magnetic field and is the basis on which the MR signal is detected.

In the absence of an external magnetic field, the spins are randomly distributed and cancel each other out, resulting in no net magnetization. However, in an applied magnetic field (B0), a proton can adopt two possible energy states: parallel (same

direction as B0) or anti-parallel (opposite direction as B0). In an equilibrium state, protons tend to align in parallel direction with B0 as this is a lower energy state and hence more stable than anti-parallel. The sum of these small magnetic dipole moments gives rise to a net magnetization in the longitudinal direction (same direction as B0). The magnetic field components of the dipole moments in the transverse plane remain random and thus cancel out. The Lamour frequency is the precession frequency at which spins naturally rotate around B0. To convert/excite from one energy state to the other, electromagnetic energy is either absorbed (to assume a high energy state) or released (to return to low energy state).

In order to detect MR signal, spins have to be set into precession and the net magnetization must be tipped away from the static magnetic field (B0) from the longitudinal to the transverse plane. This is achieved by introducing another rotating electromagnetic field (B1), called the radiofrequency (RF) pulse, at the Larmour frequency in the direction that interacts with the rotating spins. The precessing spins induce a changing voltage flux in the receiving coil, and this produces the MR signal. The RF pulse can be adjusted to tune the amount of rotation from the equilibrium and the magnetization experiences different relaxations as a consequence. This determines the signal strength that can be detected at a certain acquisition time.

When the RF pulse is removed, the MR signal can decay in one of two ways, longitudinal (T1 recovery) or transverse (T2 decay) relaxation. Longitudinal relaxation occurs through energy exchange with the surrounding environment; protons return from high- to low-energy states, hence realigning the net magnetization to the same plane as B0. In contrast, transverse relaxation is caused by spin-spin interactions. Because each

spin experiences different local magnetic fields as a combination of the applied pulse and the field of their neighbouring spins, these field differences lead to spin dephasing and net reduction of transverse magnetization. In practice, another source for the dephasing effect is the local magnetic field inhomogeneity, whereby precession frequencies vary slightly due to inhomogeneous external magnetic field. The collective effect of transverse decay and inhomogeneity produces an overall relaxation time constant called T2*, and this is used specifically for fMRI. Brain tissue varies in contrast and intensity with different MR constants, which allows white matter, gray matter and CSF to be identified on MR images.

Two MR parameters that can be manipulated to adjust the amount of signal recorded and the contrast and intensity expressed are repetition time (TR) and echo time (TE). TR refers to the interval between successive RF pulse applications, while TE is the interval between the application of the excitation pulse and the acquisition of data. Numerous contrast mechanisms can be produced, that include flow, magnetic susceptibility differences, magnetization transfer contrast, tissue saturation methods, contrast enhancing agents and diffusion. Many different physiological properties of brain tissue can be exploited to assess brain structure and function by means of MRI. These include cerebral blood flow, perfusion and metabolic oxygen level, temperature differences and water diffusion. Although the BOLD signal is strongly dependent on changes in blood flow and volume, it is a complex indirect phenomenon. The next section focuses on the magnetic susceptibility effect used for BOLD-fMRI, to illustrate its signal formation principles.

2.3.2 How is the BOLD-fMRI signal generated? The haemodynamic response

The most prevalently used functional MRI records blood-oxygenation-level-dependent (BOLD) response. BOLD-fMRI is based on the coupling of MR signal changes with the change of local blood flow as a proxy for changes in brain activity based on changes in blood flow. The principle of fMRI is grounded on the local susceptibility property that is modulated by the oxygenation level of the blood, which is a proxy for neuronal activity. BOLD-fMRI measures blood flow changes in the brain during the performance of a cognitive task, the application of sensory stimuli or even during "rest". However, contrary to what the name suggests, the BOLD effect is actually dependent on blood *de*oxygenation due to special magnetic properties of deoxygenated blood.

Haemoglobin (Hb), an iron-containing protein complex, is a major component of red blood cells in the mammalian bloodstream. Hb transports oxygen and other gases to cells in the body for metabolism. The magnetic properties of Hb depend on the relative concentration of oxyhaemoglobin (oxyHb) and deoxyhaemoglobin (deoxyHb; Pauling and Coryell, 1936) and provide the basis for the BOLD signal (Ogawa et al., 1992; Kwong et al., 1992). OxyHb is diamagnetic and does not affect the magnetic field strength, while deoxyHb is paramagnetic and distorts local magnetic fields. The differential magnetic properties of Hb generate microscopic magnetic field gradient inhomogeneities around blood vessels and thus shorten T2* according to its level of oxygenation (Thulborn et al., 1982), leading to faster dephasing and signal dropout, and producing differences in signal strength (Huettel, Song and McCarthy, 2004). This is

referred to as the BOLD effect. When neural activity increases, the amount of oxygenated blood delivered to that area typically increases while levels of deoxyHb decrease. The BOLD signal captures the displacement of deoxyHb by oxygenated blood as the former affects magnetic fields but the latter does not. The relative decrease in deoxygenated blood produces the BOLD effect.

Relative amounts of oxyHb and deoxyHb in the capillary bed of a tissue are dependent on regional blood flow and oxygen consumption. When neural activity increases, there is an initial increase in oxygen consumption. Oxygen is taken from diamagnetic oxyHb, leaving behind paramagnetic deoxyHb, which decreases MR signal (Ernst and Hennig 1994). After about 4-6 seconds, there is a relative increase of blood flow over oxygen consumption. This slightly delayed delivery of fresh oxygenated blood results in a decrease of deoxyHb, and the MR signal increases (Bandettini et al. 1992). It is this delayed decrease of deoxyHb level that characterizes the positive MR signals detected in BOLD-fMRI experiments. Subsequently, the MR signal then drops, with the increase of deoxyHb due to a decrease of blood flow (Frahm et al. 1996). After about 12-20 seconds, the signal returns to baseline. This entire process of change in oxygen consumption is referred to as the haemodynamic response function.

2.3.3 What does BOLD-fMRI measure? Neurophysiological basis of the BOLD signal

BOLD-fMRI has been a backbone technique in the neurosciences for almost 20 years. The majority of functional neuroimaging studies assume that the molecular coupling of events and physiological changes underlying the BOLD response are

capturing neuronal activity. However, the nature of neuronal activity represented by BOLD responses is still an actively researched topic (Bartolo et al., 2011; Magri et al., 2012; Yen et al., 2011). How exactly neuronal activity triggers the overcompensation of blood supply is still partially unknown. Neuronal activity changes can readily occur at millisecond levels within a spatial scale of hundreds of transiently synchronized neurons, but the BOLD changes usually come after one or two seconds and with a massive over-perfusion covering a much broader spatial territory than the underlying neuronal activity.

PET and fMRI studies have documented the parallel increase of blood flow and glucose utilization in response to local increases in neuronal activity but minimal increase in oxygen consumption. Although it is a general principle in brain physiology that neuronal activity is tightly coupled with blood flow and energy metabolism, the actual cellular and molecular mechanisms underlying this coupling are nevertheless not yet established.

Intensive research has been conducted on potential links between neurovascular and metabolic coupling. Thus far, glutamate, an excitatory neurotransmitter in the brain, has been deemed the central candidate for both processes (Magistretti, 2009). Astrocytes, a type of glial cell in the central nervous system, also play key roles (Haydon and Camignoto, 2006). Local vasodilation is caused by nitric oxide, a potent vasodilator, released by the activation of postsynaptic glutamatergic receptors in neurons and astrocytes, while glucose metabolism takes place with glutamate transporter and astrocyte-mediated glycolysis.

Many studies combined fMRI with EEG or optical imaging in an effort to reveal physiological basis of BOLD signal, but these two techniques have their own limitations

that prevent precise characterization. Optical imaging essentially also measures haemodynamic responses while EEG suffers from poor spatial resolution and imprecise localization of the underlying electromagnetic field.

To combat these limitations, studies have also used microelectrode recordings, a prevalent technique in the animal literature, to directly relate the neuronal firing pattern, local field potentials with the BOLD signal. Micro-electrode recording can precisely quantify neuronal activity at a single neuron, multiple neurons or neuronal population level. Specifically, single-unit (SUA; Hubel and Wiesel, 1959) and multi-unit activity (MUA; Legatt, Arezzo and Vaughan, 1980) reflect primarily the spiking (firing rate) output of a specific or a small set of neurons. In contrast, local field potential (LFP) represents a weighted average of synchronized dendritic input currents (Mitzdorf, 1987). As a result, the combination of fMRI with microelectrode recording can not only address the question of the neuronal substrate for BOLD signal but also potentially differentiate the source between the spiking activity (SUA/MUA) and integrated dendritic activity (LFP).

A seminal paper by Logothetis and colleagues (2001) used a monkey model to investigate the relation between neuronal firing rates during electrophysiological recordings coupled with fMRI. Specifically, SUA, MUA and LFP recordings were made in the visual cortex. A transient increase in BOLD signal was found at the onset of the visual stimulus that persisted until the stimulus ended. Concurrently, both LFP and MUA increased during stimulation. However, they found that the increase in LFPs during stimulation was significantly stronger than that of MUA. Furthermore, while MUA subsequently returned to baseline shortly after stimulus presentation (adaptation),

LFPs were sustained throughout the stimulus duration and were better correlated with the BOLD signal. In addition, convolving neuronal activity with the neural-vascular impulse response function to predict the BOLD signal, the average LFP response was always found to give better estimates of the true BOLD signal than MUA. Therefore, BOLD activation likely reflects incoming integrated input and local processing (i.e., LFP – integrative activity at neuronal dendritic sites) rather than spiking output activity (i.e., MUA – axonal firing rate in a population of neurons). The findings show that a localized increase in BOLD contrast directly and monotonically reflects an increase in the underlying neural activity.

Following this key paper, a series of studies have been performed and consistent findings have been reported (Logothetis and Pfeuffer, 2004; Logothetis and Wandell, 2004; Logothetis, 2003; Goense and Logothetis, 2008). One study by Mukamel et al (2005), recorded SUA and LFPs in two epileptic patients who were monitored with intracranial electrodes placed in Heschl's gyrus, and BOLD-fMRI signals in 11 healthy participants, while viewing a movie segment. Averaged spiking activity (SUA) was convolved with a standard haemodynamic response function to derive a "spike predictor". This predictor highly correlated with averaged BOLD signals from ROIs within the Heschl's gyrus of each subject, suggesting the BOLD contrast can be a reliable measure of neuronal firing rates.

Such studies demonstrate that BOLD responses may be comprised of complex neuronal activity with many components of input and output processing. Reviews suggest that BOLD-fMRI response may be capturing both pre- and post-synaptic activity (Heeger and Rees, 2002), and others have suggested that it most closely reflects

excitatory synaptic activity rather than action potential (Logothetis, 2008). Overall, although the exact mechanism underlying the coupling between neuronal activity and haemodynamic response measured by BOLD signal remains partially elusive, empirical data support the neuronal basis for the observed BOLD-fMRI signal and hence pave the way for its application in human functional studies.

CHAPTER 3: AIMS AND HYPOTHESES

Compared to the number of adult fMRI studies that utilized the N-back task, only a few have examined paediatric populations – the field of developmental cognitive neuroscience still lacks a substantive body of literature tracing normative neurodevelopment of WM. Furthermore, there are some pieces of conflicting literature – while some studies found an increase in BOLD-response in the frontoparietal WM network with age, others have shown the opposite.

Based on 18 fMRI studies examining WM development from a thorough literature search (Table 1.1), we observed that the majority of these studies (10/18) have utilized the N-back task as the measure of WM, all but one study used verbal or nameable stimuli, and studies were equally divided in the WM processing for object locations or identity. Moreover, we noted that many of these studies collected data from very small sample sizes of children with either relatively narrow age ranges (e.g., ignoring the mid- to late- adolescent years) or averaged across wide age ranges.

The primary purpose of the current study was to provide an account of the functional anatomic organization of WM processes involved in performing a visual pattern N-back task over a broad range of ages. This task involves WM for the identity of colourful abstract and complex patterns that are difficult to name and requires more perceptual processing, a stimulus type that has not yet been used with developmental neuroimaging. In the present experiment, we employed the 0-back and 1-back tasks. In terms of cognitive requirements, both tasks require the goal of each task to be kept in mind, scanning the visual display, identifying the target and making a motor response.

However, the 1-back task requires an additional component of maintaining a representation of the previous stimuli in mind and updating that representation with each subsequent trial, a process which we classify as a simple WM process. Hence, the 1-back should be more cognitive taxing than the 0-back task and thus should exhibit a greater developmental trend. With this in mind, we have two specific aims with regards to N-back behavioural performance and its corresponding neuroimaging data.

Aim #1:

To evaluate possible changes in behavioural performance across development.

Hypotheses and rationale: The 0-back and 1-back conditions are relatively easy tasks and all participants were expected to achieve near-ceiling performance. Therefore, we hypothesized that the younger age cohort should still be able to perform at similar accuracy levels (i.e., not statistically different) as their older counterparts. We expected that performance (i.e., accuracy) would mature rapidly over the early school-age years with these simple WM tasks. However, as previous research have documented the improvement in global processing speed with advancing age (Kail, 1986; 1988), we predicted that children would take longer to respond than their older counterparts, as the adult-level of inhibition and processing speed develops more gradually through childhood and adolescence. The adolescent age group was expected to have levels of performance that resemble more closely those of the adult group.

Aim #2:

To examine what brain regions are commonly and differently active across development during simple WM tasks, in both signal magnitude and spatial extent of activations.

Hypotheses and rationale: On the basis of adult neuroimaging data (Owen et al., 2005; Rottschy et al., 2012) and more specifically findings from Ragland et al. (2002), we expected that a simple WM task effect (1-back > 0-back) would recruit the canonical WM network consisting of frontal and parietal areas in adults. Adolescents, who are presumably more cognitively mature, would show distributions of functional brain activity that would bear more similarity to that of adults than children. For children, we expected that the frontal regions would be involved to a lesser degree (in either extent or magnitude or both), and may be complemented by the engagement of other earlier maturing region.

Task-related but age-invariant regions should include common brain areas across age groups that can differentiate between the cognitive brain systems subserving the two task conditions (i.e., the additional component of "updating" processes in 1-back). We expected these regions to be composed primarily of the regions within the core WM frontoparietal network with higher signal magnitudes during 1-back. In contrast, age-related but task-invariant regions should comprise cortical areas that underlie the common cognitive substrate between the two task conditions (i.e., the common component of sustained attention) and that has a more protracted time course. Thus, we expected these regions to be within the general dorsal cingulate attentional network. We also predicted that the activation pattern would vary across task conditions as a function

of age, i.e., an interaction depicting developmental trends for the simple WM load. This is more of an exploratory analysis so we do not have specific predictions.

CHAPTER 4: METHODS

4.1 Participants

A total of 84 healthy individuals (age range = 6.14 – 36.13 years, 45 females, mean age 15.9±7.1years; 68 right-handed) who reported no history of visual impairments, neurological or psychiatric disorders, major medical disorders, learning disorders, and/or mental retardation, participated in the present study. Recruitment was done through flyers, advertisements, and word-of-mouth in the Greater Toronto Area. All participants received a movie pass or bookstore gift card as an appreciation for their time and effort. This study was approved by the Research Ethics Board at the Hospital for Sick Children. Participants older than 16 years gave informed consent, while younger participants gave verbal assent and their parents gave informed written consent.

Participants with excessive motion, poor image quality/artifact and/or missing scans/functional data were excluded from behavioural and imaging data analyses (see Appendix A). Data from 65 participants who successfully performed both the 0-back and 1-back task conditions were included in the final analyses discussed in this thesis. For group analysis purposes, this sample was divided into three age groups as follows: children (6-11 years, n = 22), adolescents (12-17 years, n = 22) and adults (18-36 years, n = 21). A chi-square test confirmed there was no bias in sex distribution across age groups (χ^2 = 4.412, P = 0.11). For more detailed demographics on these age groups, see Table 4.1. This division was informed partly by an attempt to equate sample size across the groups, which also coincided with general agreement that the period of gradual

transition between childhood and adulthood beginning with puberty usually takes place between 12-17 years of age (Dahl, 2004; Dorn et al., 2006; Spear, 2000).

Estimated IQs based on combined scores from the Vocabulary and Matrix Reasoning subtests of the *Weschler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999) were obtained from the majority of participants under the age of 17 years (*n* = 39/44).

Table 4.1.

Demographic information of the age groups

		Children	***Adolescents***	***Adults***
Sample size (after exclusion)		22	22	21
Age range (in years)		6 – 11	12 – 17	18– 36
Sex (N, %)		13 F (59%)	10 F (45%)	15 F (71%)
Handedness (N, %)		21 R (95%)	19 R (86%)	20 R (95%)
Mean age ± SD	**Overall**	8.69 ± 1.56	14.9 ± 1.50	23.9 ± 5.6
(in years)	**Female**	8.60 ± 1.59	15.5 ± 1.24	24.9 ± 6.0
	Male	8.93 ± 1.60	14.5 ± 1.59	21.5 ± 3.4

4.2 Stimuli and task

Participants performed a visual patterns WM task with three conditions. This task is most typically known as the *N*-back and the conditions presented were 0-, 1-, and 2-back. As one of the ways to optimize data collection, here we used a block-design paradigm to isolate activation related to the task effect as much as possible and this also allowed the task to be brief enough to be feasible for young children. Instructions and a short practice were given outside the scanner prior to scanning; instructions were also repeated verbally to the participant at the beginning of each run through the intercom. Stimuli used in the practice task were different from those used during the experiment.

Stimuli consisted of complex abstract colourful patterns presented on a grey background (Figure 4.1B). These stimuli are artificial and were chosen to meet the need for stimuli that were difficult to name. Each condition corresponded to one run. Each condition-run consisted of three 32-second task blocks, where participants were shown a series of 48 stimuli and four 16-second baseline/rest blocks, where participants fixated on a colourful cross (Figure 4.1A). There were 48 stimulus presentations in each condition-run, out of which 16 were target trials in the 0- and 1-back conditions, and 15 were target trials in the 2-back condition. No lure trials (e.g., 1-back target trial embedded in a 2-back run) or stimulus repeats (other than target trials) were presented to minimize confusion and optimize performance for younger participants.

Participants were instructed to focus on the centre of the screen, and pressed a button only to the target trials using their dominant hand. In the 0-back condition, target trials were solid blue squares. In the 1-back condition, participants identified targets as any stimulus that immediately repeated. In the 2-back condition, participants indicated

when the current stimulus matched the one presented two trials previously. The order of the conditions was counterbalanced across participants, with the blue square condition being always presented in between the other two conditions; however, some completed only the 0- and 1-back conditions (n = 9/65), and the final number of participants presented with a sequence of 2-0-1-back was 23/65 and 33/65 completed the sequence 1-0-2-back.

Each stimulus was presented for 1000ms interleaved with an ISI of 1000ms, during which a simple fixation cross was presented on grey background. Stimuli were displayed and responses recorded using Presentation software (Neurobehavioral Systems Inc., CA). Participants viewed stimuli through MR-compatible goggles (CinemaVision, Resonance Technology Inc., CA) and responded using MR-compatible keypad (LUMItouch, Photon Control Inc., Burnaby, BC, Canada). **Only data from the 0- and 1-back conditions were included for the analyses in this thesis as only a subset of all participants (n = 40/65) achieved satisfactory performance (i.e., ≥60%) on the 2-back. However, both the 0-back and the 1-back task still proved to be difficult or cognitively taxing for young children, and we believe that WM is required for the performance of these tasks.**

4.3 MRI procedures and acquisition

All MR images were collected on a 1.5T Signa Twin EXCITE3 scanner (GE-Medical Systems, Milwaukee, WI) with a product eight-channel head coil at the MRI facility of the Hospital for Sick Children. Foam padding was used to minimize head motion comfortably during scanning. A set of high-resolution T1-weighted whole-brain 3D SPGR images was acquired using an axial fast spoiled gradient recalled (SPGR) sequence (TE/TR/flip angle = 9ms/4.2ms/15°, 116 slices, voxel size = $1\times1\times1.5mm^3$, 2 NEX, 7 minutes) as an anatomical reference prior to the acquisition of functional images. Participants watched their choice of movie through MRI-compatible goggles during anatomical scan acquisition. A standard gradient-recalled echo-planar imaging sequence (TR/TE/flip angle = 2000ms/40ms/90°, voxel size = $3.75\times3.75\times5mm^3$, 22–26 axial slices) was used to acquire T2*-weighted functional images during the visual memory paradigm.

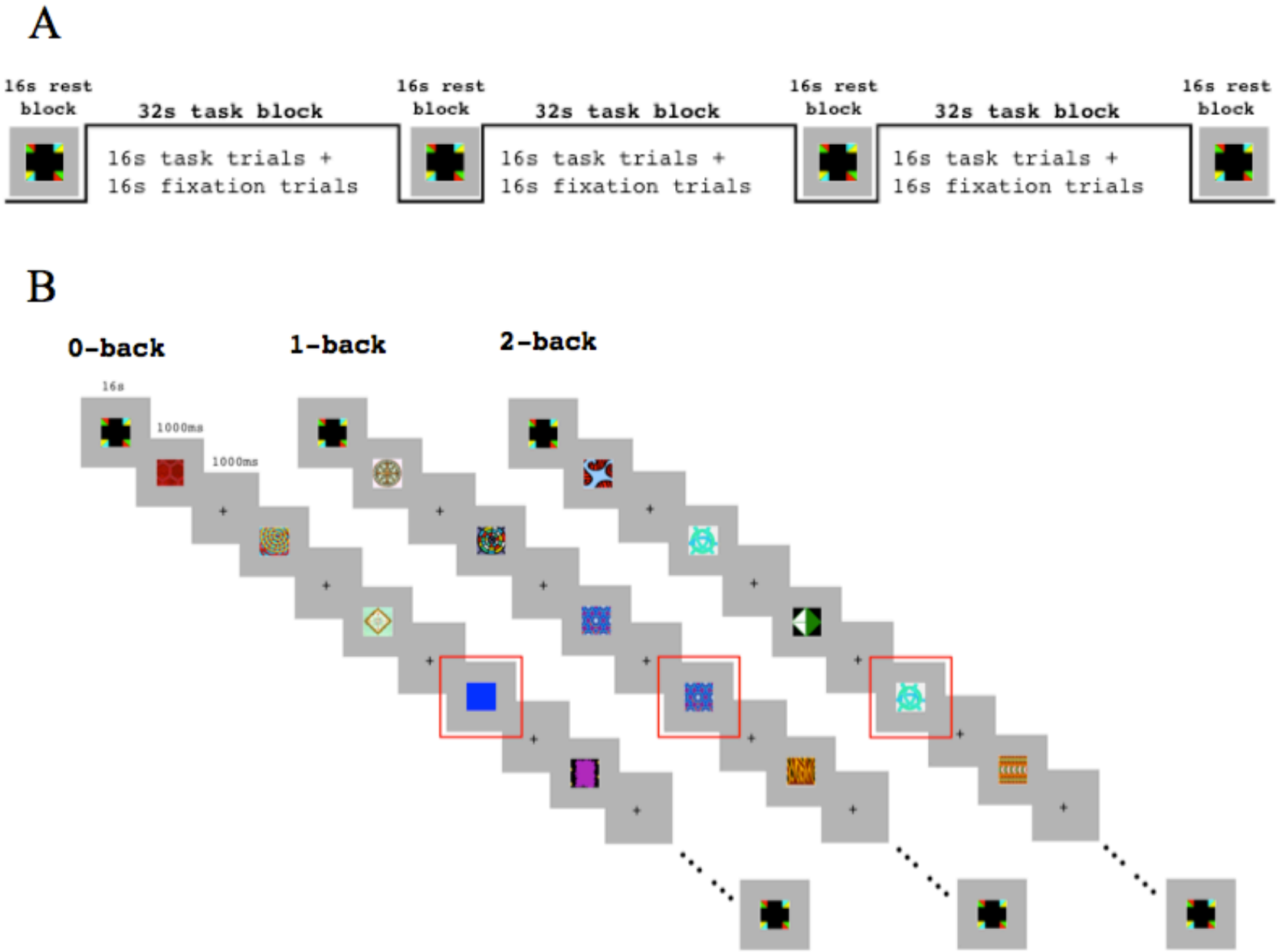

Figure 4.1. Experimental design schematic. **A.** fMRI paradigm task design. Each run contained four 16-s rest block (colourful cross baseline) interleaved with three 32-s task blocks (16 task trials + 16 fixation trials). There were 16 stimulus presentations per task-block, therefore 48 stimulus presentations per run. **B.** Examples of presentation sequences in each block. Box in red indicates targets in each of the specified conditions. 0-back and 1-back runs each contained 16 targets.

4.4 Behavioural data analyses

Behavioural analyses were performed using *SPSS 19.0 for Mac* (IBM). Two measures, accuracy and reaction time (RT) for correct responses, were calculated for each N-back task condition. Accuracy was defined as the percentage of trials in which subjects correctly identified the target (after subtracting the number of false positive or error responses), out of all trials presented. RT was calculated for correct response trials only.

To assess overall performance differences between the age groups, repeated measures ANOVAs were performed on each behavioural measure, with a between-subject factor of age groups (i.e., children, adolescents and adults) and sex, and the within-subject factor of task condition (i.e., 0- and 1-back). If the ANOVA produced a significant main effect, post-hoc tests were performed with Tukey's HSD and paired *t*-tests. Additionally, to examine the relation between age and behavioural performance measures these variables were analyzed using bivariate and partial correlations.

4.5 fMRI data analyses

4.4.2.1 Preprocessing and first level single-subject analysis

Imaging data were processed and analyzed using AFNI – Analysis of Functional Neuroimages (Cox, 1996). First, a motion-correction algorithm was applied to align each volume in the time series with an arbitrarily chosen base volume (here, we selected the ninth image of the time series), yielding three rotational (pitch, yaw, roll) and three

translational (x, y, z) motion parameters across the time series for each participant using AFNI's *3dvolreg*.

Then, an outlier algorithm (*3dToutcount*) was used to censor any motion artifact spikes for quality control purposes. Functional data were transformed (using *@auto_tlrc*) into standard Talairach coordinate space for structure localization and comparison among subjects (Talairach and Tournoux, 1988). We then applied a spatial smoothing Gaussian filter (full-width half maximum [FWHM]=10mm) to account for anatomic variability (*3dblur*). And finally, data were subjected to signal intensity normalization to generate a percent signal change value for each voxel.

Statistical analysis at the single-subject level treated each voxel according to a general linear model (GLM) using AFNI's *3dDeconvolve* program, modeled using a fixed haemodynamic response function, covarying for the estimated six motion parameters and linear trends. This process yielded fit coefficients representing BOLD response contrast (in percent signal change values) between 1-back and 0-back (contrast of most interest), 1-back and baseline, and 0-back and baseline, in each voxel for every subject.

4.4.2.2 Motion assessment and quality assurance

For each subject, the initial stage of data processing involved a quality assurance routine to visually evaluate the alignment of functional and anatomical volumes, potential image artifacts, and within-run movement. For each run, time points with appreciable head motion were noted and this information was used to guide selection of the base volume for motion correction using *3dvolreg*. Data were re-inspected following motion

correction, and time points that remained problematic were later censored from individual statistical analyses (which removes motion-affected volumes from the dataset during model estimation, while preserving temporal continuity).

We also ensured that the absolute amount of motion per volume per run, i.e., the estimated maximum displacement in any direction (maximum excursion), did not exceed the single voxel size of 3.75mm. This threshold criterion was chosen based on previous paediatric motion work done in our lab (Evans et al., 2010). All volumes with >3.75mm of within-run maximum displacement were censored in the single-subject analysis. Runs where large portions of data were affected by motion, i.e., >30% (24/80) of total volume per run needed to be censored, were dropped from subsequent analyses; the data of three young participants had to be removed for excessive motion. Correlations and repeated measures ANOVAs of average movement (in mm) in both runs were applied to examine possible age-related within-run movement effects. To test if motion is associated with behavioural performance, partial correlations were also used.

4.4.2.3 Second-level whole-brain group analysis

To examine within-group brain maps and between-group differences at the whole brain level, a one-way random effect ANOVA was conducted for the WM effect contrast (1-back vs. 0-back) for each age group and for each planned age group linear comparison (adults vs. children, adolescents vs. children, adults vs. adolescents). Common patterns of activations and deactivations between the age groups for each given contrast and between tasks for each age group were identified by conjunction analyses, which determined the overlapping regions in the brain among a set of contrasts. We also

examined simple effects of neural responses during task performance and baseline fixation so we repeated these procedures for the 1-back vs. baseline and 0-back vs. baseline contrasts.

Another second-level random effect analysis was performed to assess the main effects of the task condition, age group and interactions between groups and conditions, using the GroupAna program in AFNI implemented through MATLAB (Mathworks Inc., Natick, MA), with *age groups* (children, adolescents, and adults) as the between-subject factor (fixed), *task contrasts* (0-back vs. baseline, 1-back vs. baseline) as the within-subject factor (fixed) and *subjects* as a random factor (2×3 factorial design).

We examined all significant clusters from the each of the main effect terms as well as the interaction term to determine the nature of these effects. All significant clusters were first entered into a functional ROI mask using AFNI's *3dClust* program, and then used to extract mean percent signal change for each subject's corresponding contrast images (0-back vs. baseline, 1-back vs. baseline). Regions that showed a main effect of task were masked out to examine common regions between the age groups that differentiated between the tasks in signal magnitude. Regions that showed a main effect of age were masked out to examine regions that showed a similar developmental trend between the tasks. And finally and most importantly, regions that showed an interaction effect were masked out to examine regions that depicted developmental trends for the simple WM load. Extracted percent signal change values for each ROI were plotted graphically.

Multiple comparisons corrected threshold was determined by AFNI's *3dClustSim*. We discovered that 26 voxels was the minimum number of voxels that should constitute

a significant cluster at an individual voxel threshold of $P < 0.005$ and a minimum spatial extent of $P < 0.05$ (cluster threshold). All results were reported at this threshold except for the interaction term of the 2×3 ANOVA. As the interaction term of the mixed effect ANOVA was more of an exploratory analysis and what we're most interested in, we used a more liberal threshold of $P < 0.01$ with 10 contiguous voxel clusters (uncorrected for multiple comparisons). Regional labels for all significant clusters were confirmed using the Talairach Daemon function (Lancaster et al., 2000; Ward, 1997) imbedded in AFNI. Within each region of statistical significance, we reported the peak coordinates and their locations by gyri and Brodmann Areas, in radiological convention, in Talairach space (Talairach and Tournoux, 1988).

4.4.2.4 Region of Interest analysis

Besides the whole-brain analysis, we also used a region of interest approach to identity brain regions showing developmental changes associated with known components of N-back tasks of the identity-monitoring type using visual stimuli (Owen et al., 2005). The analysis served two purposes: i) to verify our whole-brain analyses and ii) to isolate weaker effects that did not survive at the whole-brain level to compare with known brain effects elicited by similar N-back tasks in the literature.

We first created regional masks, composed of spheres with 8-mm radius, for each coordinate reported from Owen et al. (2005). See Table 4.2 for list of regions and coordinates. We then applied these masks to each individual's first-level linear WM effect contrasts (1-back vs. 0-back) and extracted values of mean percent signal change with each region individually. These extracted values were then entered into ANOVAs

and *t*-tests, as appropriate, treating subjects as a random factor, in SPSS (*Ver. 19.0* for Mac).

First, for each region of interest, we conducted a repeated measures ANOVA with task (0-back and 1-back) as a within-subject factor and age group as a between-subject factor. We were interested in identifying regions that showed a main effect of task or age, and a task by age interaction. Significant regions were then subjected to post-hoc testing. To examine between-group differences, we conducted one-way ANOVAs for each contrast. And finally, we performed paired *t*-tests with task conditions (0-back and 1-back) for each region of interest to identify task differences within-groups. We also correlated the percent signal change values from each subject with age to identity regions that showed linear age-related effects.

Table 4.2.

Regions of interest, coordinates taken ALE meta-analysis of fMRI studies that used N-back tasks of the identity-monitoring type using visual stimuli (Owen et al., 2005)

Regions of interest	Hem.	BA	*Talairach coordinates*		
			x	***y***	***z***
Lateral premotor cortex	L.	6/8	-38	-20	50
Dorsal cingulate	-	32	0	-26	36
Dorsolateral prefrontal cortex	L.	46/9	-42	-30	24
Dorsolateral prefrontal cortex a	R.	46/9	44	-4	32
Dorsolateral prefrontal cortex b	R.	46/9	40	-26	24
Frontal pole a	R.	10	32	-42	10
Frontal pole b	R.	10	28	-62	-4
Inferior parietal lobule	R.	40	30	54	40
Inferior parietal lobule	L.	40	-58	36	44

CHAPTER 5: RESULTS

5.1 Behavioural Assessment

Table 5.1 presents performance on the 2-subtest WASI. All of those who completed these measures scored at or above the age norm. A sex effect was found for the two-subtest IQ measured by WASI where females' IQs (M = 117.6, SD = 9.1) were higher than males (M = 109.1, SD = 11.8; t (37) = 2.562, P = 0.015). Table 5.3 presents the result of the correlations between behavioural performance on the fMRI task and on these behavioural measures. An interesting finding was the negative correlation between IQ and accuracy on the 0-back task (R = -0.325, P = 0.044), indicating that higher IQ was associated with worse performance on 0-back. No statistically significant correlations between other variables were found. In the present study, given that only a subset of the sample completed each behavioural measure, these findings should not be overly interpreted.

Behavioural performance data (i.e., accuracy and reaction time) of the entire sample are summarized in Table 5.2. The comparison of performance data between the two task conditions across the three age groups is presented in bar graphs (Figure 5.1) and across the entire age range is presented as scatter plots in Figure 5.2. Repeated measures ANOVA for accuracy (percent correct) indicated a significant main effect of task (F (1, 60) = 9.516, P = 0.03, η^2 = 0.14) as well as age (F (2, 60) = 9.538, P = 0.00, η^2 = 0.24). However, there was no age × condition interaction. Paired-sample t-tests were followed up to investigate these effects further. As expected, accuracy on the 1-back task was significantly lower than 0-back: participants overall made more errors or were less

accurate on 1-back (92% correct trials) than 0-back (96% correct trials; t (62) = 3.12, P = 0.003). Accuracy was significantly higher in adults than children for both task conditions (0-back: t (24.2) = 2.84, P = 0.009; 1-back: t (26.6) = 3.06, P = 0.005). Adolescents were more accurate than children for the 1-back task (t (3.44) = 22.3, P = 0.002) but not in the 0-back condition. The accuracy of adults was not significantly different from adolescents for both conditions. Adolescents made significantly more errors for 1-back than 0-back (t (20) = 3.35, P = 0.003), whereas children and adults performed on a similar level of accuracy for both tasks. No sex effects were found.

Repeated measures ANOVA for RT also revealed a significant main effect of task (F (1, 60) = 43.06, P = 0.00, η^2 = 0.42), and age (F (2, 60) = 11.89, P = 0.00, η^2 = 0.28). There was also no age × condition interaction. All participants responded faster for the 0-back than 1-back condition (t (62) = 6.58, P = 0.000). Children were significantly slower than adults (0-back: t (37.5) = 3.69, P = 0.001; 1-back: t (40) = 3.7, P = 0.001) as well as adolescents (0-back: t (30.1) = 3.89, P = 0.001; 1-back: t (32.7) = 3.17, P = 0.003) in both task conditions. There was no significant difference between adults and adolescents. All age groups responded faster for 0-back than 1-back (children: t (21) = 3.69, P = 0.001; adolescents: t (20) = 4.52, P = 0.000; adults: t (19) = 4.63, P = 0.000). There were no effects of sex on RTs.

We also examined the relation between age and behavioural performance for the entire sample, with age as a continuous variable. Accuracy and RT both showed significant improvements with age extending into late adolescence. Age was positively associated with accuracy (0-back: R = 0.356, P = 0.004; 1-back: R = 0.374, P = 0.003), and negatively associated with response time (0-back: R = -0.431, P = 0.000; 1-back: R =

-0.42, $P = 0.001$; Table 5.3). See Figure 5.2 for the scatter plots of age and performance (i.e. percentage correct and response time). Neither slopes of the accuracy nor response time regression lines differed significantly between the two task conditions ($F = 0.266$, $P = 0.85$ for accuracy; $F = 0.645$, $P = 0.72$ for RT).

Table 5.1

2-subtest WASI scores for children and adolescents

	2-subtest WASI (IQ)
Sample size	39/44
Age range	6 – 17 years
Mean age ± SD	12.3 ± 4 years
Mean score ± SD	114 ± 11.1

Table 5.2.

Summary of Behavioural Performance for entire sample (N=65)

	Mean accuracy ± SD (percentage correct)		
	0-back	***1-back***	***Overall***
All participants	0.96 ± 0.08	0.92 ± 0.11	0.94 ± 0.10
Female	0.96 ± 0.08	0.94 ± 0.09	0.95 ± 0.09
Male	0.97 ± 0.07	0.89 ± 0.13	0.93 ± 0.11

	Mean reaction time ± SD (msec)		
	0-back	***1-back***	***Overall***
All participants	451 ± 89	516 ± 125	484 ± 131
Female	461 ± 98	517 ± 136	489 ± 121
Male	438 ± 76	514 ± 110	476 ± 101

These behavioural variables were also highly correlated with one another, as presented in Table 5.3. Accuracy and reaction times on both tasks were highly predictive of each other, indicating a high functional similarity between the N-back task conditions. Reaction times were negatively correlated with accuracy, i.e., RTs decreased as accuracy increased. Given such high inter-correlations between these three variables (i.e., age, accuracy, and reaction time); partial correlations were used to test for the main contributor. These partial correlations are presented in Table 5.4.

Controlling for age (Table 5.4A) did not affect the significance level of the correlations between RT and accuracy, suggesting that the relation between RT and accuracy is robust and is not an age-related phenomenon. RT and accuracy were then each partialled out to determine if either was driving the age effects. The positive correlation between age and accuracy failed to remain significant after controlling for RT (Table 5.4C); while RT remained strongly correlated with age even after controlling for accuracy (Table 5.4D). This suggests that RT improvements over age are more robust than accuracy increments and that for these tasks the relation between age and accuracy may be explained by changes in RT. This is in line with our relatively low difficulty tasks where participants performed largely at ceiling.

Overall, our behavioural data showed that adolescents and adults are more accurate than children in performing both the 0-back and the 1-back task condition, indicating that visual WM matures from childhood through adolescence and adulthood. All participants took a longer time to respond in the more cognitively demanding 1-back task, with adolescents and adults showing the ubiquitously found faster responses than children, suggesting a better control of inhibitory control or motor planning with age.

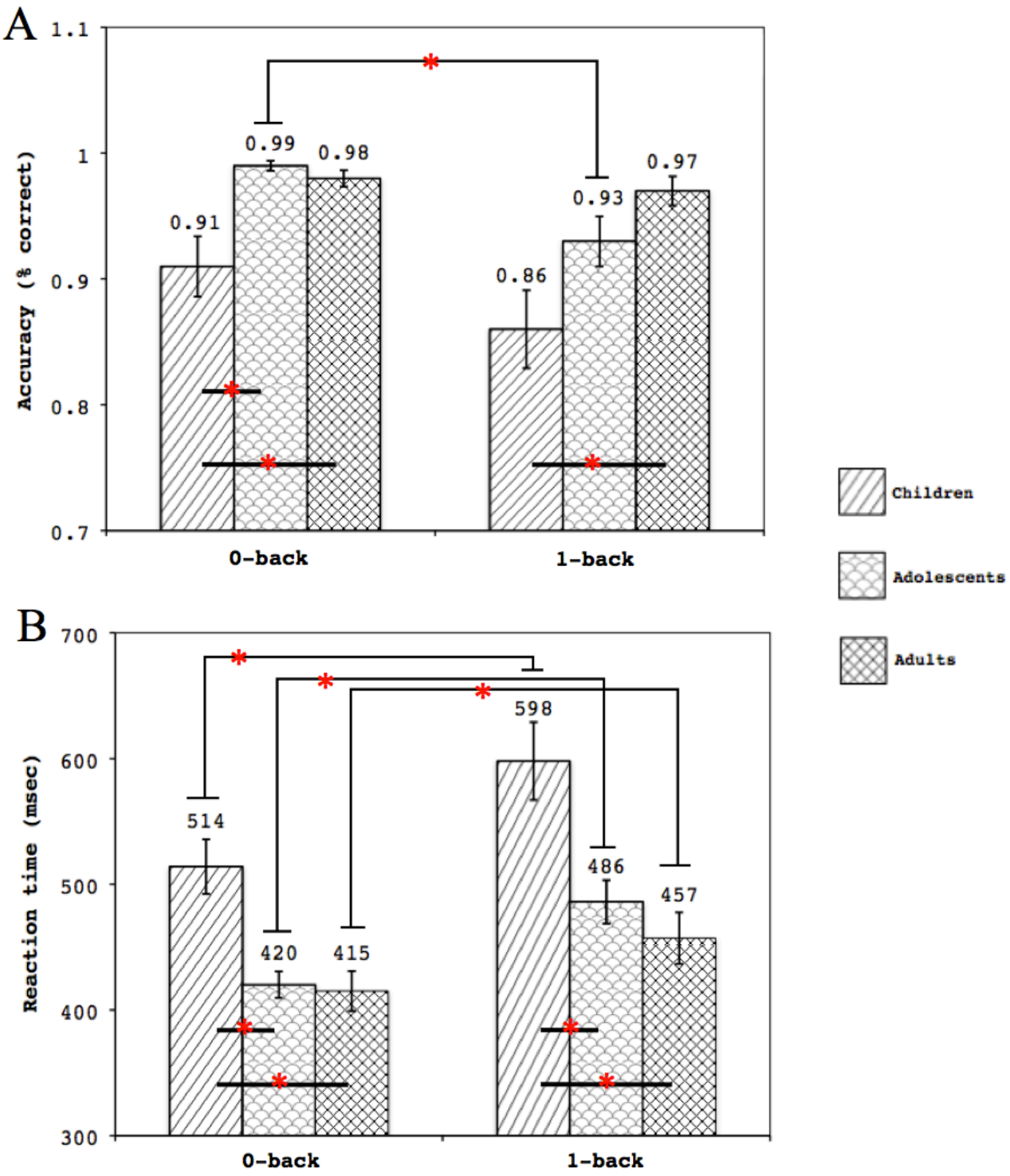

Figure 5.1. Behavioural performance by children, adolescents and adults for each task condition. **A)** Mean accuracy (percentage correct) for 0- and 1-back tasks, showing children as less accurate than both adolescents and adults for 0-back and children as less accurate than adults for 1-back, but no interaction. Only adolescents demonstrated worse performance for 1-back than 0-back. **B.** Mean reaction times for correct response trials, showing slower times for the more difficult 1-back across all three age groups, and children as slower than both adolescents and adults for both tasks, but no interaction.

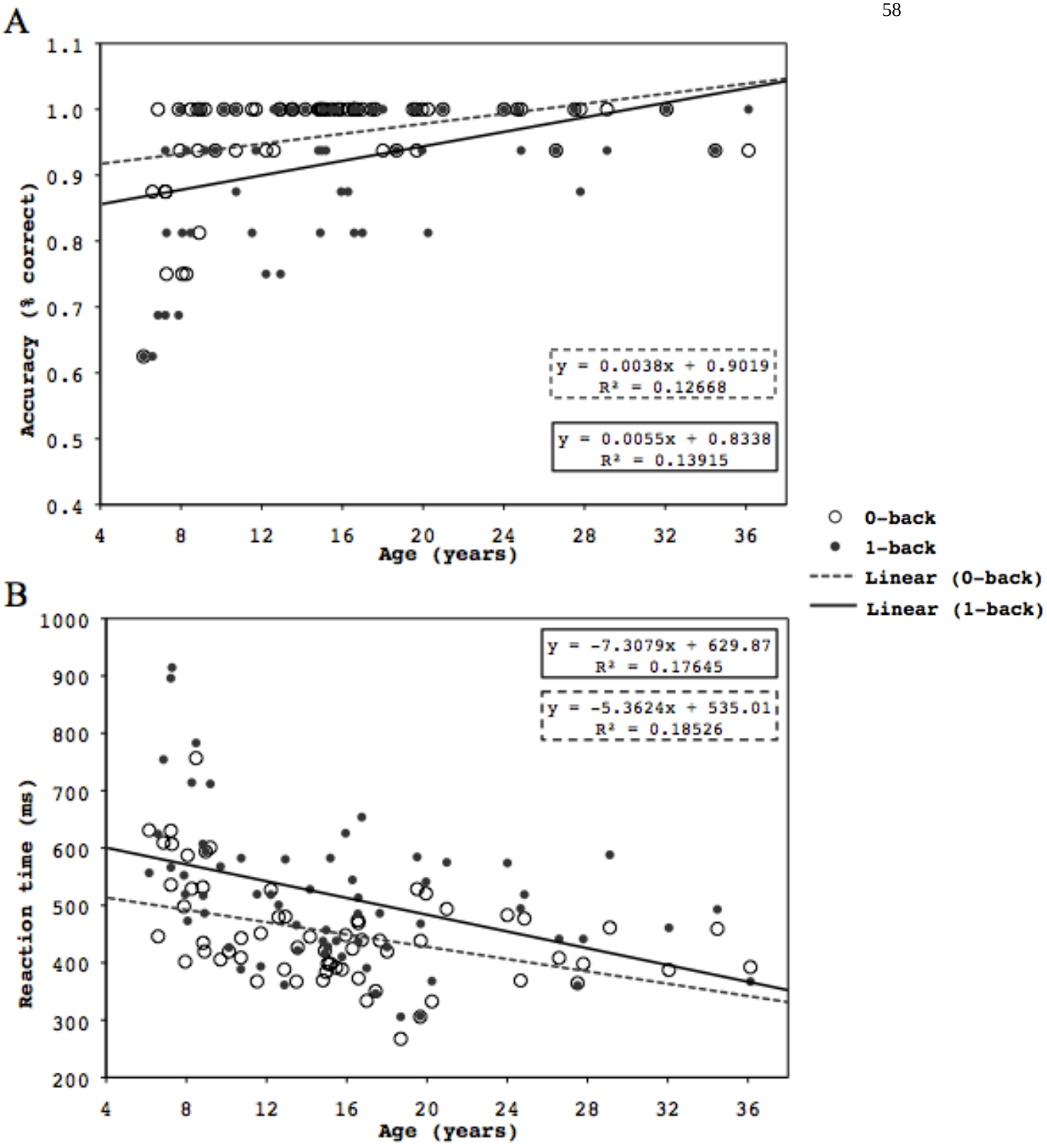

Figure 5.2. Scatter plots depicting behavioural performance on both tasks as a function of age (years): **A)** accuracy (percentage correct) and **B)** reaction times. Age differences were more strongly related to performance measure on the more demanding 1-back task than 0-back, indicated by steeper slopes, but not significantly different.

5.3 Motion Assessment

Head motion was examined using an estimate of within-run maximum displacement, derived for each subject from the parameters generated by AFNI's *3dvolreg* realignment process. The overall average within-run maximum displacements were 0.47 mm for 0-back and 0.44 mm for 1-back (Table 5.5A), and were highly predictive of each other. Within-run maximum displacement on the 0-back task was significantly correlated with age, 0-back accuracy and 0-back RT (Table 5.3). Within-run maximum displacement on the 1-back task negatively predicted 1-back accuracy (Table 5.3). However, controlling for motion measures in a partial correlation analysis did not affect the inter-correlations between age and behavioural performance variables (Table 5.4B). There was a sex effect for maximum displacement (Table 5.5A), where males exhibited significantly more motion than females overall on the 0-back task (t (37.3) = 2.33, P = 0.025) as well as a relatively higher motion on 1-back task (t (63) = 1.88, P = 0.06). Males also demonstrated age-related motion effects in both runs, whereas females only showed age-related motion effects in the 0-back condition (Table 5.5A).

Repeated measures ANOVAs of maximum displacement were also conducted to assess possible within-run movement differences between age groups. Even after applying the strict motion criteria, there was a significant main effect of age (F (2, 62) = 6.625, P = 0.002, η^2 = 0.176). Children showed more head motion than adults during both task conditions (0-back: t (22.9) = 3.99, P = 0.001; 1-back: t (42) = 2.07, P = 0.045); adolescents also moved more than adults in the 0-back condition (t (22.7) = 2.32, P = 0.03). Sex effects were present in the youngest age group, with greater motion in males

(0-back: M = 1.01, SD = 0.61; 1-back: M = 0.87, SD = 0.6) compared to females (0-back: M = 0.5, SD = 0.39; 1-back: M = 0.33, SD = 0.14) for both 0-back (t (20) = 2.43, P = 0.025) and 1-back (t (8.63) = 2.64, P = 0.028).

Table 5.3.

Correlation Matrix of Behavioural Performance and Demographic Variables

	Age	Gender	IQ	0B PC	1B PC	0B RT	1B RT	0B motion	1B motion
Age	1	-	-	-	-	-	-	-	-
Gender	-0.202	1	-	-	-	-	-	-	-
IQ	-0.137	-0.388*	1	-	-	-	-	-	-
0B PC	*0.356**	0.045	-0.325*	1	-	-	-	-	-
1B PC	*0.374**	-0.188	0.015	0.358*	1	-	-	-	-
0B RT	-0.431**	-0.131	0.078	-0.386**	-0.367**	1	-	-	-
1B RT	-0.42**	-0.014	0.084	-0.295*	-0.4**	0.784**	1	-	-
0B motion	-0.415**	0.307*	0.213	-0.381**	-0.378**	0.264*	0.187	1	-
1B motion	-0.219	0.231	0.089	-0.085	-0.374**	-0.072	0.016	0.447**	1

Note. PC = percentage correct. RT = reaction time. Motion refers to measure of within-run maximum displacement. 0B = 0-back condition. 1B = 1-back condition. WM1 = WMTB-C central executive composite score WM2 = WMTB-C visuospatial sketchpad composite score.
* = $p < 0.05$. ** = $p < 0.01$.

Table 5.4.

Partial Correlation Tables

A. Controlling for age

	0B PC	1B PC	0B RT	1B RT
0B PC	1			
1B PC	0.259*	1		
0B RT	-0.275*	-0.246*	1	
1B RT	-0.171	-0.289*	0.737**	1

B. Controlling for motion

	Age	0B RT	1B RT	0B PC	1B PC
Age	1				
0B RT	-0.386**	1			
1B RT	-0.388**	0.78**	1		
0B PC	-.247*	-0.306*	0.24	1	
1B PC	0.262*	-0.374**	-0.394**	0.286*	1

C. Controlling for RT

	Age	0B PC	1B PC
Age	1		
0B PC	*0.233*	1	
1B PC	*0.235*	0.26*	1

D. Controlling for PC

	Age	0B RT	1B RT
Age	1		
0B RT	-0.287*	1	
1B RT	-0.287*	0.74**	1

Note. PC = percentage correct. RT = reaction time. Motion refers to measure of within-run maximum displacement. 0B = 0-back condition. 1B = 1-back condition.
* = $p < 0.05$. ** = $p < 0.01$. Highlighted correlation coefficients were significant before controlling for RT. (see Table 5.3)

Table 5.5.

Summary of Motion Data for A) Entire Sample and B) Three Age Groups

A. All participants

		0-back	1-back	Overall
Mean ± SD (all participants)		0.47 ± 0.44 mm	0.44 ± 0.36 mm	-
Female (N= 38)	**Mean ± SD**	0.36 ± 0.31 mm	0.37 ± 0.28 mm	0.36 ± 0.29 mm
	Correlation with age	-0.346*	-0.063	-
Male (N= 27)	**Mean ± SD**	0.63 ± 0.55 mm	0.54 ± 0.44 mm	0.58 ± 0.50 mm
	Correlation with age	-0.542**	-0.397*	-

Note. *=$p<0.05$. **=$p<0.01$.

B. Three age groups

	Children N=22, 6-11yrs	Adolescents N=21, 12-17yrs	Adults N=22, 17-36yrs
0-back	0.71 ± 0.54 mm	0.47 ± 0.43 mm	0.24 ± 0.12 mm
1-back	0.55 ± 0.47 mm	0.44 ± 0.35 mm	0.33 ± 0.18 mm
Overall	0.63 ± 0.51 mm	0.45 ± 0.39 mm	0.29 ± 0.16 mm

5.4 fMRI results

Three contrasts were computed from the single-subject level analysis: 1-back vs. 0-back, 0-back vs. baseline fixation, and 1-back vs. baseline fixation. We were most interested in the 1-back vs. 0-back contrast as this contrast taps into the WM component – 1-back is typically seen as the WM condition and 0-back as the control condition. Therefore, first we examined the modulation of neural resources in response to WM by contrasting the two conditions for all age groups (1-back > 0-back). To investigate this WM contrast further, we examined the task vs. baseline contrasts and looked for areas of greater activity for the task blocks than the baseline blocks (task-induced activations) as well as areas of greater activity during baseline than task (task-induced deactivations). Then, we probed for areas that showed main effects of age, task conditions and their interaction, and assessed the nature of these effects by examining the magnitude of activation. Finally, we used a region of interest approach to examine *a priori* regions from past literature.

5.4.1 Whole-brain within-group and conjunction analyses

First, we examined examine the effect of simple WM demand on neural responses in each age group separately, by performing an one-way ANOVA with age groups as between-subject factors for the 1-back > 0-back contrast.

1-back vs. 0-back. Results for this contrast are illustrated in Figure 5.3 and Table 5.6. This contrast was examined to reveal fMRI changes related to WM

maintenance while minimizing demands on the central executive and controlling for perceptual and motor components. Both children and adolescents displayed an increased in activation for WM (1-back > 0-back) in bilateral visual cortices and cerebellar regions – children activated left lingual/inferior occipital gyrus (BA 17/18) and right cerebellar declive/fusiform gyrus (BA 19), while adolescents activated bilateral cerebellar declive and lingual/fusiform gyrus (BA 17/18/19). Children showed additional activation in the right middle occipital/temporal gyrus/precuneus (BA 19/31) and right middle/inferior frontal gyrus (BA 9/8). We did not find any significant clusters that were more active in the reverse contrast (0-back > 1-back) for both age groups.

For adults, we did not find any clusters that passed the multiple comparisons threshold in either the forward (1-back > 0-back) or the reverse contrast (0-back > 1-back). However, we did find two sub-threshold clusters that survived the voxel-wise threshold of $P < 0.005$ but not the cluster-wise correction in the right cuneus/lingual gyrus (BA 17; *talairach coordinates*: 22, -91, 0; 22 voxels; $t = 3.92$) and the left lingual gyrus (BA 18; *talairach coordinates:* -15, -87, -15; 18 voxels, t = 3.23). Although these clusters are not strictly statistically significant, these areas do agree with the finding in children and adolescents. Adults also did not show any difference in activations in the reverse contrast (0-back > 1-back).

As our findings in adults did not replicate past literature, we examined this contrast further by examining the individual contrasts of 1-back vs. baseline and 0-back vs. baseline contrasts in all age groups. Conjunction analyses allowed us to common areas of activation and deactivation across the three groups and examine the extent to which similar regions might differ (Figure 5.3 and 5.4 D and E).

Table 5.6

Regions activated for the contrast of 1-back vs. 0-back.

Brain region	Hem.	BA	*Talairach coordinates*			Cluster size (voxels)	t-value
			x	*y*	*z*		
1-back > 0-back							
Children (n=22, 6-11 yrs)							
LG / cuneus / IOG	L.	17/18	-8	-98	-12	227	3.75
Declive / FG	R.	19	34	-77	-28	58	3.59
MOG / MTG / precuneus	R.	19/31	30	-79	18	33	3.22
MFG / IFG	R.	9/8	55	12	39	26	3.32
Adolescents (n=22, 12-17 yrs)							
Declive / LG / FG	R.	18/19	19	-82	-23	120	3.22
	L.	17/18	-8	-93	-11	97	4.27
Declive / FG	L.	18/19	-26	-81	29	72	4.55
Adults (n=21, 18-36 yrs)							
No significant activations at corrected threshold							

Note. nBA = no Brodmann's Area. Bil. = Bilateral. L. = Left. R. = Right. Volume per voxel 3.75x3.75x5mm= 70.3 mm3. *x, y, z* are peak coordinates of each cluster.

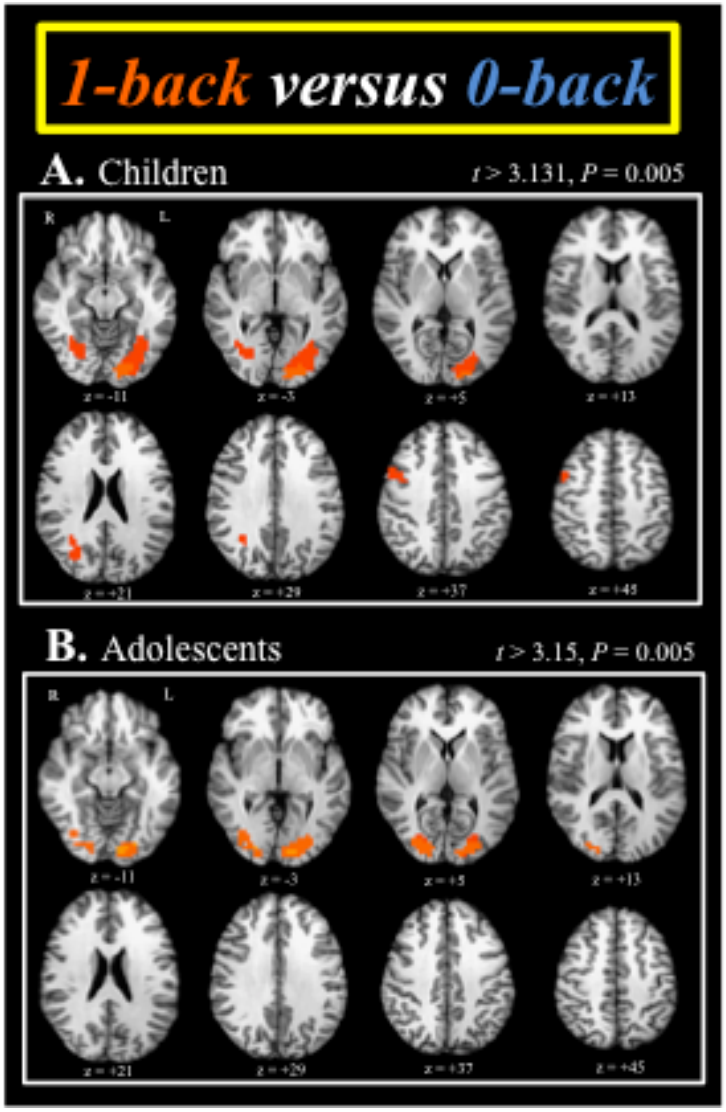

Figure 5.3. Brain regions showing significant fMRI response ($p < 0.005$, 26-voxel clusters) to 1-back relative to 0-back in A) children and B) adolescents. Axial slices are in radiological convention (left hemisphere is on the right). Adults did not demonstrate significant activations for this contrast.

Task-induced activation

1-back vs. baseline fixation. Results for this contrast are illustrated in Figure 5.4 and Table 5.7. As revealed by conjunction analysis, children, adolescents and adults demonstrated common task-induced activations (1-back > 0-back) in the bilateral visual cortices including inferior/middle occipital gyri and lingual gyri (BA 17/18/19); bilateral superior/medial frontal gyri and cingulate gyri (BA 24/32); as well as bilateral insula (BA 13). Both adolescents and adults activated subcortical regions of the putamen and caudate but this varied with hemispheric location – localized to the left for the adolescents and bilaterally for adults. The left precentral gyrus (BA 6) and the left inferior parietal lobule (BA 40) were also commonly activated for adolescents and adults. Adults additionally activated large clusters in the bilateral inferior frontal gyrus (BA 47) that extended into the insula (BA 13). Adolescents demonstrated additional activation in left middle/inferior frontal gyrus (BA 9)

0-back vs. baseline fixation. Results for this contrast are illustrated in Figure 5.5 and Table 5.8. The only common area of task-induced activation (0-back > baseline) across children, adolescents, and adults was found in the bilateral visual cortices including the inferior/middle occipital gyri, fusiform gyri, and lingual gyri (BA 17/18/19). Children and adolescents did not activate any other additional areas, whereas adults additionally activated the left postcentral/precentral gyrus (BA 3/2) and bilateral inferior parietal lobule (BA 7/40), right medial frontal/cingulate gyrus (BA 32/6/24), right middle/superior frontal gyri (BA 9/46), right cerebellar regions (BA 37/19), and right insula/inferior frontal gyrus (BA 13 and 45).

Conjunction of task vs. baseline contrasts. The conjunction analysis of 0-back vs. baseline and 1-back vs. baseline contrasts revealed that adults activated analogous regions including across these contrasts, while children and adolescents did not (Figure 5.6 and Table 5.9).

Task-induced deactivation

Areas of greater activity during baseline than task blocks (i.e., deactivated by the task) are usually referred to as the default mode network (Raichle et al., 2001), which typically involves the precuneus and posterior cingulate regions, as well as medial frontal and temporal regions. Deactivations during 0-back in children were mostly concentrated in bilateral cuneus/posterior cingulate cortex (BA 18/30/23) and large areas of bilateral superior temporal cortices (BA 22 and 42); and during 1-back in bilateral precuneus / cuneus / posterior cingulate (BA7/31). For adolescents, a large cluster of deactivation was found in bilateral cuneus, precuneus and posterior cingulate (BA 18/31/23) during the 0-back task; and in bilateral posterior cingulate/precuneus/cuneus (BA7/31/18) during 1-back. In adults, deactivations occurred in bilateral cuneus/precuneus/posterior cingulate (BA 31/23) and left angular/middle temporal gyrus (BA 39) during 0-back; and in much greater volumes in bilateral precuneus/cuneus (BA 31/18), and bilateral angular/middle temporal gyrus (BA 39 and 19) during 1-back.

Summary of findings

Overall, we found several concordant areas of activation and deactivations across all age groups for both task vs. baseline contrasts. For the 0-back vs. baseline contrast, common areas of activation for all ages were the bilateral visual cortices and common areas of deactivation were bilateral precuneus. For the 1-back vs. baseline contrast, we found additional commonly activated areas in the cingulate gyrus and insula. We also found that both children and adolescents only activated the visual cortices during 0-back vs. baseline but engaged more areas during 1-back vs. baseline; whereas adults activated analogous set of regions during both task vs. baseline contrasts.

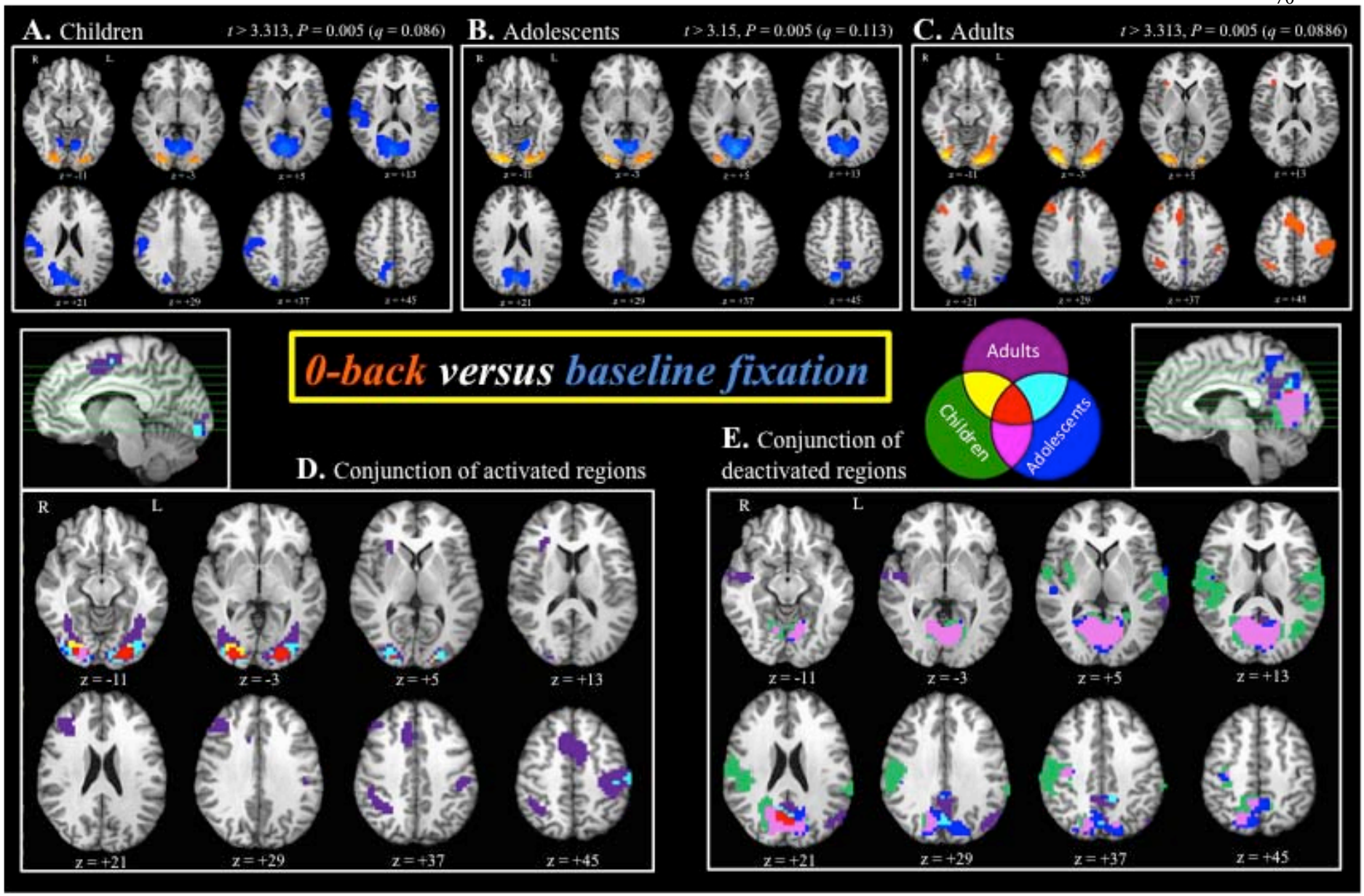

Figure 5.4. Brain regions showing significant fMRI response ($p < 0.005$, 26-voxel clusters) to 0-back relative to baseline fixation in A) children, B) adolescents and C) adults. A conjunction of these brain regions demonstrate common task-induced D) activated areas and E) deactivated areas, across age groups. Axial slices are in radiological convention (left hemisphere is on the right).

Table 5.7.

Regions of activations and deactivations during the performance of 0-back.

Brain region	Hem.	BA	*Talairach coordinates*			Cluster size (voxels)	t-value
			x	*y*	*z*		
0-back > Baseline							
Children (n=22, 6-11 yrs)							
IOG / FG/ LG	L.	18/17	-23	-93	-17	47	3.49
LG / IOG / cuneus	R.	17/18	22	-93	-11	40	5.17
Adolescents (n=22, 12-17 yrs)							
IOG / FG / MOG / LG	L.	18/19	-22	-90	-10	90	4.13
IOG / LG / MOG / FG	R.	18	26	-90	-14	78	6.09
Adults (n=21, 18-36 yrs)							
FG / LG / MOG	L.	18/19	-26	-79	-11	241	5.12
PostCG / PreCG / IPL	L.	3/2/40	-42	-27	53	175	4.81
MeFG / CingG / SFG	R.	32/6/24	2	4	50	127	4.13
IOG / LG / MOG	R.	18	30	-89	-11	121	6.19
MFG / SFG	R.	9/46	49	28	34	61	3.36
Culmen / declive / LG	R.	37/19	37	-55	-27	58	3.89
IPL / SPL	R.	7/40	41	-50	40	37	3.62
Insula / IFG	R.	13/45	33	22	12	28	3.50
Baseline > 0-back							
Children (n=22, 6-11 yrs)							
LG / cuneus / PCC	Bil.	18/30/23	4	-74	5	578	-6.93
STG / PostCG	R.	42/40/43/22	65	-21	10	219	-3.83
STG	L.	22/42/21	-65	-13	5	71	-3.44
Adolescents (n=22, 12-17 yrs)							
Cuneus / precuneus / PCC	Bil.	18/31/23	3	-74	16	643	-3.28
Adults (n=21, 18-36 yrs)							
Cuneus / precuneus / PCC	Bil.	31/23	0	-75	18	56	-3.26
AG / MTG	L.	39	-49	-73	29	39	-4.07

Note. nBA = no Brodmann's Area. Bil. = Bilateral. L. = Left. R. = Right. Volume per voxel 3.75x3.75x5mm= 70.3 mm3. *x, y, z* are peak coordinates of each cluster.

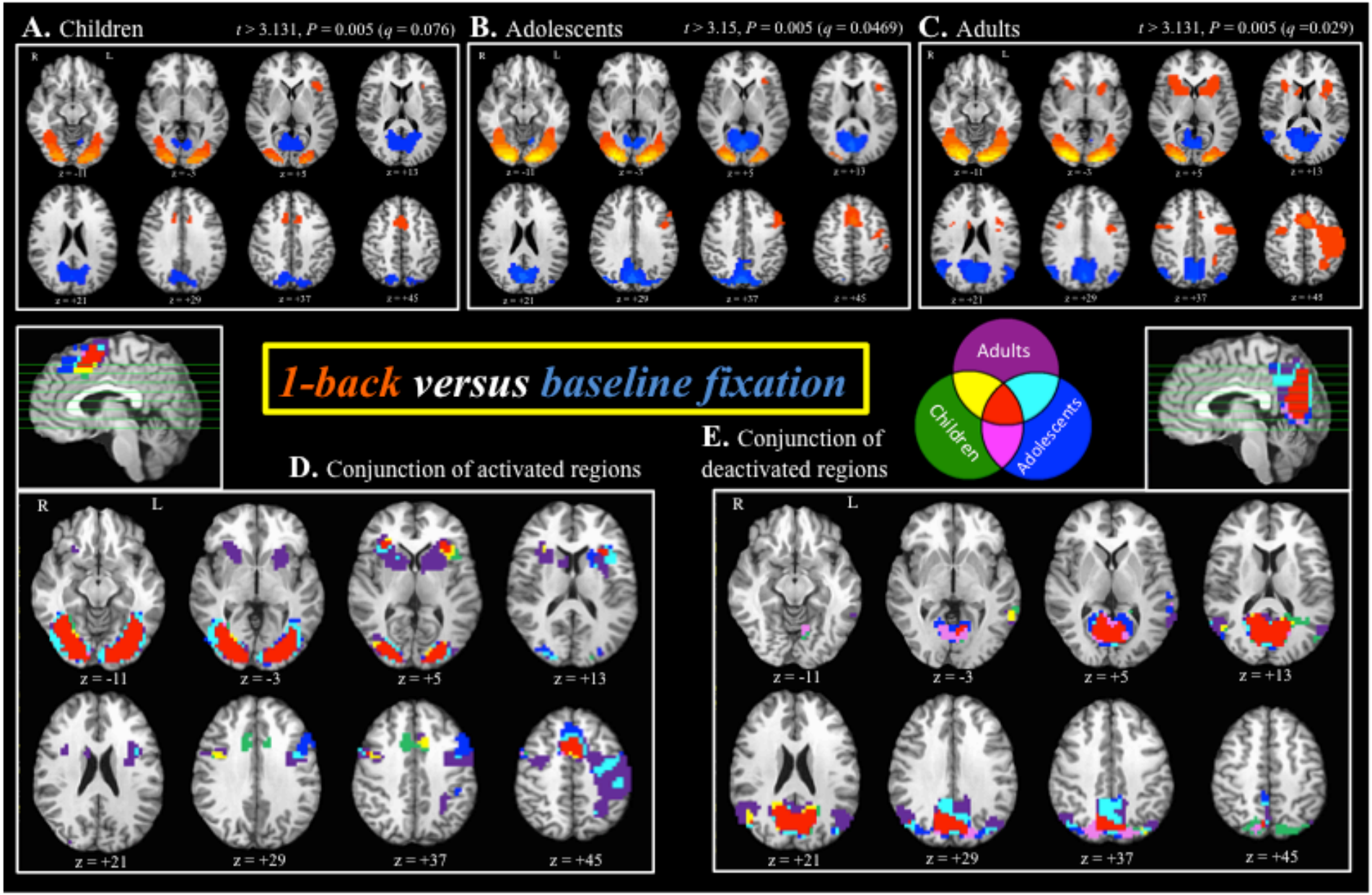

Figure 5.5. Brain regions showing significant fMRI response ($p < 0.005$, 26-voxel clusters) to 1-back relative to baseline fixation in A) children, B) adolescents and C) adults. A conjunction of these brain regions demonstrate common task-induced D) activated areas and E) deactivated areas, across age groups. Axial slices are in radiological convention (left hemisphere is on the right).

Table 5.8.

Regions of activations and deactivations during the performance of 1-back.

Brain region	Hem.	BA	*Talairach coordinates*			Cluster size (voxels)	t-value
			x	*y*	*z*		
1-back > Baseline							
Children (n=22, 6-11 yrs)							
IOG / FG / LG / MOG	L.	17/18/19	-19	-93	-17	309	6.3
IOG / MOG / FG / LG	R.	18/19	26	-89	-17	258	4.58
MeFG / SFG / CingG	R.	6/32/24	1	6	51	140	4
Insula	L.	13	-38	14	6	28	4.35
Adolescents (n=22, 12-17 yrs)							
IOG / LG / FG	L.	17/18	-11	-93	-17	491	8.81
IOG / LG / MOG	R.	18/17	30	-89	-11	437	9.50
SFG / MeFG / CingG	Bil.	6/32/24	0	4	55	146	4.90
PreCG / MFG / SFG	L.	6/4	-34	-12	65	79	3.63
Lentiform nucleus / putamen / caudate / insula	L.	13	-15	6	11	37	3.26
MFG / IFG / PreCG	L.	9/8/6	-54	8	39	34	3.61
Adults (n=21, 18-36 yrs)							
SFG / MeFG / CingG / insula / preCG / caudate	Bil.	6/32/24	0	4	55	838	5.08
LG / IOG / MOG	R.	18/17	26	-93	-11	465	7.33
LG / IOG	L.	17/18	-15	-98	-12	446	7.71
IFG / insula / putamen / caudate	R.	47/13/45	34	26	1	148	4.20
PreCG / MFG	R.	6	40	-4	43	65	3.52
Baseline > 1-back							
Children (n=22, 6-11 yrs)							
Precuneus / cuneus / PCC	Bil.	7/31	4	-72	40	539	-3.69
Adolescents (n=22, 12-17 yrs)							
PCC/ precuneus / cuneus	Bil.	7/31/18	4	-80	39	658	-3.84
Adults (n=21, 18-36 yrs)							
Precuneus / cuneus	Bil.	31/18/7	4	-75	23	541	-6.08
MTG / AG /STG	R.	39/19	53	-72	23	101	-5.21
Precuneus / AG / MTG	L.	19/39	-38	-80	34	75	-4.93

Note. nBA = no Brodmann's Area. Bil. = Bilateral. L. = Left. R. = Right. Volume per voxel 3.75x3.75x5mm= 70.3 mm3. *x, y, z* are peak coordinates of each cluster.

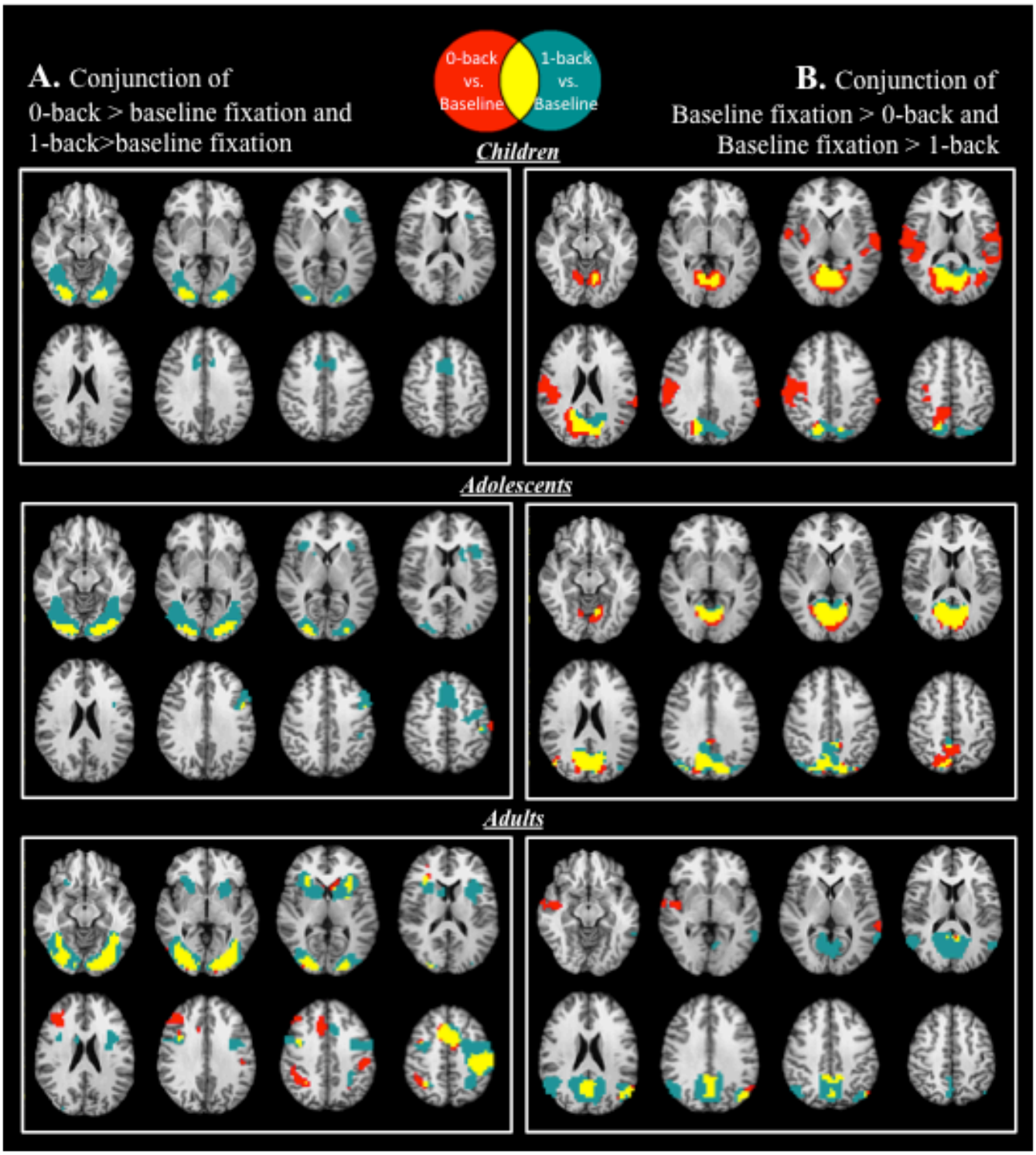

Figure 5.6. Within-group conjunction between the 0-back vs. baseline and 1-back vs. baseline contrasts. Panel A displays conjunction of task-positive areas. Panel B displayed deactivated areas.

Table 5.9.

Within-group comparisons of 0-back vs. baseline and 1-back vs. baseline in children, adolescents and adults. Peak Talairach coordinates within the same clusters are group together, demonstrating common areas of activation from conjunction analysis.

Brain region	BA	0-back vs. baseline												1-back vs. baseline											
		Children				Adolescents				Adults				Children				Adolescents				Adults			
		Talairach coordinates			Size	Talairach coordinates			Size	Talairach coordinates			Size	Talairach coordinates			Size	Talairach coordinates			Size	Talairach coordinates			Size
Task-induced activations		*x*	*y*	*z*		*x*	*y*	*z*		*x*	*y*	*z*		*x*	*y*	*z*		*x*	*y*	*z*		*x*	*y*	*z*	
L. OG / LG	18	-23	-93	-17	47	-22	-90	-10	90	-26	-79	-11	241	-19	-93	-17	309	-11	-93	-17	491	-15	-98	-12	446
R. OG / LG	18	22	-93	-11	40	26	-90	-14	78	30	-89	-11	121	26	-89	-17	258	30	-89	-11	437	26	-93	-11	465
L. IPL	40	-				-				-42	-27	53	175	-				-				-			
R. MeFG / CingG	32/24	-				-				2	4	50	127	1	6	51	140	0	4	55	146	0	4	55	838
R. MFG / SFG	9/4/6	-				-				49	28	34	61	-				-				-			
R. LG	37/19	-				-				37	-55	-27	58	-				-				-			
R. IPL / SPL	7/40	-				-				41	-50	40	37	-				-				-			
R. Insula / IFG	13/45	-				-				33	22	12	28	-				-				34	26	1	148
L. Insula	13	-				-				-				-38	14	6	28	-15	6	11	37	-			
L. PreCG / MFG	4/6	-				-				-				-				-34	-12	65	79	-			
L. MFG / IFG	9/8/6	-				-				-				-				-54	8	39	34	-			
R. PreCG / MFG	6	-				-				-				-				-				40	-4	43	65
Task-induced deactivations																									
Bil. Cuneus / precuneus	23/31	4	-74	5	578	3	-74	16	643	0	-75	18	56	4	-72	40	539	4	-80	39	658	4	-75	23	541
R. STG	42	65	-21	10	219	-				-				-				-				-			
L. STG	42	-65	-13	5	71	-				-				-				-				-			
L. AG / MTG	39/19	-				-				-49	-73	29	39	-				-				-38	-80	34	75
R. AG / MTG	39/19	-				-				-				-				-				53	-72	23	101

Note. Size refers to cluster size, i.e., number of voxels

5.4.2 Whole-brain between-group comparisons

To better elucidate developmental changes in activity, we further probed for between-group differences on fMRI activation for all three contrasts (Table 5.10).

Adults vs. children. (Figure 5.7A and C). Adults demonstrated greater extent and magnitude of activation than children in large areas of right inferior/superior parietal lobule and postcentral gyrus (BA 40/5/7), left insula (BA 13) and a smaller area in left postcentral gyrus and inferior parietal lobule (BA 1/3/2/40) for the 0-back vs. baseline contrast. Children did not show any areas of greater activation than adults. We also did not detect any significant differences for the 1-back vs. baseline contrast. Children activated the right inferior/superior parietal lobule (BA 40) more than adults for the 1-back vs. 0-back contrast.

Adolescents vs. children. We did not find any significant differences in activation patterns between adolescents and children.

Adults vs. adolescents. (Figure 5.7B) 0-back vs. baseline. Major regions of greater activation in adults than adolescents included right inferior parietal lobule/supramarginal gyrus (SMG / BA 40) and bilateral lingual gyri (BA 18). Adolescents did not show any areas of greater activation than adults. We also did not detect any significant differences for the 1-back vs. baseline or 1-back vs. 0-back contrast.

Table 5.10.

Regions showing between-group differences

Brain region	Hem.	BA	*Talairach coordinates*			Cluster size (voxels)	t-value
			x	*y*	*z*		
0-back > Baseline							
Adults > Children							
IPL / PostCG / SPL	R.	40/5/7	41	-50	57	278	3.04
Insula	L.	13	-38	-2	11	31	3.31
PostCG / IPL	L.	1/3/2/40	-57	-27	42	27	3.31
Adults > Adolescents							
IPL / SMG	R.	40	45	-38	42	39	3.52
LG	Bil.	18	0	-78	-10	26	3.49
1-back vs. 0-back							
Children > Adults							
IPL / SPL	R.	40	45	-50	50	96	-3.36

Note. nBA = no Brodmann's Area. Bil. = Bilateral. L. = Left. R. = Right. Volume per voxel 3.75x3.75x5mm= 70.3 mm3. *x, y, z* are peak coordinates of each cluster.

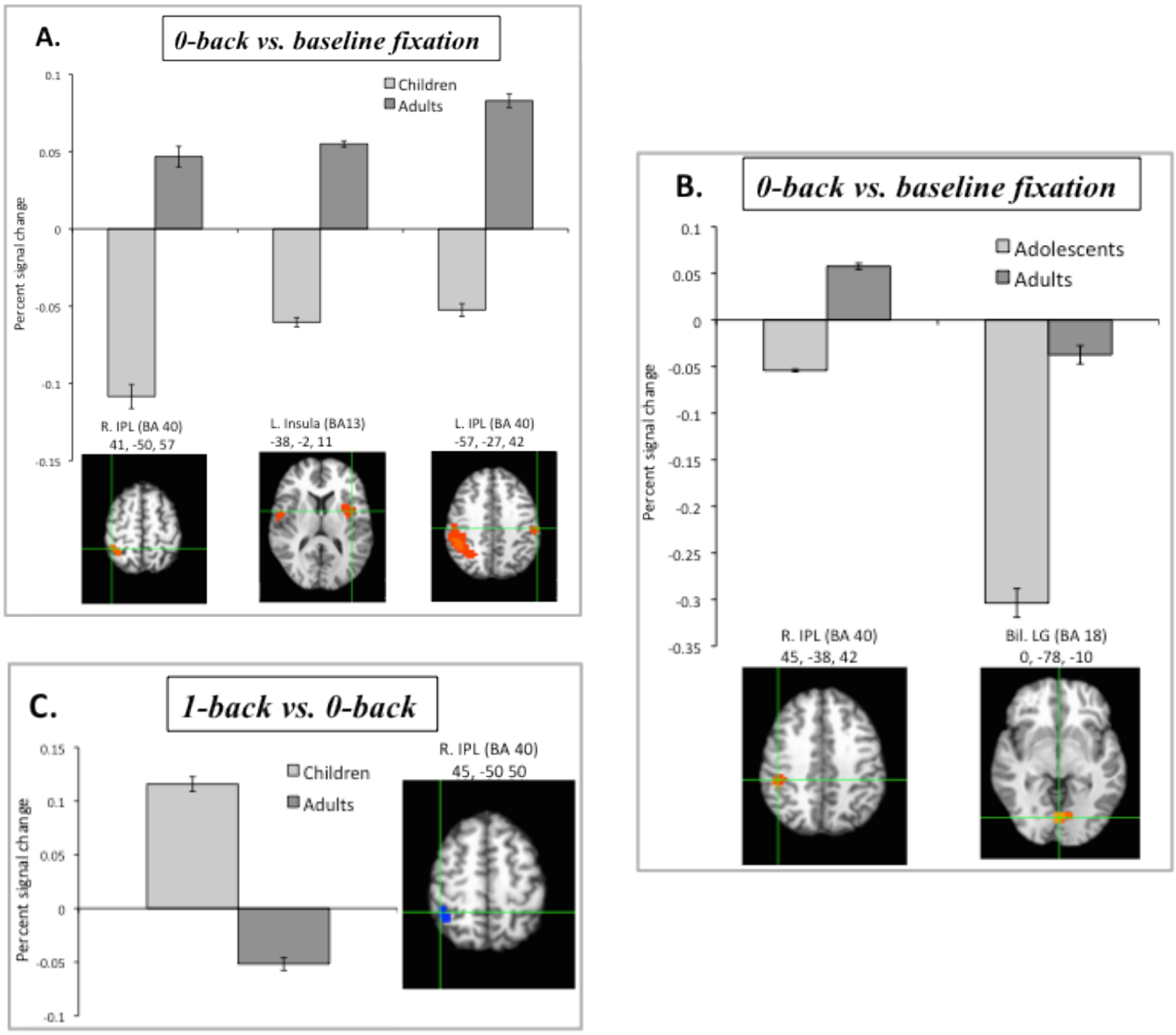

Figure 5.7. Bar graphs depicting signal change difference in brain regions between A) adults and children ($t < 2.96$, $p < 0.005$, 26-voxel clusters) during 0-back vs. baseline, B) adults and adolescents ($t < 2.964$, $p < 0.005$, 26-voxel clusters) during 0-back vs. baseline, and C) adults and children ($t < 2.96$, $p < 0.005$, 26-voxel clusters) during 1-back vs. 0-back. Axial slices are in radiological convention.

5.4.3 ANOVA results

Results from the *GroupAna* analysis are shown in Table 5.11 and Figures 5.8, 5.9 and 5.10. To probe activation patterns in each of regions for each effect term identified by this ANOVA, we extracted mean percent signal change for all significant clusters in every subject, and plotted them as mean group values as a function of age groups (Figure 5.8, 5.9 and 5.10). Regions with a main effect of age were those that showed the most robust age-related changes (positive or negative) collapsing across both task conditions (Figure 5.8). In other words, these were the regions that exhibited similarities in activation patterns between task conditions but differences with age group, thereby denoting an age-related effect. Regions with a main effect of task were those that demonstrated differing magnitude of activity between the two tasks across all age groups (Figure 5.9). In other words, these were the regions that behaved differently in the two task conditions without significant age-related changes and therefore were less varied among the age groups. Finally and most importantly, we examined the age group by task interaction term to determine what types of interactions are occurring (Figure 5.10).

Main effect of age group. The ANOVA yielded three regions that showed a main effect of age (Table 5.11A, Figure 5.9). These regions included bilateral lingual gyrus/cuneus (BA 18), left insula (BA 13) and right precentral/postcentral gyrus (BA4/3/2/6). In all of these regions, the magnitude of activity generally followed the expected pattern of progressively increasing activity with older age – with brain activity being lowest in the child group and becoming higher with the older age groups (see line graphs in Figure 5.9).

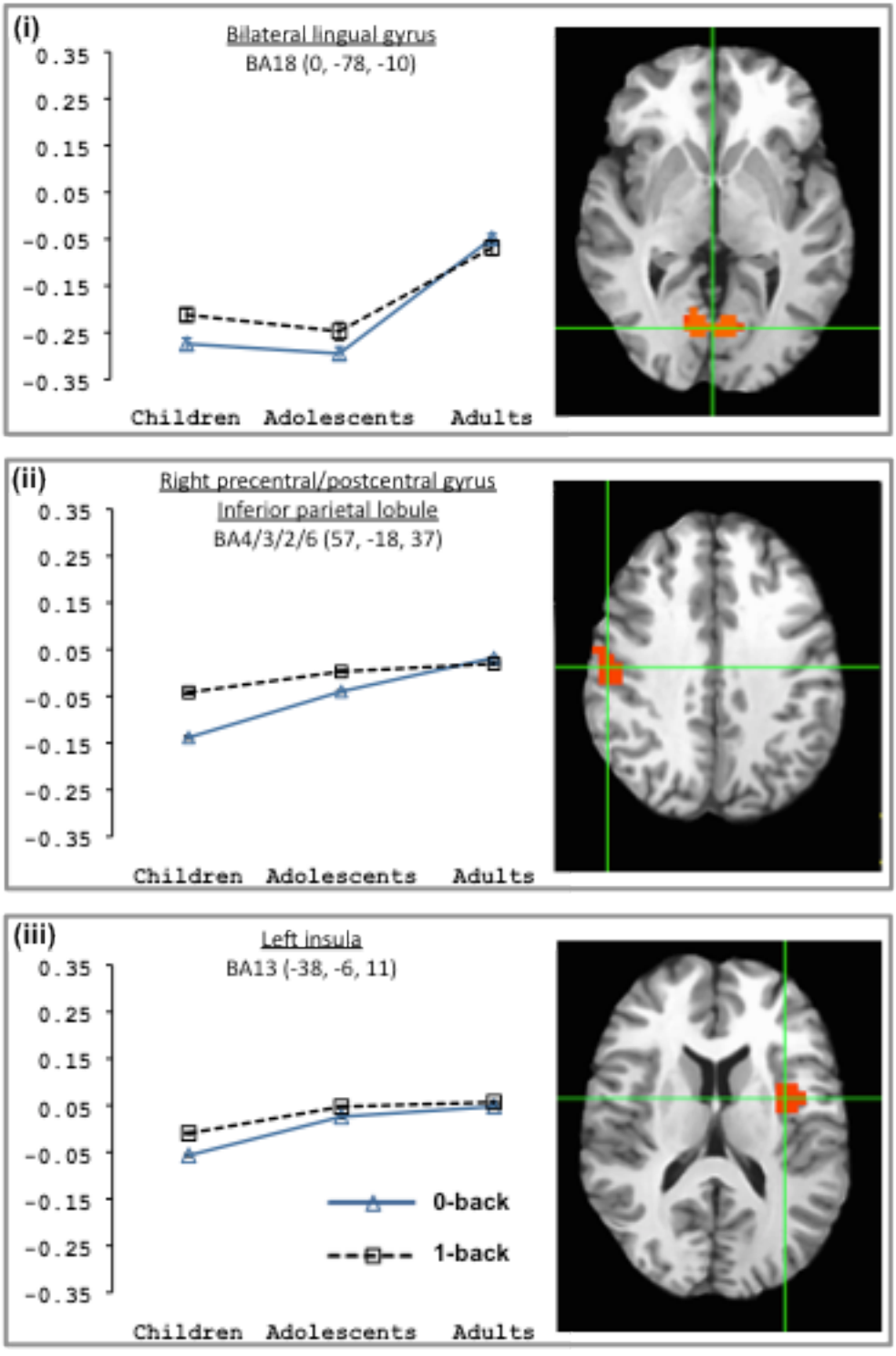

Figure 5.8. Three regions (i-iii) demonstrating a main effect of age ($F > 5.461$, $P < 0.005$) displayed on axial slices. Mean percent signal change for the significant clusters were extracted from the contrast images of 0-back vs. baseline and 1-back vs. baseline, for every subject, averaged within each age group. The scale of the line plots was kept consistent for ease in visual comparison. The y-axes are percent signal change values and the x-axes are the age groups.

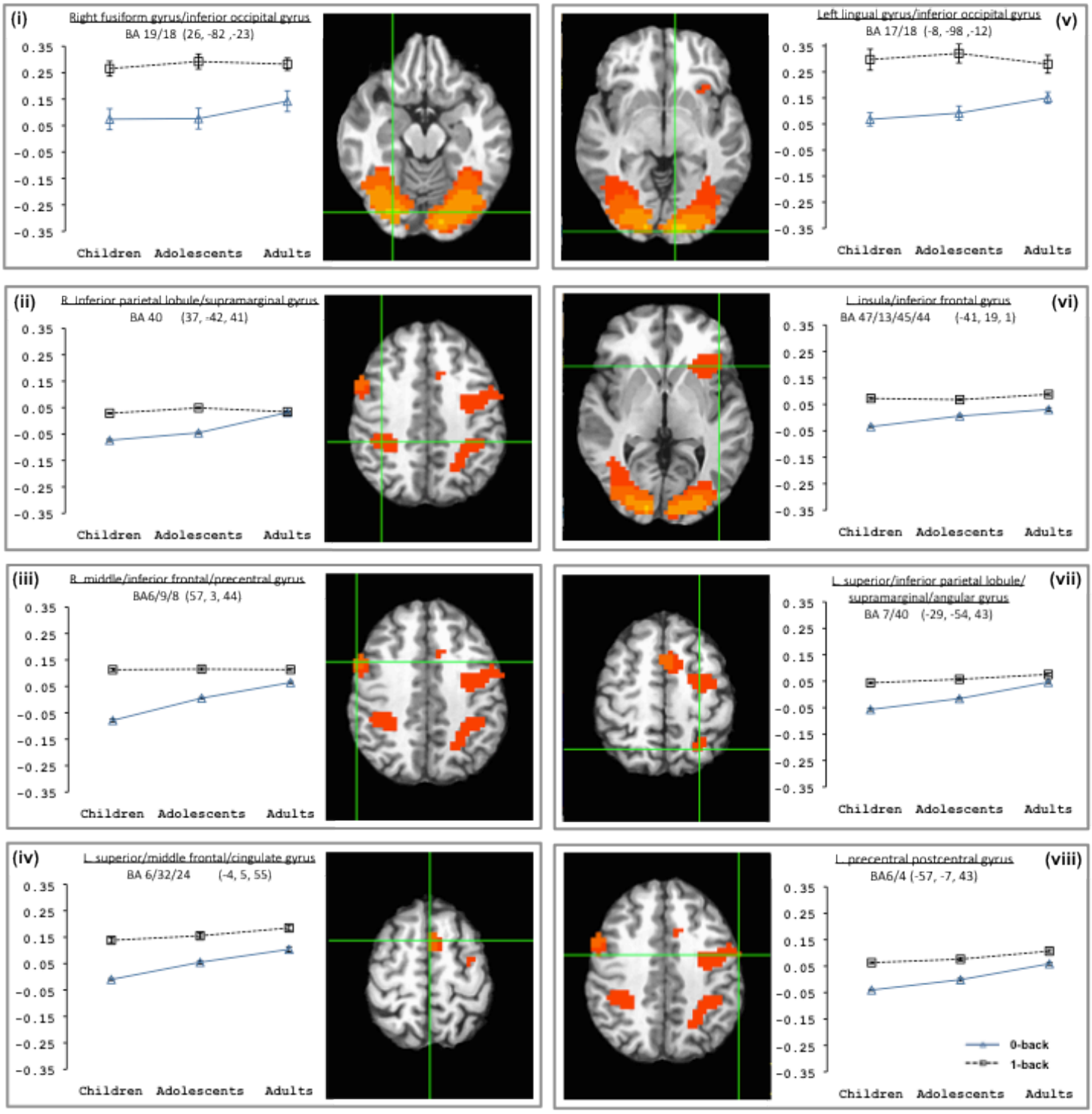

Figure 5.9. Eight regions (i-viii) demonstrating a main effect of task ($F > 8.454$, $P < 0.005$). Mean percent signal change for the significant clusters were extracted from the contrast images of 0-back vs. baseline and 1-back vs. baseline, for every subject, averaged within each age group. The scale of the line plots was kept consistent for ease in visual comparison. The y-axes are percent signal change values and the x-axes are the age groups.

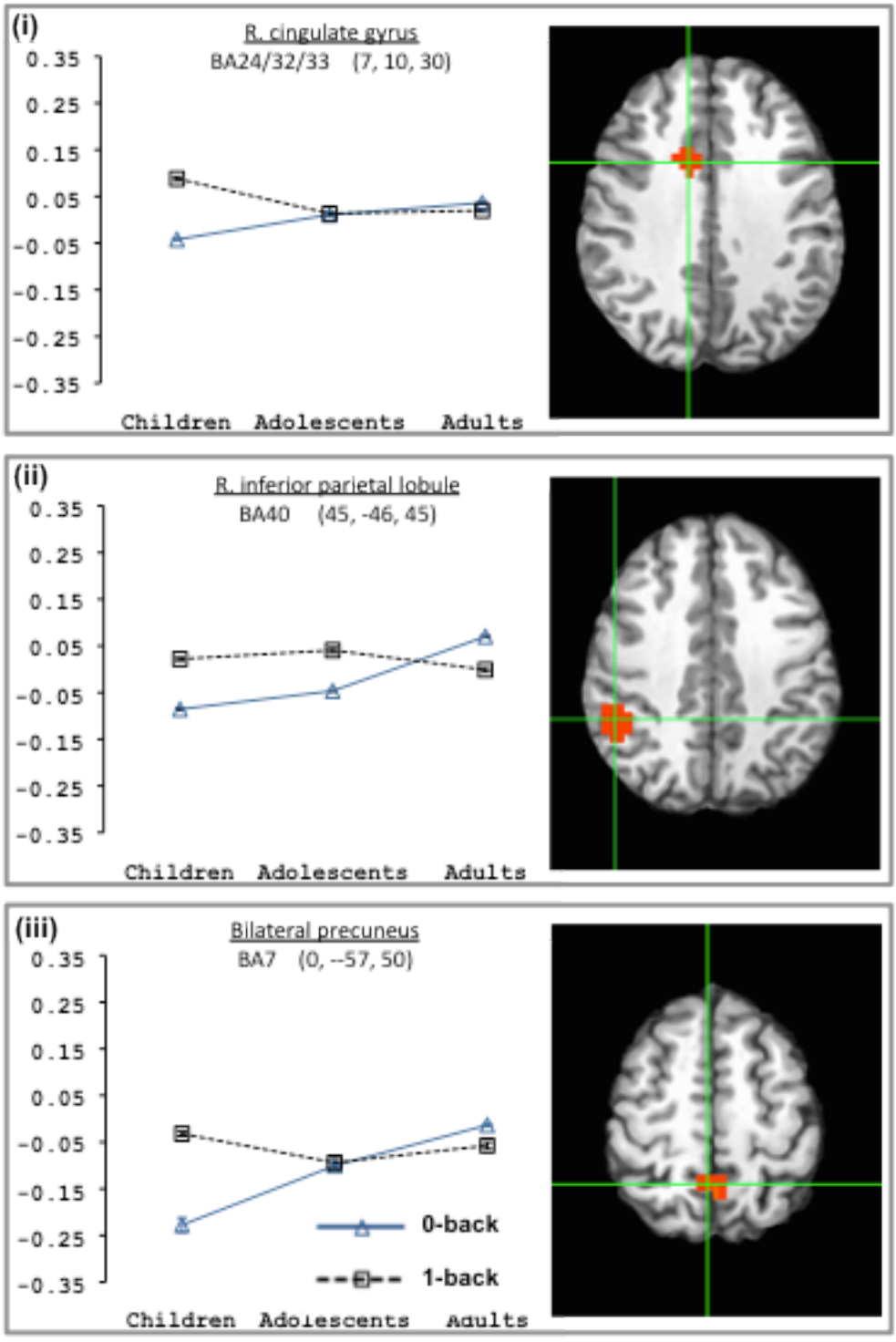

Figure 5.10. Three regions (i-iii) demonstrating a significant age by task interaction ($F <$ 4.96, p< 0.01, uncorrected). Mean percent signal change for the significant clusters were extracted from the contrast images of 0-back vs. baseline and 1-back vs. baseline, for every subject, averaged within each age group. The scale of the line plots was kept consistent for ease in visual comparison. The y-axes are percent signal change values and the x-axes are the age groups.

Table 5.11.

Regions showing A) a main effect of age, B) a main effect of task and C) an age by task interaction.

Brain region	Hem.	BA	*Talairach coordinates*			Cluster size (voxels)	F-value
			x	*y*	*z*		
A. Main effect of Age (*P* < 0.005, 26-voxel clusters)							
Increased with age (positively related)							
LG / declive	Bil.	18	0	-78	-10	42	8.61
Insula	L.	13	-38	-6	11	27	6.22
PreCG / PostCG / IPL	R.	4/3/2/6	57	-18	37	26	9.15
Decreased with age (negatively related)							
NONE							
B. Main effect of task (*P* < 0.005, 26-voxel clusters)							
1-back > 0-back							
LG / cuneus / IOG	L.	17/18	-8	-98	-12	508	35.33
Declive / FG / IOG / LG / MOG	R.	19/18	26	-82	-23	488	21.09
Insula / IFG	L.	47/13/45/44	-41	19	1	92	9.69
PreCG / postCG	L.	6/4	-57	-7	43	78	9.60
SPL / IPL / SMG / AG	L.	7/40	-29	-54	43	54	11.56
SFG / MFG / CingG	L	6/32/24	-4	5	55	45	13.83
IPL / SMG	R.	40	37	-42	41	37	15.27
MFG / PreCG / IFG	R.	6/8/9	57	4	44	27	14.6
C. Age by task interaction (*P* < 0.01, 10-voxel clusters)							
IPL	R.	40	45	-46	45	36	6.83
Precuneus	Bil.	7	0	-57	50	22	6.27
CingG	R.	24/32/33	7	10	30	15	7.69

Note. nBA = no Brodmann's Area. Bil. = Bilateral. L. = Left. R. = Right. Volume per voxel 3.75x3.75x5mm= 70.3 mm3. x, y, z are peak coordinates of each cluster.

Bilateral lingual gyrus/cuneus (BA 18; Figure 5.9.i) showed deactivation as part of the default mode network, and depicted a unique pattern of age-related change, where children and adolescents demonstrated a similar level of deactivation while adults were markedly different and showed less deactivation. The right precentral/postcentral gyrus (BA 4/3/2/6; Figure 5.9.ii) and the left insula (BA 13; Figure 5.9.iii) were activated by tasks. A positive linear increase in signal magnitude with age was observed in the right precentral/postcentral gyrus (BA 4; Figure 5.9.ii) showing a change across age groups in 0-back and no change age-related change in the 1-back. The age-related pattern observed in left insula (BA 13; Figure 5.9.iii) was characterized by an increase in magnitude of activity from children to adolescents (i.e., steeper rate of change between children and adolescents), which then plateaus, becoming more similar between adolescents and adults.

The main effect of age highlighted regions with age-related changes, therefore signal magnitude and pattern of activity across age groups observed in most regions was similar between the two tasks, compared to the regions detected by the main effect of task (discussed below). However, these areas did manifest a noticeable difference between the tasks in that activity levels were reliably higher during 1-back than 0-back, and this difference was more apparent in children.

Main effect of task. Eight regions showed a significant main effect of task that did not interact with age (Table 5.11B, Figure 5.9). These areas of constant activation across age groups included the bilateral lingual gyrus (BA 17/18/19), left insula/inferior frontal gyrus (BA 47/13/45/44), left precentral/postcentral gyrus (BA 6/4), bilateral

superior/inferior parietal lobule (BA 7/40), left superior/middle frontal gyrus and cingulate gyrus (BA 6/32/24), and right middle/inferior frontal/precentral gyrus (BA 6/8/9).

In all of these regions we found consistently higher signal magnitude during 1-back than 0-back and they were all areas of task-induced positive activations. The main effect of task primarily teased out the brain areas that responded to the two tasks with the differential magnitude of activity. Hence, amongst these regions, a minimal effect of age was observed compared with regions identified by the main effect of age (previous section). Nevertheless, there are some age effects that may be highlighted in that more marked age-related changes (a steep decline with age) were observed for 0-back (Figure 5.9.iii, iv, vii, viii) than 1-back.

Age by task interaction. Interaction effects were observed in three regions (Table 5.11C, Figure 5.10), including the right inferior parietal lobule (BA 40), bilateral precuneus (BA 7), and right cingulate gyrus (BA 24/32/33). Plotting the mean percent signal change in these significant clusters revealed that the interaction effects we observed were generally due to greater task difference in signal magnitude in children compared to relatively more similar levels of activation between the tasks in adolescents and adults, although this varied somewhat with regions. Within right cingulate gyrus (BA 24/32/33; Figures 5.10.i), the child group showed greater activity during 1-back compared with 0-back whereas for the adolescent and adult groups, the magnitude of activity in these regions did not differ between the tasks. Another region that had a similar interaction pattern was the bilateral precuneus (BA 7; Figure 5.10.iii), a task-

negative region that was consistently deactivated for both tasks across all three age groups. Deactivations in this area during 0-back showed a somewhat linear positive age effect, whilst deactivations during 1-back were largely stable across the age groups. We again observed that children showed the greatest difference of deactivation between the two much – greater deactivation during 0-back than 1-back, while adolescents and adults did not. In the right inferior parietal lobule (BA 40; Figure 5.10.ii), both the child and adolescent groups showed high activity for 1-back compared to 0-back, while activity for the adult group was reversed.

5.4.4 Region of interest analysis

We conducted the final set of analyses on fMRI data on nine *a priori* regions of interest from Owen et al. (2005). This was done to investigate age-related changes in regions that are known to be respond to WM demands. Specifically, we picked a set of regions that were generated from a quantitative meta-analysis of N-back tasks that were of the identity-monitoring type and that used non-verbal stimuli (Owen et al., 2005). First, we applied a repeated measures ANOVA for each region of interest. As shown in Table 5.11, four regions of interest showed a significant main effect of task ($P < 0.05$), including dorsal cingulate (BA 32; F (1, 62) = 5.165, P = 0.027), right dorsolateral PFC a (BA 46/9; F (1, 62) = 4.513, P = 0.038), right frontal pole a (BA 10; F (1, 62) = 5.287, P = 0.025) and right inferior parietal lobule (BA 40; F (1 62) = 6.246, P = 0.015). Two regions showed a trend towards significance ($P < 0.1$): left dorsolateral PFC (BA 46/9; F (1, 62) = 3.591, P = 0.063) and right frontal pole b (BA 10; F (1, 62) = 2.891, P = 0.094)). In all of these regions, the difference in activity between task and baseline was

greater for 1-back than 0-back. Two regions showed a significant main effect of group: right inferior parietal lobule (BA 40; F (2, 62) = 3.511, P = 0.036) and left inferior parietal lobule (BA 40; F (2, 62) = 3.625, P = 0.032). Post-hoc analyses revealed that adults demonstrated higher activation than children in both regions. We did not find significant interaction effects in any of the regions of interest at the $P < 0.05$ level. Three regions showed very weak interaction effects at $P < 0.2$: right dorsolateral PFC a (BA 46/9; F (2, 62) = 2.099, P = 0.131), right dorsolateral PFC b (BA 46/9; F (2, 62) = 1.788, P = 0.176) and right inferior parietal lobule (BA 40; F (2, 62) = 2.157, P = 0.124). The nature of the interaction was depicted by an age effect during 0-back vs. baseline and more constant level of activation during 1-back

Next, we conducted a one-way ANOVA for each region of interest from each contrast. As shown in Table 5.12, three regions demonstrated a significant between-group effect during 0-back vs. baseline ($P < 0.05$), including right dorsolateral PFC b (BA 46/9; F (2, 64) = 3.682, P = 0.031), right inferior parietal lobule (BA 40; F (2, 64) = 4.906, P = 0.011) and left inferior parietal lobule (BA 40; F (2, 64) = 3.32, P = 0.043). Two other regions showed a trend towards significance ($P < 0.1$): right dorsolateral PFC a (BA 46/9; F (2, 64) = 2.849, P = 0.065) and right frontal pole a (BA 10; F (2, 64) = 2.79, P = 0.069). Post-hoc analyses revealed that, in all of these regions, adults displayed higher activation than children. We did not find any significant between-group effects for the 1-back vs. baseline contrast.

Finally, we conducted paired t-tests for each region of interest between the tasks within each age group. Five regions demonstrated a significant between-task effect in children: dorsal cingulate (BA 32; t (21) = -2.181, P = 0.041), left dorsolateral PFC (BA

46/9; *t* (21) = -2.115, *P* = 0.047), right dorsolateral PFC a (BA 46/9; *t* (21) = -3.052, *P* = 0.006), right frontal pole a (BA 10; *t* (21) = -2.119, *P* = 0.046) and right inferior parietal lobule (BA 40; *t* (21) = -2.353, *P* =0.028). In all of these regions, children demonstrated more activity during 1-back than 0-back. We found one region that showed a trend towards significance for adolescents: right inferior parietal lobule (BA 40; *t* (21) = -1.856, *P* = 0.078), which was also more activated in 1-back than 0-back. We did not find any significant between-task effects for adults. Figure 5.11 depicts the mean group percent signal change values extracted from these regions of interest.

We also observed linear increases in activity with age in several regions during 0-back vs. baseline, by correlating percent signal change values with age. Five regions increased in activation with age significantly (*P* < 0.05): right dorsolateral PFC a (BA 46/9; *R* = 0.292, *P* = 0.018), right dorsolateral PFC b (BA 46/9; *R* =0.317, *P* = 0.01), right frontal pole a (BA 10; *R* = 0.274, *P* = 0.027), right inferior parietal lobule (BA 40; *R* = 0.35, *P* = 0.004, left inferior parietal lobule (BA 40; *R* = 0.271, *P* = 0.029). Two other regions showed a trend towards significance (*P* < 0.1): dorsal cingulate (*R* = 0.213, *P* = 0.088) and left dorsolateral PFC (BA 46/9; *R* = 0.201, *P* = 0.11). We did not find any significant linear effects for activations during 1-back vs. baseline.

Table 5.12.

Between-group between-contrast ROI analyses: repeated measures ANOVA

Regions of interest	**BA**	***Main effect of task***		***Main effect of group***		***Task by group interaction***
L. Lateral premotor	6/8	F (1, 62) =0.935 P = 0.337		F (2, 62) = 0.181 P = 0.835		F (2, 62) = 0.19 P = 0.827
Dorsal cingulate	32	***F* (1, 62) = 5.165 *P* = 0.027****	**1-back > 0-back**	F (2, 62) = 0.934 P = 0.398		F (2, 62) = 0.61 P = 0.547
L. dorsolateral PFC	46/9	***F* (1, 62) = 3.591 *P* = 0.063***	**1-back > 0-back**	F (2, 62) = 0.777 P = 0.464		F (2, 62) = 1.014 P = 0.369
R. dorsolateral PFC a	46/9	***F* (1, 62) = 4.513 *P* = 0.038****	**1-back > 0-back**	F (2, 62) = 1.558 P = 0.219		***F* (2, 62) = 2.099 *P* = 0.131†**
R. dorsolateral PFC b	46/9	F (1, 62) = 0.633 P = 0.429		F (2, 62) = 1.852 P = 0.165		F (2, 62) = 1.788 P = 0.176
R. Frontal pole a	10	***F* (1, 62) = 5.287 *P* = 0.025****	**1-back > 0-back**	F (2, 62) = 1.714 P = 0.189		F (2, 62) = 1.297 P = 0.281
R. Frontal pole b	10	***F* (1, 62) = 2.891 *P* = 0.094***	**1-back > 0-back**	F (2, 62) = 0.189 P = 0.829		F (2, 62) = 0.804 P = 0.452
R. Inferior parietal lobule	40	***F* (1, 62) = 6.246 *P* = 0.015****	**1-back > 0-back**	***F* (2, 62) = 3.511 *P* = 0.036****	**Adults > Children**	***F* (2, 62) = 2.157 *P* = 0.124†**
L. Inferior parietal lobule	40	F (1, 62) = 1.022 P = 0.316		***F* (2, 62) = 3.625 *P* = 0.032****	**Adults > Children**	F (2, 62) = 0.513 P = 0.601

* denotes $P < 0.1$. ** denotes $P < 0.05$. † denotes $P < 0.15$.

Table 5.13.

Within-contrast ROI analyses: one-way ANOVA

Regions of interest	**BA**	***0-back vs. baseline***		***1-back vs. baseline***
L. Lateral premotor	6/8	*F* (2, 64) = 0.041 *P* = 0.96		*F* (2, 64) = 0.386 *P* = 0.681
Dorsal cingulate	32	*F* (2, 64) = 1.362 *P* = 0.264		*F* (2, 64) = 0.163 *P* = 0.85
L. dorsolateral PFC	46/9	*F* (2, 64) = 1.663 *P* = 0.198		*F* (2, 64) = 0.055 *P* = 0.946
R. dorsolateral PFC a	46/9	***F* (2, 64) = 2.849** ***P* = 0.065***	**Adults > Children**	*F* (2, 64) = 0.108 *P* = 0.897
R. dorsolateral PFC b	46/9	***F* (2, 64) = 3.682** ***P* = 0.031****	**Adults > Children**	*F* (2, 64) = 0.172 *P* = 0.842
R. Frontal pole a	10	***F* (2, 64) = 2.79** ***P* = 0.069***	**Adults > Children**	*F* (2, 64) = 0.261 *P* = 0.771
R. Frontal pole b	10	*F* (2, 64) = 0.802 *P* = 0.453		*F* (2, 64) = 0.072 *P* = 0.931
R. Inferior parietal lobule	40	***F* (2, 64) = 4.906** ***P* = 0.011****	**Adults > Children**	*F* (2, 64) = 0.902 *P* = 0.411
L. Inferior parietal lobule	40	***F* (2, 64) = 3.32** ***P* = 0.043****	**Adults > Children**	*F* (2, 64) = 1.245 *P* = 0.295

* denotes $P < 0.1$. ** denotes $P < 0.05$.

Table 5.14.

Within-group ROI analyses: paired t-tests

Regions of interest	**BA**	***Children***		***Adolescents***		***Adults***
L. Lateral premotor	6/8	*t* (21) = -0.122 *P* = 0.904		*t* (21) = -1.050 *P* = 0.306		*t* (20) = -0.634 *P* = 0.533
Dorsal cingulate	32	***t* (21) = -2.181 *P* = 0.041****	**1-back > 0-back**	*t* (21) = -0.928 *P* = 0.364		*t* (20) = -0.693 *P* = 0.496
L. dorsolateral PFC	46/9	***t* (21) = -2.115 *P* = 0.047****	**1-back > 0-back**	*t* (21) = -0.846 *P* = 0.407		*t* (20) = -0.231 *P* = 0.82
R. dorsolateral PFC a	46/9	***t* (21) = -3.052 *P* = 0.006****	**1-back > 0-back**	*t* (21) = -0.91 *P* = 0.373		*t* (20) = 0.084 *P* = 0.934
R. dorsolateral PFC b	46/9	*t* (21) = -1.477 *P* = 0.155		*t* (21) = -0.764 *P* = 0.453		*t* (20) = 1.456 *P* = 0.161
R. Frontal pole a	10	***t* (21) = -2.119 *P* = 0.046****	**1-back > 0-back**	*t* (21) = -1.083 *P* = 0.291		*t* (20) = -0.515 *P* = 0.612
R. Frontal pole b	10	*t* (21) = -1.594 *P* = 0.126		*t* (21) = -1.27 *P* = 0.218		*t* (20) = -0.291 *P* = 0.774
R. Inferior parietal lobule	40	***t* (21) = -2.353 *P* = 0.028****	**1-back > 0-back**	***t* (21) = -1.856 *P* = 0.078 ***	**1-back > 0-back**	*t* (20) = 0.392 *P* = 0.699
L. Inferior parietal lobule	40	*t* (21) = -1.218 *P* = 0.237		*t* (21) = -0.441 *P* = 0.664		*t* (20) = 0.04 *P* = 0.969

* denotes $P < 0.1$. ** denotes $P < 0.05$.

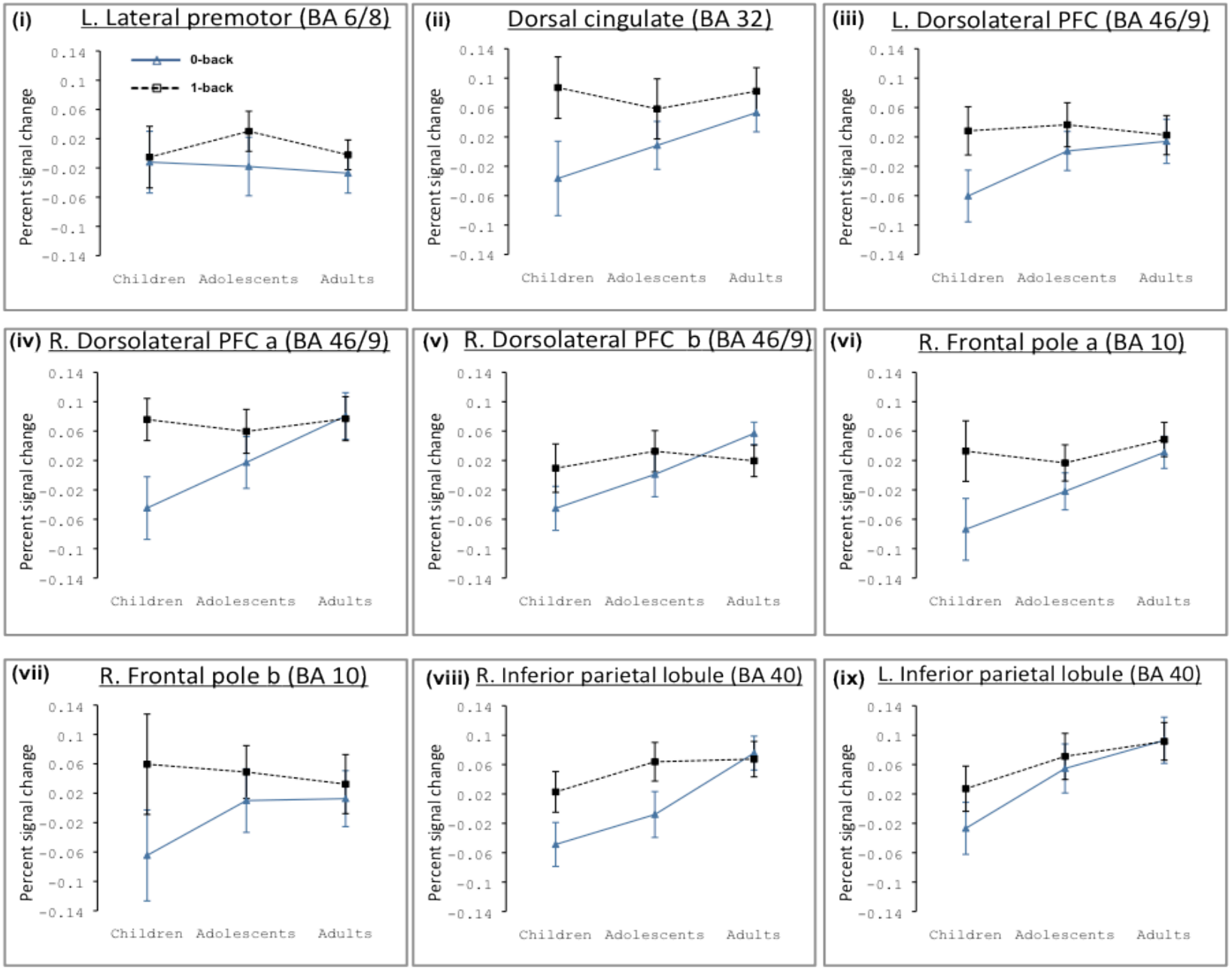

Figure 5.11. Line graphs depicting mean group percent signal change values extracted from visual identity-monitoring type N-back coordinates (Owen et al., 2005).

CHAPTER 6: DISCUSSION

Visual WM is the cognitive mechanism that encodes, maintains, manipulates, and retrieves visual and spatial information over the short-term (Sperling, 1960). WM has been investigated extensively in adults revealing the importance of the frontal and parietal lobe regions in the mature brain. While there is a wealth of information on WM and its associated neural processes in the adult neuroimaging literature, the number of WM neuroimaging studies with children and adolescents is more limited. The main goal of this thesis was to investigate the quantitative and qualitative changes in neural correlates over a large age range during an identity-monitoring N-back task using complex visual patterns. To our knowledge, this study is the first to test this stimulus type in an N-back task with developmental samples.

6.1 Behavioural changes in 0-back and 1-back performance

Behavioural results provide evidence showing that WM performance continues to mature into the late adolescence period and early adulthood, as we found that accuracy increased and RT decreased with age in both tasks. This finding is not in accordance with our hypothesis that performance should be similar across ages. We found that behavioural performance differentiated between the three age groups, but to different extents in the two task conditions. More specifically, this behavioural differentiation in age groups was more apparent at the 0-back than the 1-back level. In the 0-back condition, children made significantly more errors and took a longer time to respond than both adolescents and adults, while adults and adolescents performed similarly. In the 1-

back condition, the accuracy was not different between children and adolescents, and adults and adolescents, however children performed significantly worse than adults.

A possible explanation for the unexpected performance differences is that participants of different ages may be using different strategies to perform the same tasks. Age-related improvements in N-back task performance have also been associated with the development of the ability to recode presented material into a verbal format at around 7-8 years of age (Kemps et al., 2000; Pickering, 2001). Furthermore, for tasks of a similar nature, adults reported attempting to form verbal descriptions of stimuli even when the task was designed to be non-linguistic (Ragland et al., 2002). It is possible that our children and adolescent samples also tried to form verbal representations and this ability would be less developed in children and consequently affecting their performance. The development of strategy use is in and of itself a relevant and important area of research that can be investigated (Cowan et al., 2006; van Leijenhorst et al., 2006). Future studies should mandate a debriefing of strategy use.

The 1-back task was designed to place a greater demand on WM cognitive processes of maintenance, updating and temporal coding than 0-back; participants should be more prone to making errors and also respond more slowly on 1-back. We found that RT was indeed significantly longer on the "more difficult" 1-back task for all three age groups; however, only adolescents were less accurate in 1-back compared with 0-back. The fact that children did not perform significantly worse in 1-back than 0-back was unexpected, but further inspection of the data revealed that children showed a trend toward significance (t (21) = 1.844, P = 0.08). The adults only demonstrated a very subtle difference in accuracy between the two tasks as expected. An alternative

explanation is that adolescents are typically less eager to perform well compared to children, and may have not exerted the extra effort for the 1-back, as it was evident in the accuracy but not response times.

We found that age correlated with both accuracy and RT, demonstrating linear age-related improvements. Much greater variability in task performance was observed at younger ages (Figure 5.2). Improvements in accuracy with age occurred at a very slow rate, i.e., ~0.4% per year for 0-back and ~0.6% per year for 1-back. Accuracy reached asymptotic levels between 16-20 years for 0-back, and between 20-24 years for 1-back. In contrast, RT on both task conditions troughed at around the same age span of 20-24 years, indicating that a common, fundamental mechanism, such as age-related increases in myelination/white matter density (Hagmann et al., 2010), might be driving the decrease in RT over age across both tasks. Age-related slopes of accuracy and RT between the two task conditions were not significantly different, suggesting that these tasks are comparable in their relation to age. Our partial correlation results suggest that the slight improvement in accuracy with age is primarily driven by increased processing speed. Younger children may be more easily distracted and less able to focus their attention than their older counterparts (Davidson et al., 2006), possibly reflecting immature cognitive control, which develops gradually over childhood (Davidson et al., 2006).

In summary, our findings demonstrated that adolescents and adults have faster processing speed than children. In addition, the finding that N-back task performance improves with age and that adults were superior in their performance than children is in line with the past findings which reported that WM continues to develop into young

adulthood, and a mature level of performance begins at around 15-19 years of age (e.g., Luciana and Nelson, 1998; Gathercole, 1999; Luna et al., 2004; Huizinga et al., 2006).

6.2 Functional anatomic organization of visual N-back WM task in the developing brain

We were not able to replicate previous findings from Ragland and colleagues (2002) who used a similar complex abstract pattern N-back task, and found 1-back > 0-back activation in left inferior parietal cortex (BA 40), left lingual gyrus (BA 19), left dorsolateral PFC (BA 9/46) and bilateral precentral gyrus (BA 6) and thereby showing an effect of load, even at the lowest load possible. Our adult sample did not show any regions with greater activation in 1-back compared with 0-back. Only children and adolescents displayed areas that were more active in the 1-back minus 0-back contrast, including bilateral visual cortices (BA 17/18/19) in both groups and in children, additional activations in right middle/inferior frontal gyrus (BA 9/8). The absence of 1-back > 0-back activity in adults in our case came as a surprise. In fact, the frontal activation found in children seems in more accordance with the adult finding in Ragland et al. (2002). One possibility for the absence of a difference between tasks in adults is our experimental design. The pre-defined target in our 0-back condition was a solid blue square, as opposed to a specific stimulus pattern in Ragland et al. (2002). Furthermore, Ragland et al. (2002) presented stimulus repeats within a small set of stimuli, which significantly increased task difficulty. It is therefore likely that our 1-back task was not as cognitively challenging for adults but possibly a difficult enough task for children for them to recruit frontal regions. We did not make the same choices as Ragland et al. (2002) in our design, as we were constrained to ensure that the task could be performed

at young ages. In addition, our baseline fixation block was specific for each task since each task corresponded to each block. By having each run corresponding to each task runs into the risk of producing different baseline fixations, which might have compromised our results.

Nevertheless, to investigate this further, we went on to examine the contrast of each task against its own baseline condition. Specifically, we used conjunction analyses to first identity the common regions of activation and deactivation across age groups and examine the differing extents of activation with these common regions. Both 0-back and 1-back tasks elicited reliable positive activation in core visual areas (inferior and middle occipital gyrus, lingual and fusiform gyri, BA 17/18/19), that were common throughout all age groups, indicating that participants were actively engaged during the task and reflecting the nature of our visually presented experimental stimuli. However, the 1-back task also recruited several additional common regions across age groups including the bilateral insula and cingulate gyrus, two important areas known to be engaged in WM processes (Owen et al., 2005). We also found substantial neuroanatomical overlap between task-induced deactivations in posterior brain regions, including the cuneus, precuneus and posterior cingulate. These deactivated regions constitute some of the brain areas within the default-mode network, a distinct group of regions that is engaged during passive mental state or the absence of cognitive task performance (Gusnard and Raichle, 2001; Raichle et al., 2001). It has been suggested that the default mode network reflects ongoing thoughts, mind-wandering and self-referential mental states (e.g., Gusnard and Raichle, 2001) and had been suggested to reflect reallocation of resources to areas needed for task performance (McKiernan et al., 2003). The common theme of

deactivations in posterior brain regions for all age groups suggest that default mode properties emerged early in development and are operational in young children.

Varying extent of activation and deactivation in these common regions was observed across development. During 0-back vs. baseline, adults exhibited visibly larger extent of task-positive activation in the core visual cortices than adolescents and children, while children and adolescents displayed noticeably larger extent of deactivation than adults in the precuneus. In contrast, in the 1-back vs. baseline comparison, although some task-positive activations (in bilateral cingulate gyrus and anterior insula) were still more extensive in adults, volumes of activation and deactivation were much more consistent across the age groups. It is likely that there are age-related effects in the toggle between the task-positive network and the default mode. Future work should investigate whether such effects might exist in development.

Our next set of conjunction analyses examined common regions of activations and deactivations within each age group, across tasks. Adults were found to activate a similar set of regions during both tasks, while children and adolescents only shared visual cortex activation. This finding corroborates the absence of 1-back > 0-back activation in adults. As the data have shown, between-task activation in adults was largely overlapping, i.e., adults recruited similar regions during 0-back and 1-back, whereas children and adolescents only showed an overlap of visual areas.

Direct contrast of brain activation between age groups revealed more pronounced between-group differences during 0-back, mirroring our conjunction analyses. Adults displayed greater activity in IPL (BA 40) than both children and adolescent, in left insula (BA 13) than children and bilateral lingual gyrus than adolescents. We did not find

between-group differences for the 1-back vs. baseline contrast as expected given that the between-group activations during 1-back vs. baseline mostly overlapped. And for the 1-back vs. 0-back contrast, children exhibited greater activation in right IPL (BA 40) than adults. Note that this is more lateral than the right IPL that showed a main effect of task.

Besides examining simple task vs. baseline effects to identify common areas of activation and deactivation, and delineate age-related changes in activation, we conducted whole-brain ANOVA analyses to identify areas might that differ in signal magnitude between tasks as a function of age, i.e., an interaction. Interaction effects were found in the right IPL (BA 40), which showed a higher signal magnitude in 1-back than 0-back in both children and adolescents but the reverse in adults; the right cingulate gyrus (BA 32/24) and bilateral precuneus (BA 7), which both showed a much greater between-task difference in magnitude in children than in adolescents and adults.

There were two secondary goals for the whole-brain ANOVA analyses: to identify task-variant but age-invariant regions (main effect of task), and task-invariant but age-variant regions (main effect of age). These served to confirm and further delineate our findings from conjunction analyses and between-group contrasts. The main effect of task identified a set of regions that did not further interact with age and they included many of the commonly activated regions that emerged from our conjunction analyses, such as the bilateral visual areas, left insula (BA 13), left precentral/postcentral gyrus (BA 6) and cingulate gyrus (BA 6/32). Some additional areas were bilateral IPL (BA 7/40) and right middle/inferior frontal gyrus (BA 6/9). Such findings are in line previous adult studies of the N-back WM task (Owen et al., 2005) and support the theory that the neural network important for WM is in place at an early age, but continues to refine and

develop with age and may differ in these changes with specific task demands (Chee and Choo, 2004; Gould et al., 2006; Jansma et al., 2007; McKiernan et al., 2003). The main effect of age identified regions that showed similar age-related effects for both tasks. These included the bilateral lingual gyrus (BA 19), right precentral gyrus (BA 6) and left insula (BA 13). We did not find any age-related changes in frontal regions as hypothesized. For all regions from the ANOVA analyses, we found consistently higher signal magnitudes during 1-back than 0-back, confirming our hypothesis that 1-back is more cognitive demanding.

Results from the region of interest analysis further corroborated the findings from the whole-brain analysis and also delineated age-related changes in frontal regions that were not detected in whole-brain analysis. First, all regions of interest showed higher signal magnitude during the 1-back than 0-back task. Second, adults almost always had greater signal intensities than children. Third, between-task difference in signal magnitude was almost always greatest in children and decreased with age. And fourth, strong age-related trends were observed for 0-back. We found significant positive correlations between age and several key regions involved in identity-monitoring variant of N-back tasks using visual stimuli type, including right dorsolateral PFC and bilateral IPL.

Results converged on a number of principal regions, including the visual cortices (lingual and fusiform gyrus), dorsal cingulate (BA 32), the insular cortices (BA 13) and IPL (BA 40), to be engaged during 0-back and 1-back task performance. The fusiform gyrus is part of the occipito-temporal network and is associated with encoding object properties such as colour, shape and texture and object categorization (Tan et al., 2005;

Amedi et al., 2005). The left fusiform gyrus has been suggested to integrate features into elaborate schemes that represent whole words or objects, possibly having a role in the visual recognition of stimuli to assimilate features; while the right fusiform gyrus, is biased towards global rather than local processing (Arsalidou and Taylor, 2011). During 1-back vs. baseline fixation, we found additional commonly recruited task-positive regions in bilateral cingulate gyrus (BA 32) and anterior insula (BA 13). This supports past findings, as the dorsal subdivision of the cingulate gyrus (BA 32) has been shown to have a key role in cognitive rather than emotional processes (Bush et al., 2000), and is suggested to be involved in error monitoring and integration of information (Wang et al., 2005; Milham and Banich, 2005). It is also involved in coordinating and integrating activity of multiple attentional systems (Milham and Banich, 2005). The insular cortices (BA 13) are associated with execution of responses, error processing and were proposed to be part of a network responsible for toggling between other competing brain networks (executive control network and default-mode network) during information processing (Sridharam et al., 2008; Uddin and Menon, 2010; Arsalidou and Taylor, 2011). IPL is believed to act as the temporary information storage system used by the phonological loop and visual information in WM (Baddeley, 2003).

Children and adolescents may be less able to recruit areas related to task-specific processing relative to adults (Luna et al., 2010). Some researchers have proposed that the increased recruitment in dorsolateral PFC in adolescents may reflect additional mental effort required to attain the same performance level as adults (Luna et al., 2010). Our data did not reveal increased dorsolateral PFC activity at the whole-brain level; we found that adolescents displayed an activation pattern more similar to children than adults

despite performing just as well as adults on the 0-back. Our finding that children and adolescents recruited similar resources during 0-back, that was distinct from adults, suggests a possible developmental transition towards the use of a more functionally or task-specific network in the purportedly less demanding 0-back task. Memory, attention and inhibition have been suggested to be parts of a single construct of a common underlying neural circuitry (Casey et al., 2000). Although these processes are not easily separable from each other (behaviourally and physiologically) in adults, for children and adolescents, the underlying brain mechanisms undergo a more prolonged development for the 0-back task. Another plausible explanation is that children and adolescents might not as be engaged or attentive during 0-back since its requirement was to just look for a blue square and this can be accomplished relatively easily without the need to marshal as many cognitive resources.

The 0-back task may be viewed as a task that primarily calls for attentional processes to ignore non-target distracters, just like a continuous performance task used for the maintenance of vigilance, and requires intact impulse control/inhibition. Active attention plays a key role in successfully and efficiently encoding and retrieving information. Improvements in WM or the ability to attend voluntarily to some attributes of the stimulus array and to ignore others, improves with age. Tasks that implicate task-relevant and task-irrelevant features, such as the n-back, were found to be better measures of WM in adults (Engle, 2001; Engle and Kane, 2004) and across development (Arsalidou et al., 2010). Although visual functioning in school-aged children may be fully developed, there are still marked improvements that are still occurring in the voluntary deployment of attention (Arsalidou et al., 2010). Studies have shown that

attention can modulate neuronal activity in both dorsal and ventral visual streams. Furthermore, the changes in memory load with increasing N are not easily quantifiable, because cognitive demand increases non-linearly from one level to the next. In terms of brain function, these abrupt changes in demand may be manifested in increased activation in the relevant areas of processing or even require an alternative network which may represent a different strategic approach for the task.

To summarize, we found a stronger developmental trend for the purportedly less demanding 0-back task (than 1-back) and several key regions known to be involved in attentive processes engaged during these tasks. These findings raise some question on the assumptions of what these tasks are really measuring. The 0-back task is typically used as a control condition as it does not require any manipulation and/or updating of continuous stimuli, while the 1-back task was presumed to carry the WM demand as it requires a constant updating of continuous stimuli. It is likely that in this study, our 1-back task might not be a real WM task, given that we found little to no developmental changes in its associated brain responses. Indeed, some researchers have proposed that the N-back tasks only involve executive processing when N is greater than one (Jaeggi et al., 2003; 2008; Oberauer, 2005; Smith & Jonides, 1997). Taken together, our findings portray a novel developmental perspective between the nature of cognitive tasks and their associated brain responses.

6.4 Limitations

Small power. One issue that arises when trying to interpret differences between age groups (e.g., children and adults), or between normal volunteers and clinical populations, is that of statistical power,. Using a standard 1.5 Tesla scanner, reliable

differences may reflect a change of only 1-2% in the magnitude of the MR signal (Kwong et al., 1992). One concern in paediatric or clinical fMRI is the feasibility of detecting group differences when the signal intensities are quite small. This issue of power becomes more evident when variance due to movement artefact, unreliable measures of cognition or other sources such as developmental changes is added to the equation. Investigators should be aware that paediatric research often requires larger sample sizes, to achieve sufficient statistical power, and compared to adult samples, child samples are not as easy to obtain. In the present study, despite employing a relatively large sample, our power were still quite small. However, we believe that these are robust effects as significant clusters survived stringent multiple comparisons correction.

Age vs. Performance. Behavioural performance plays an important role in the interpretation of developmental differences. Behavioural data are essential for evaluating whether the participant is performing the desired task and can aid in determining whether group differences in MR measurements may be attributable to maturation alone, or to age-related improvements in performance. However, in any study of development, a potential confound is the possible differing task performance between age groups (Johnson 2001; Palmer et al., 2004; Schlaggar et al, 2002). While children are capable of performing many adult-level tasks, their accuracy and speed of information is almost always worse when compared to adults. One solution is to pick a task that all age groups can perform at a high level of accuracy that is essentially at ceiling (Poldrack, 2000). In the present study, we ran into this issue if performance differences despite following this suggestion.

A number of strategies have been proposed to deal with this confound. One solution is to parametrically manipulate the task difficulty until performance equates, usually by increasing task difficulty for the adult group. However, this is only useful if task difficulty increases monotonically (e.g., a go-no-go task). In addition, this creates the rather obvious concern, that because the task is no longer the same between groups, and therefore it is not measuring the same brain processes. Another solution is to partial out the performance in analyses. However, this assumes linearity in the relation between age and performance with brain activity, which is rarely the case.

A third technique is to create subsets of scanned individuals from each group who have overlapping performance on the task. These performance-matched groups can then be compared to the whole group or the remaining unmatched individuals to show which regions of differences are driven by performance effects, and which may be capturing functional group differences. We took steps in this regard by imposing a criterion on performance. Even after excluding those with the worst performance, behavioural differences still exist; further exclusions would have compromised the power of the experiment. In addition, it was very difficult to establish a performance-matched group for both tasks, as those who performed worse on 0-back were not necessarily worse performers on the 1-back. Based on our results, we strongly believe that the difference in performance is an inherent nature of developmental samples and most likely did not affect our neuroimaging results, especially given that while adolescents and adults did not show behavioural differences, differences in brain responses (that were similar to children) were found.

6.5 Conclusions

In this study, we delineated the qualitative and quantitative developmental changes in fMRI-BOLD responses associated with a visual patterns N-back task. We have demonstrated that activity varied by age. Activity in left insula and bilateral lingual gyrus regions is associated with maturation (age). Importantly, the observed difference between children/adolescents and adults may reflect cognitive strategy use that is age-dependent. We also provide evidence showing neural changes associated with development from childhood and adolescence, into adulthood. In summary, our findings illustrate the complex nature of cognitive and brain development. Some general principles of brain development were validated while other novel findings were uncovered. To our knowledge, this is the first study that has used a visual identity-matching variant of the N-back task in a developmental population.

The results of the present study allowed the following conclusions to be drawn:

1. Performance improves with age, reflecting the maturation of underlying cognitive processes and brain systems.
2. Children, adolescents and adults recruit similar cortical networks in the processing of WM information (1-back) but when WM demands are lowered other processes are implicated (0-back). Specifically, children and adolescents recruited similar neural resources that are different from adults.
3. Deactivation mechanisms present in adults are operational in young children but continue to develop.

4. Key regions, identified in previous studies on WM in adults decrease in WM-related activity with age.

6.7 Future directions

A full understanding of human functional brain development represents a particularly daunting task. It is clear that any one technique will not be able to sufficiently elucidate the complete nature of brain maturation and cognitive development. Advances in non-invasive neuroimaging techniques such as EEG, DTI, fMRI, optical imaging and others will undoubtedly add to our understanding. Quantitative meta-analyses will also aid in our knowledge of the development of specific cognitive domains. The data presented in this thesis could be subjected to connectivity analyses to elucidate how the interaction of brain networks might contribute to the function of WM. Furthermore, we could also couple our functional data with the structural data collected to delineate structure-to-function relations.

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Appendix A. List of all participant demographic information

Participants with excessive motion (*n* = 1 on 0-back, n = 1 on 1-back), poor image quality/artifact (*n* = 10), and missing scans/functional data (*n* = 1 on 0-back, *n* = 1 on 1-back, *n* = 3 on both) were excluded from analyses. Data from 65 participants who performed both 0-back and 1-back tasks were used in analysis of task effects in each task and the analysis for interaction effects. Table A1.displays the details demographic of all 84 participants and whether they were included or excluded in the analysis for this thesis.

Table A1.

Detailed listing of all participants

Subject ID	Handedness	Sex	Age	2-subtest IQ	0-back accuracy	1-back accuracy	Include/exclude in analysis	Reason for exclusion
C166	Right	F	6.1	118	0.625	0.625	Include	
C188	Right	M	6.6	105	0.875	0.625	Include	
C171	Right	F	6.9	104	1.000	0.688	Include	
C127	Right	M	7.2	90	0.813	0.625	Exclude	high motion during 1-back
C190	Right	M	7.2	135	0.875	0.688	Include	
C170	Right	F	7.2	132	0.875	0.938	Include	
C130	Right	F	7.3	135	0.750	0.813	Include	
C016	Right	M	7.8	109	0.938	0.938	Exclude	high motion during 0-back
C007	Right	M	7.9	131	1.000	0.688	Include	
C191	Right	F	7.9	125	0.938	1.000	Include	
C165	Right	M	8.1	122	0.750	0.813	Include	
C159	Left	F	8.3	114	0.750	0.938	Include	
C175	Right	F	8.5	106	1.000	0.813	Include	
C021	Left	F	8.8	Not obtained	1.000	0.938	Exclude	artifact
C032	Right	M	8.8	Not obtained	1.000	1.000	Include	
C198	Right	F	8.8	118	0.938	1.000	Include	

C169	Right	M	8.9	115	0.813	1.000	Include	
C124	Right	F	9.0	120	1.000	1.000	Include	
C029	Right	F	9.2	Not obtained	1.000	0.938	Include	
C189	Right	M	9.7	111	0.938	0.938	Include	
C197	Right	F	10.1	90	1.000	1.000	Include	
C044	Right	M	10.6	Not obtained	1.000	missing	Exclude	missing 0-back MRI
C050	Right	F	10.7	Not obtained	0.938	1.000	Include	
C120	Right	M	10.7	Not obtained	1.000	0.875	Include	
C184	Right	M	11.3	106	1.000	0.938	Exclude	artifact
C177	Right	M	11.5	102	1.000	0.813	Include	
C161	Right	F	11.5	114	0.938	0.813	Exclude	missing MRI
C151	Right	F	11.7	120	1.000	0.938	Include	
C155	Right	M	12.2	101	0.938	0.750	Include	
C176	Left	M	12.6	121	0.938	1.000	Include	
C121	Right	F	12.9	Not obtained	1.000	1.000	Include	
C196	Right	M	12.9	88	1.000	0.750	Include	
C059	Right	M	13.0	113	0.875	0.938	Exclude	artifact
C183	Left	M	13.5	116	1.000	1.000	Exclude	artifact
C178	Right	M	13.5	104	1.000	1.000	Include	
C072	Right	M	13.5	116	1.000	1.000	Include	
C206	Left	M	14.2	96	1.000	1.000	Include	
C076	Right	F	14.6	83	1.000	1.000	Exclude	artifact
C162	Right	M	14.6	113	1.000	0.938	Exclude	missing MRI
C100	Right	M	14.8	Not obtained	1.000	0.938	Include	
C143	Right	F	14.9	128	1.000	0.813	Include	
C078	Right	F	15.0	102	1.000	0.938	Include	
C172	Right	M	15.0	121	1.000	1.000	Include	
C180	Right	F	15.2	107	1.000	0.938	Include	
C071	Right	F	15.5	126	1.000	1.000	Include	
C141	Right	F	15.7	116	1.000	1.000	Exclude	artifact
C179	Right	M	15.8	123	1.000	1.000	Include	
C204	Right	F	15.9	103	1.000	0.875	Include	
C212	Right	M	16.3	121	1.000	0.875	Include	
C103	Right	M	16.5	Not obtained	1.000	1.000	Exclude	artifact

C181	Right	F	16.6	108	1.000	1.000	Include	
C205	Right	F	16.6	109	1.000	1.000	Include	
C123	Right	M	16.6	123	1.000	0.813	Include	
C107	Right	M	16.7	Not obtained	1.000	1.000	Exclude	artifact
C160	Right	M	16.7	110	1.000	1.000	Include	
C108	Right	M	16.7	Not obtained	1.000	1.000	Exclude	artifact
C182	Right	F	17.0	112	1.000	0.813	Include	
C144	Right	F	17.4	Not obtained	1.000	1.000	Include	
C210	Right	F	17.5	120	1.000	1.000	Exclude	missing MRI
C207	Right	M	17.6	109	1.000	1.000	Include	
C215	Right	F	18.0	123	0.938	1.000	Include	
G140	Left	F	18.7	Not obtained	0.938	0.938	Include	
G137	Right	F	19.5	Not obtained	1.000	1.000	Include	
G070	Right	M	19.7	Not obtained	1.000	1.000	Include	
G135	Right	F	19.7	Not obtained	0.938	1.000	Include	
G138	Right	M	19.9	Not obtained	1.000	0.938	Include	
G051	Right	M	20.2	Not obtained	1.00	0.81	Include	
G047	Right	F	20.8	Not obtained	1.00	1.00	Include	
G111	Left	F	21.0	Not obtained	1.00	1.00	Include	
G085	Right	F	23.3	Not obtained	1.00	1.00	Exclude	artifact
G054	Right	F	24.0	Not obtained	1.00	1.00	Include	
G031	Right	M	24.7	Not obtained	1.00	1.00	Include	
G088	Right	F	24.9	Not obtained	1.00	0.94	Include	
G015	Right	M	26.6	Not obtained	0.94	0.94	Include	
G028	Right	F	27.4	Not obtained	1.00	1.00	Include	
G073	Right	F	27.5	Not obtained	1.00	1.00	Include	
G079	Right	M	27.6	Not obtained	1.00	0.94	Exclude	artifact
G066	Right	F	27.8	Not obtained	1.00	0.88	Include	
G097	Right	F	28.9	Not obtained	1.00	1.00	Exclude	artifact
G067	Right	F	29.1	Not obtained	1.00	0.94	Include	
G091	Right	M	29.7	Not obtained	1.00	1.00	Exclude	missing 0-back MRI
G033	Right	F	32.1	Not obtained	1.00	1.00	Include	
G034	Right	F	34.5	Not obtained	0.94	0.94	Include	
G064	Right	F	36.1	Not obtained	0.94	1.00	Include	