NEUROPSYCHOLOGY AND FUNCTIONAL BRAIN ORGANISATION OF WORKING MEMORY IN CHILDREN AND ADOLESCENTS WITH AGENESIS OF THE CORPUS CALLOSUM

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Thèse

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ABSTRACT

Background: The corpus callosum is the largest brain white matter pathway. Its main function is to coordinate and transfer information between the two hemispheres, thus contributing to higher cognitive functions including working memory (WM). Developmental absence of the corpus callosum, or Agenesis of the Corpus Callosum (AgCC), is one of the most common brain malformations but its consequences on neurobehavioural functioning and functional brain organisation in school-age children are not well understood.

Aims: The goal of the current work was: 1) To describe the impact of AgCC on neurobehavioural functioning, including WM functions, in school-age children; and investigate the role of age, social, and neurological factors that might underlie neurobehavioural outcomes in children with AgCC; 2) To investigate the functional brain organisation of WM in school-age children with AgCC using functional magnetic resonance imaging (fMRI).

Methods: 28 children diagnosed with AgCC based on MRI and a control sample of 16 typically developing children, aged 8 to 17 years, completed a neurobehavioural assessment and brain imaging with anatomical T1 sequences and an fMRI task (AgCC, n=9; controls, n=16) tapping WM processes, i.e., encoding, maintenance and retrieval. Parents and teachers completed questionnaires to evaluate executive, behavioural and social functions.

Results: In our cohort, ~50% experienced general intellectual, academic, executive, social and/or behavioural difficulties and ~20% reached a level comparable to typically developing children. Social risk was found to have an important impact on variability in functional outcomes. Additional brain anomalies or complete AgCC were associated with lower mathematics performance and poorer executive functioning. fMRI findings showed that globally similar brain regions were recruited in the AgCC and the control groups during the WM task, despite significant disparity in brain development, i.e., bilateral occipito-frontal activations during verbal encoding, and bilateral fronto-parietal executive control network during retrieval. However, there were notable differences in activations between groups that might reflect different susceptibility to concurrent tasks during WM, subsequent to different degrees of hemispheric lateralisation during the task.

Conclusion: This work constitutes the first comprehensive report of cognitive, executive, behavioural and social consequences of AgCC in school-age children, and provides a first step towards a better understanding of functional brain networks underlying higher cognitive functions in children with AgCC.

DECLARATION

The following declaration page, signed by the candidate:

This is to certify that:

i. The thesis comprises only my original work towards the PhD except where indicated in the Preface,

ii. Due acknowledgement has been made in the text to all other material used,

iii. The thesis is fewer than 100 000 words in length, exclusive of tables, maps, bibliographies and appendices as approved by the Research Higher Degrees Committee.

PREFACE

Publications

Journal publications (published, under review or in preparation) derived from this thesis and from the larger study are presented below. Publications marked with the star are included as part of this dissertation (*).

Published

Siffredi, V., Anderson, V., Leventer, R., Spencer-Smith, M. M. (2013). Neuropsychological profile of agenesis of the corpus callosum: A systematic review. *Developmental Neuropsychology, 38*(1)*, 36-57.*

*** Siffredi, V.**, Barrouillet, P., Spencer-Smith, M., Vaessen, M., Anderson, V., Vuilleumier, P. (2017). Examining distinct working memory processes in children and adolescents using fMRI: Results and validation of a modified Brown-Peterson paradigm. PLoS One, 12(7), e0179959. doi: 10.1371/journal.pone.0179959.

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In press

*** Siffredi, V.**, Anderson, V., McIlroy, A., Wood, A., Leventer, R., & Spencer-Smith, M. A neurobehavioural profile for agenesis of the corpus callosum? Cognitive, academic, social and behavioural functioning in school-age children. In press in Journal of the International Neuropsychological Society.

In Preparation

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This statement provides explanation of the contribution of all parties involved in the multi-authored paper included as part of this dissertation (*).

Publications and contributions of co-authors:

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Siffredi, V.	Study design, data collection, data analyses, manuscript preparation, editing, submission and revision
Anderson, V.	Study conceptualisation, study design, supervision on data collection, review manuscript, editing
McIlroy, A.	Data collection, review manuscript, editing
Wood, A.	Study conceptualisation, study design, review manuscript, editing
Leventer, R.	Study conceptualisation, review manuscript, editing
Spencer-Smith, M.M.	Study conceptualisation, study design, supervision on data analyses and data collection, review manuscript, editing

Examining distinct working memory processes in children and adolescents using fMRI: results and validation of a modified Brown-Peterson paradigm	
Siffredi, V.	Study conceptualisation, study design, data collection, data analyses, manuscript preparation, editing, submission and revision
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Vaessen, M.	Review manuscript
Anderson, V.	Study conceptualisation, review manuscript, editing
Vuilleumier, P.	Study conceptualisation, study design, supervision on data analyses, review manuscript, editing

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Spencer-Smith, M.M.	Study conceptualisation, study design, review manuscript, editing
Barrouillet, P.	Study conceptualisation, study design, review manuscript, editing
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Leventer, R. J.	Study design, review manuscript, editing
Anderson, V.	Study conceptualisation, review manuscript, editing
Vuilleumier, P.	Study conceptualisation, study design, supervision on data analyses, review manuscript, editing

Talks at scientific conferences

Siffredi, V., Spencer-Smith, M. M., Anderson, V., McIlroy, A., Vaessen, M., Leventer, R., Vuilleumier, P. A brain without corpus callosum: cognitive, structural and functional consequences using a developmental perspective. Organisation for Human Brain Mapping, Alpine Chapter, Salzburg, November 2016.

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Siffredi, V., McIlroy, A., Anderson, V., Wood, A., Leventer, R. J., Spencer-Smith, M. M. Language and communication in children with agenesis of the corpus callosum: cognitive and structural predictors. Federation for European Neuroscience Societies, Milan, Italy, July 2014.

Siffredi, V., McIlroy, A., Anderson, V., Barrouillet, P., Vuilleumier, P., Wood, A., Leventer, R. J., Spencer-Smith, M. M. Investigating the predictive role of working memory for mathematics achievement in children with a developmental absence of the corpus callosum. International Conference on Working Memory, Cambridge, UK, July 2014

Siffredi, V., McIlroy, A., Anderson, V., Wood, A., Leventer, R., Spencer-Smith, M. M. 2014. Language and communication outcomes in children with agenesis of the corpus callosum. 4th UK Paediatric Neuropsychology Symposium, London, UK, May 2014.

Poster presented at local conferences

Siffredi, V., Spencer-Smith, M. M., Vaessen, M. J., Barrouillet, P., Leventer, R. J., Anderson, V., Vuilleumier, P. A working memory fMRI study of agenesis of the corpus callosum. NCCR SYNAPSY Conference, Geneva, April 2016.

Siffredi, V., Spencer-Smith, M. M., Vaessen, M. J., Barrouillet, P., Leventer, R. J., Anderson, V., Vuilleumier, P. Neural correlates of working memory in children with agenesis of the corpus callosum. Research Day: Centre d'imagerie biomedicale and Brain Behavioural Laboratory (CIBM/BBL), Geneva, May 2016.

Siffredi, V., McIlroy, A., Anderson, V., Wood, A., Leventer, R. J., Spencer-Smith, M. M. Language and communication in children with agenesis of the corpus callosum. NNCR Affective Science Annual Forum, Geneva, March 2006.

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ABBREVIATIONS

Corpus Callosum (CC)

Agenesis of the Corpus Callosum (AgCC)

Working Memory (WM)

Typically Developing (TD)

Intellectual Quotient (IQ)

Autistic Spectrum Disorder (ASD)

Attentional Deficit Hyperactivity Disorder (ADHD)

Magnetic Resonance Imaging (MRI)

Functional MRI (fMRI)

Diffusion Tensor MR Imaging (DTI)

Central Nervous System (CNS)

Dorsolateral Prefrontal Cortex (DLPFC)

Ventrolateral Prefrontal Cortex (VLPFC)

Wechsler Intelligence Scale for Children (WISC)

PREAMBLE

With approximately 190 million axon fibres, the corpus callosum (CC) is the largest white matter pathway that connects homologous structures in both hemispheres (Edwards, Sherr, Barkovich, & Richards, 2014). Its main function is not only to coordinate and transfer sensory and motor information between hemispheres, but also to subserve transfer of information for various cognitive functions (Richards, Planchez, & Ren, 2004; Schulte & Müller-Oehring, 2010). Developmental absence of the CC is a congenital brain malformation known as Agenesis of the Corpus Callosum (AgCC) (Francesco, Maria-Edgarda, Giovanni, Dandolo, & Giulio, 2006; Lynn K. Paul et al., 2007; Raybaud, 2010). It results in the complete or partial failure of callosal fibres to cross the midline and form connections in the neocortex between the two cerebral hemispheres (dos Santos et al., 2002). AgCC is one of the most common brain malformation with an estimated prevalence of at least 1 to 7 per 4000 live births (Chiappedi & Bejor, 2010; Glass, Shaw, Ma, & Sherr, 2008; Guillem, Fabre, Cans, Robert-Gnansia, & Jouk, 2003; L. W. Wang, Huang, & Yeh, 2004). Evidence suggests that the timing of the malformation or insult occurring in the CC is a critical factor for compensation by anatomical and functional plasticity, which in turn will impact on neurobehavioural outcomes. Adult patients having undergone a callosotomy (surgical disconnection of the cerebral hemisphere involving cutting fibres of the CC, e.g., to alleviate severe intractable epilepsy) have important impairments in inter-hemispheric integration, affecting motor control, spatial orientation, vision, hearing, and language. This is known as a disconnection or "split-brain" syndrome. In contrast, individuals with AgCC show very little evidence of inter-hemispheric disconnection, and do not present with typical "split-brain" deficits (Jea et al., 2008; Lassonde, 1994). Nevertheless, AgCC can alter neurodevelopment and neurobehavioural functioning, with an impact on general intellectual, academic, executive, social and behavioural abilities in both childhood and adulthood (e.g., Fischer et al., 1992; Moutard et al., 2003; Panos et al., 2001; Paul et al., 2014).

A cognitive function of particular interest is working memory (WM), the ability to simultaneously maintain and manipulate information in mind over a brief period of time for goal-oriented behaviour (Baddeley, 1986; Just & Carpenter, 1992). During childhood, WM is

a major building block for the development of other complex cognitive activities and learning (e.g., reasoning, language), and it is linked to academic performance and achievement (P. J. Anderson, 2008; Barrouillet, Lepine, & Camos, 2008; Gathercole & Pickering, 2000; Gathercole, Pickering, Knight, & Stegmann, 2004; Kyllonen & Christal, 1990). WM is underpinned by a widespread network of interacting brain regions, including prefrontal, anterior cingulate and parietal regions (Klingberg, 2006; Klingberg, Forssberg, & Westerberg, 2002; Spencer-Smith, Ritter, Murner-Lavanchy, et al., 2013). Thus, transfer and integration of information within, but also across the cerebral hemispheres, is inherent to this network (Haxby, Petit, Ungerleider, & Courtney, 2000; Klingberg, 2006; Klingberg et al., 2002; Klingberg, O'Sullivan, & Roland, 1997). In typically developing individuals, efficient WM is therefore likely to engage interhemispheric connectivity through the CC (Richards et al., 2004).

Despite the importance of the CC for WM and the crucial role of WM for the development of other cognitive functions, the impact of AgCC on WM during childhood has not been explored, and clinical case studies in adults are contradictory. Similarly, other neurobehavioural outcomes in the AgCC population are not well understood, especially in children, partly due to the small sample size and important heterogeneity of this population, but also limitations in the current literature, such as a lack of information about individual's medical details and a lack of strict recruitment procedure. Finally, the functional brain organisation of cognitive functions in the absence of CC is poorly understood, and the neural network underpinning WM in individuals with AgCC has never been investigated, be they children or adults.

The aim of this thesis is to investigate neurobehavioural outcomes in a large cohort of children and adolescents with AgCC, in particular WM abilities and its functional brain organisation. The first part of this manuscript presents the theoretical framework motivating this work. The two central concepts, namely Agenesis of the Corpus Callosum (Chapter 1) and working memory (Chapter 2), are introduced using a developmental perspective. In the first chapter, the neuroanatomical characteristics and normal development of the CC are described. We continue with an introduction of the developmental absence of the CC, and review existing literature on cognitive outcomes and neuroimaging findings in individuals with AgCC. The second chapter is dedicated to WM, its models, paradigms, and neural underpinnings, while also providing an integrative view of what we know about AgCC onto

WM. This is followed by a presentation of the thesis objectives (Chapter 3) and a description of the methods used (Chapter 4). Chapters 5 to 7 are dedicated to each of the different studies completed as part of this thesis. Specifically, Chapter 5 reports neurobehavioural outcomes in our cohort of school-age children with AgCC, including intellectual, academic, executive, social, behavioural, as well as WM abilities. Chapter 6 describes an fMRI study completed in typically developing children to validate a novel WM paradigm created to be applicable in both typical and clinical paediatric populations within a large age range. Chapter 7 reports functional brain organisation of WM in children with AgCC compared with a typically developing control group using the same fMRI WM paradigm. Finally, a general discussion is proposed (Chapter 8), including a summary of the results, potential implications and limitations of the study, as well as future directions.

CHAPTER 1: Agenesis of the Corpus Callosum

1.1. The Corpus Callosum

Introduction

Cerebral commissures are bundles of nerve fibres that cross the midline of the human brain at the level of their origin. A total of five cerebral commissures potentially implicated in cognitive activities compose the human brain: the corpus callosum (CC), the anterior, hippocampal, posterior, and habenular commissures (Palmer & Mowat, 2014). The CC is the largest cerebral commissure in the brain and a major white matter pathway that connects homologous structures on both sides of the central nervous system (CNS; Paul et al., 2007; Pisani, Bianchi, Piantelli, Gramellini, & Bevilacqua, 2006; Raybaud, 2010) . It extends from the frontal lobe anteriorly to above the collicular plate posteriorly. Its main cognitive function is to coordinate and transfer information between the left and right hemispheres (Richards et al., 2004). It is implicated in interhemispheric communication for sensory, motor, visuo-motor integration, low-level and higher cognitive functions (Schulte & Müller-Oehring, 2010). Interestingly, the CC is unique to placental mammals (Paul, 2011). In addition to the CC, the anterior commissure and the hippocampal commissure are the two other major commissures in the human brain (Castellani, 2013). The anterior commissure interconnects the two temporal lobes; whereas the hippocampal commissure interconnects the left and right hippocampus (Castellani, 2013). Smaller commissures are the posterior commissure, which interconnects nuclei of the diencephalon; and the habenular commissure, in front of the pineal gland that connects the habenular nuclei on both sides of the diencephalon.

The role of these small commissures in cognitive activities is poorly understood. In addition to commissures implicated in cognition, four other commissures are purely implicated in sensory and motor processes including: a) visual fibres arising from each eye crossing the midline ventrally at the optic chiasm; b) auditory fibres arising from each hear crossing the midline at the level of the pons; c) voluntary movement and fine motricity fibres descend ventrally from the cerebral cortex and cross the midline at the medulla/spinal cord boundary;

and d) fibres implicated in coordination of left/right motor behaviours such as alternate and synchronized activities, require spinal commissural projections (Castellani, 2013).

According to Chiarello (1980), the CC is not a single body but a complex bundle of fibres with distinct components that act separately. It has also been suggested that the CC is not a passive conduit of information transfer, but rather an active body that helps for certain computationally demanding tasks in collaboration with hemispheres (Banich, 1995; Bloom & Hynd, 2005). As an illustration, emerging evidence suggests that increased callosal thickness in typical brain development correlates with intelligence (Hutchinson et al., 2009; Luders et al., 2007) and problem solving abilities (van Eimeren, Niogi, McCandliss, Holloway, & Ansari, 2008). Subtle structural changes and alterations in the CC are also frequently noted in various neurodevelopmental and psychiatric disorders, such as autistic spectrum disorder (ASD; Barnea-Goraly et al., 2004; Hardan et al., 2009) , attention deficit hyperactivity disorder (ADHD; Hynd et al., 1991; Lyoo et al., 1996) , schizophrenia (Swayze et al., 1990), mental retardation (Schaefer & Bodensteiner, 1999), developmental dyslexia (Hynd et al., 1995) and developmental language disorders (Preis, Steinmetz, Knorr, & Jancke, 2000). The wide range of disorders in which callosal abnormalities are found highlights the importance of understanding the nature of the development and function of the CC.

Structure of the corpus callosum

Fully mature, the CC is crescent-shaped and about 10 cm long (Goodyear, Bannister, Russell, & Rimmer, 2001) with approximately 190 million axon fibres (Edwards et al., 2014). The CC is topographically organized along the anteroposterior axis (Hofer & Frahm, 2006; Hofer, Merboldt, Tammer, & Frahm, 2008), such that white matter fibres passing through the CC are homotopically linked to homologous cortical regions in the left and right hemispheres. Large connections between non-homologous cortical regions, i.e., heterotopic connections, have not been observed in typically developing brains using diffusion tensor imaging (DTI; Hofer & Frahm, 2006) . In 1989, a review of experimental work with monkeys and clinical research in humans led Witelson to divide the CC into seven areas (respectively in an anterior-posterior description; Figure 1): 1) rostrum, 2) genu, 3) anterior part of the body, 4) anterior part of the midbody, 5) posterior part of the midbody, 6) posterior part of the body or isthmus, 7) splenium.

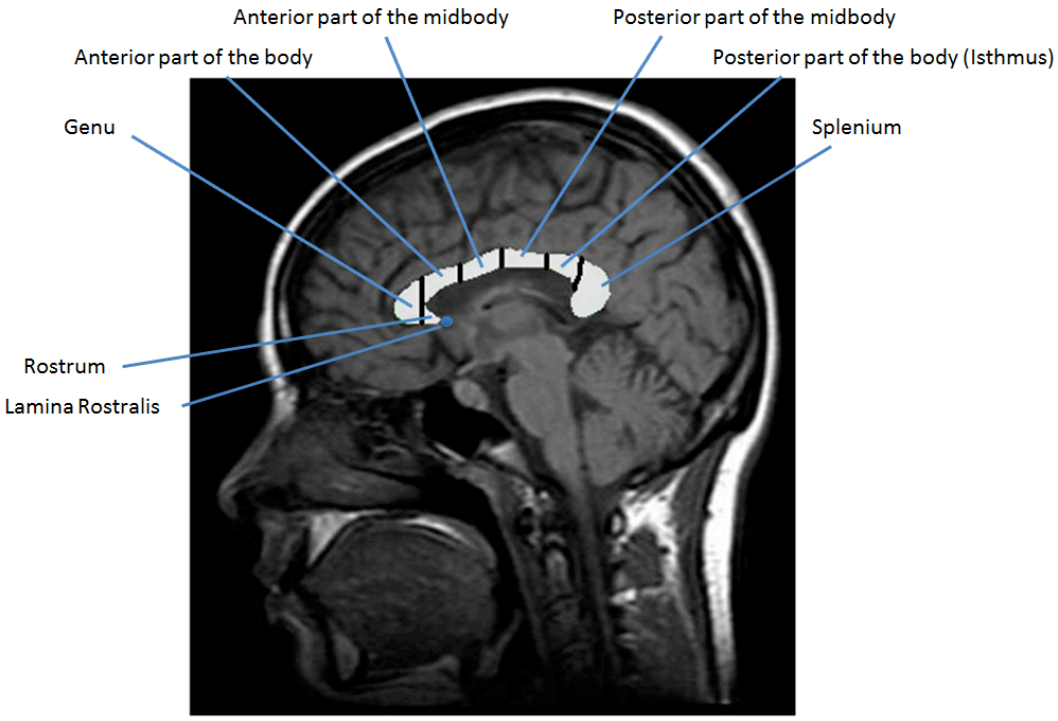

Figure 1. Witelson division of the CC (adapted from Witelson, 1989; p. 805).

Recent neuroimaging findings show that these seven different regions of the CC reflect the trajectories of neuronal fibres into subcortical nuclei and cerebral lobes (Figure 2; Abe et al., 2004; Cascio et al., 2006; Hannay, 2000; Hasan et al., 2009; Hofer & Frahm, 2006; Klaas, Hannay, Caroselli, & Fletcher, 1999; Lebel, Caverhill-Godkewitsch, & Beaulieu, 2010; Park et al., 2008). Fibres from the precentral gyrus, the orbitofrontal area, the gyrus rectus, and the inferior frontal gyrus (which corresponds to part of Broca's area) are believed to traverse the rostrum (region 1). Fibres from the anterior frontal cortices including prefrontal fibres (rostral tip of the cingulate sulcus, Brodmann's areas 25, 32 and 46) have being identified in the genu (region 2). The body has been divided into several sections. The anterior body (region 3) and anterior midbody (region 4) contains fibres from the superior frontal cortices including fibres from Brodmann's area 8 in the concavity of the arcuate sulcus (region 3) and fibres that cross from the motor cortex (region 4). The superior and posterior parietal and temporal cortices project through the posterior part of the midbody (region 5), including fibres associated with somesthetic functions (i.e., touch, somatic sensations). The most posterior part of the body known as the isthmus (region 6) also holds fibres from the posterior parietal cortex and those from the superior temporal cortex. Finally, the splenium (region 7) contains fibres crossing

from the occipital cortex (i.e., Brodmann's areas 18 and 19), and those from the inferior temporal cortex.

Additionally, this anterior-to-posterior organisation results in modality-specific regions. The rostrum appears to be implicated in transfer of higher cognitive functions. The anterior midbody transfers motor information and the posterior midbody transfers somatosensory information. Finally, the posterior part of the body (isthmus) transfers auditory information. Because of this topographic organisation, lesions of specific callosal regions result in predictable deficits in interhemispheric transfer of information (Funnell, Corballis, & Gazzaniga, 2000).

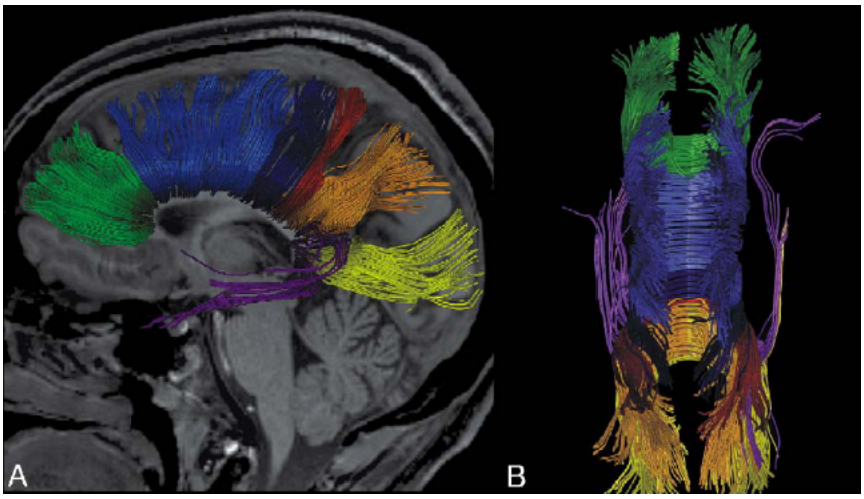

Figure 2. Sagittal (A) and top (B) views of a 3D reconstruction of all callosal fibres using DTI techniques. Bundles projecting into the prefrontal lobe (green), premotor and supplementary motor areas (light blue), primary motor cortex (dark blue), primary sensory cortex (red), parietal lobe (orange), occipital lobe (yellow), and temporal lobe (violet; reproduced from Hofer & Frahm, 2006; p 991).

Even if the majority of the callosal fibres are excitatory, there is evidence that callosal connections play both an excitatory and inhibitory function in interhemispheric communication (Bloom & Hynd, 2005; van der Knaap & van der Ham, 2011). Functional inhibition or excitation may occur at different times depending on the task or may even occur simultaneously. In addition, it is likely that the CC is involved in the development of lateralization of function and hemispheric asymmetry (Bloom & Hynd, 2005).

Development of the corpus callosum

In normal brain development, formation of the CC is a complex process. In 1968, Rakic and Yakovlev described a unique anatomical region within the brain of many mammalian species, called the commissural plate, where all telencephalic commissures initially cross the interhemispheric midline. These authors proposed that the human commissural plate can be anatomically subdivided into the massa commissuralis through which the CC and hippocampal commissure cross, and the area septalis through which the anterior commissure crosses the midline (Rakic & Yakovlev, 1968).

For many years, the prevalent theory of callosal development suggested that the CC develops in an anterior-posterior direction (Barkovich & Kjos, 1988; Byrd, Harwood-Nash, & Fitz, 1978). According to this theory, the first callosal axons cross the midline at the posterior portion of the genu. The anterior body forms second, followed by the posterior body and the splenium. Because the posterior growth occurs more rapidly than the anterior growth, the rostrum is the last part to form.

More recently, neuroimaging studies of human embryology and animal models indicated different and more detailed findings (Edwards et al., 2014). At 11-12 weeks of gestation, the first fibres cross the midline through the massa commissuralis to form the CC (Richards et al., 2004; Schell-Apacik et al., 2008). Molecules secreted by midline glial populations attracting and repelling axons have been involved in the formation of the CC by allowing axon tracts to cross the midline (Shen, Plachez, Mongi, & Richards, 2006). Neuroimaging studies of human embryology indicate that the first regions to form are the anterior body and the lamina rostralis crossing directly over the hippocampal commissure (Barkovich & Kjos, 1988; Barkovich, Lyon, & Evrard, 1992; Kier & Truwit, 1996; Paul, 2011; Rakic & Yakovlev, 1968; Richards et al., 2004). From 15 gestational weeks, the body extends bi-directionally, with more prominent anterior growth (Huang et al., 2009; Keshavana et al., 2002; Lindwall, Fothergill, & Richards, 2007; Paul, 2011; Richards et al., 2004). From 18 gestational weeks, the splenium is the last to develop (Lindwall et al., 2007). The early extension of the frontal cortex results in the posterior displacement of the hippocampal commissure together with the associated callosal splenium, while the anterior section of the CC expands (Edwards et al., 2014). By 20 gestational weeks, the CC has reached its final shape.

Callosal development involves exuberant axon growth followed by a period of synaptic pruning that extends from late in gestation through the first 2 postnatal months (Innocenti &

Price, 2005). Postnatal callosal development also involves an increase in callosal fibre direction and in external axonal structures, such as myelinisation visible in neuroimaging by 4 months. The most significant increase in external axonal structures appears between 13 and 18 months of age (Giedd, Blumenthal, Jeffries, Rajapakse, et al., 1999; Giedd et al., 1996; Pujol, Vendrell, Junque, Marti-Vilalta, & Capdevila, 1993; Rauch & Jinkins, 1994; Yakovlev & Lecours, 1967). The CC reaches a size comparable to adults at 1 to 2 year-old (Giedd, Blumenthal, Jeffries, Rajapakse, et al., 1999; Giedd et al., 1996; Pujol et al., 1993; Rauch & Jinkins, 1994). By 11 year-old, the CC has reached 90% of its maximum fibre directionality; and at 20 year-old, it has 90% of their maximum external axonal structures (Lebel et al., 2010). Thereby, the CC is among the last structures to complete postnatal maturation with myelination finally completed during early adulthood (Giedd et al., 1996; Pujol et al., 1993).

1.2. Agenesis of the Corpus Callosum

"It is reasonable to suppose that the CC has enabled the development of the many specialized systems. Therefore, disconnection of the cerebral hemispheres allows a unique cognitive state: it turns a unified perceptual system into two simpler perceptual systems that do not interact and therefore do not interfere with each other" (Gazzaniga, 2000; p.123).

Introduction

Agenesis of the corpus callosum (AgCC) is a congenital brain malformation that results in the complete or partial failure of callosal fibres to cross the midline and form connections in the neocortex between the two cerebral hemispheres (Figure 3; dos Santos et al., 2002) . In 1812, Reil made the first description of AgCC in the human brain (Reil, 1812). AgCC is of particular interest because it is among the most common brain malformations observed in humans (Dobyns, 1996).

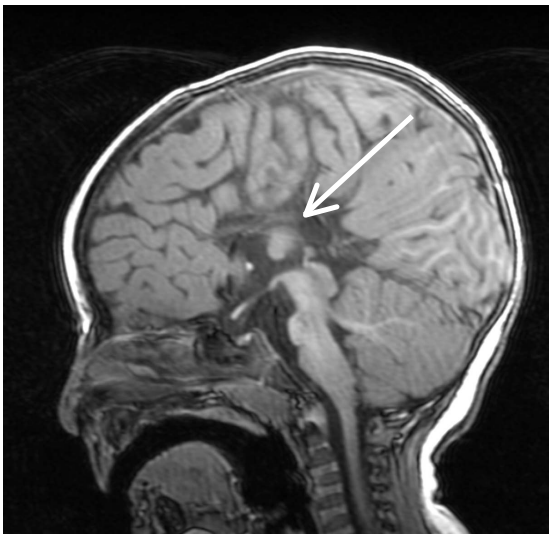

Figure 3. T1-weighted mid-sagittal MRI showing complete AgCC (arrow). Image taken from the AgCC Study of the Murdoch Children's Research Institute. As with most other cases of AgCC there is absence of the cingulate gyrus. This patient also has a hypoplastic pons (reproduced from Siffredi et al., 2013; p. 37).

Diagnosis of AgCC can be made prenatally by ultrasonography based on the visualization of characteristic changes of the cerebral hemispheres and ventricles, including the absence of the cavum septum pellucidum, colpocephaly, high-riding third ventricle, and widening of the interhemispheric fissure (visualization of the CC on ultrasound; Figure 4).

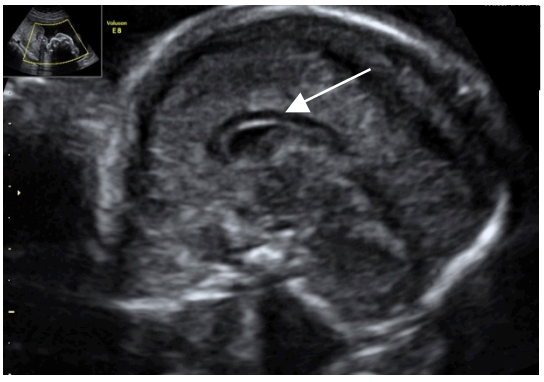

Figure 4. Visualisation of the CC on ultrasound during the 21st gestational week.

Postnatal diagnosis of AgCC is based on neuroimaging, especially magnetic resonance imaging (MRI; Pisani et al., 2006; Tang et al., 2009) . Its incidence varies as a function of both diagnostic techniques and sample populations (Chiappedi & Bejor, 2010). The rapid

advances in neuroimaging (such as stronger magnets) and its growing use in paediatric populations (including ultrasound) have resulted in an increase in the detection of patients with AgCC during foetal life and in individuals with more subtle CC anomalies (Moutard et al., 2003; Pisani et al., 2006). Ruland and colleagues (2015) found an important rise in prenatal diagnosis of CC anomalies, including AgCC, with the number of CC anomalies diagnosed multiply by three between 1999-2004 and 2009-2012. In the general population, the estimated prevalence of AgCC is at least 1 to 7 per 4000 live births (Chiappedi & Bejor, 2010; Glass et al., 2008; Guillem et al., 2003; L. W. Wang et al., 2004), while in children with developmental disabilities it is 2 to 3 per 100 (Grogono, 1968). Until recently, AgCC was most often diagnosed following a scan requested because of identified developmental delays, seizures, or known genetic syndrome. In some cases, AgCC may also be an incidental finding for an individual in whom neurological difficulties have not been suspected (e.g., following a scan after possible head injury or headache). Therefore, it is possible that current studies of AgCC are biased toward individuals with sufficient clinical need for a scan to be requested.

Heterogeneity in agenesis of the corpus callosum

Studies examining AgCC highlight that this population is heterogeneous not only in terms of CNS properties but also in terms of neuroimaging profiles, neuropsychological difficulties and clinical sequelae (Bedeschi et al., 2006; Hanna et al., 2011; Moutard et al., 2003; Shevell, 2002; Siffredi et al., 2013).

AgCC can be complete or partial (Figure 5). Complete AgCC is indicative of disruption in early embryological development and two types can be distinguished morphologically. In the first type of complete AgCC, the commissural axons fail to form (Schell-Apacik et al., 2008). In the second type of complete AgCC, axons form but are unable to cross the midline; they consecutively form large aberrant fibre bundles known as Probst bundles along the medial hemispheric walls. Probst (1901) was the first to describe these aberrant intrahemispheric longitudinal bundles of fibres (misrouted callosal fibres; Probst, 1901) . In partial AgCC, disruption in callosal development occurs slightly later in gestation so that a portion of the CC develops but the remainder does not (Huang et al., 2009; Paul, 2011; Richards et al., 2004). Knowledge of developmental processes involved in the formation of the CC could help in the differentiation between developmental damage and acquired damage (destruction) of the CC. In the case of partial AgCC due to developmental damage, it is usually the posterior portion of

the CC that is affected, including posterior body and the splenium (Barkovich, 2000). Destruction of other part of the CC is usually considered as possible sequelae of acquired damage (e.g. hypoxic ischemic injury). However, a simple model of arrested callosal development may not be sufficient to explain the complex pattern of connectivity and intra-individual variability apparent in partial AgCC (Kasprian et al., 2013; Wahl et al., 2009).

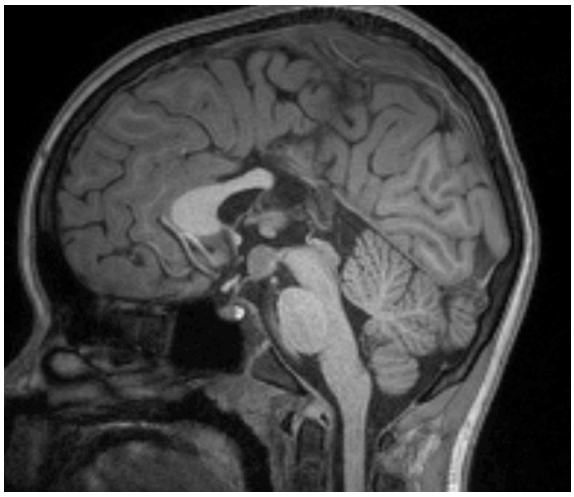

Figure 5. T1-weighted mid-sagittal magnetic resonance imaging showing partial AgCC. Image taken from the AgCC Study of the Murdoch Children's Research Institute.

Adding more complexity, AgCC may occur as an isolated condition or associated with other clinical conditions. In the case of an isolated condition (isolated AgCC), the CC appears to be the only structure directly affected. In these cases of 'primary AgCC', common concomitant anatomical changes due to the absence (complete or partial) of the CC are Probst bundles, cingulate gyrus alteration and colpocephaly (Booth, Wallace, & Happe, 2011; Lee, Kim, Cho, & Lee, 2004; Paul, 2011; Paul et al., 2007). Colpocephaly refers to the dilatation of the posterior aspect of the lateral ventricles, frequently including the temporal horns. Colpocephaly occurs because of the absence of structural support typically provided by this large white matter tract. It does not correspond to hydrocephalus (Baker & Barkovich, 1992), but may appear with a reduction of ipsilateral cortical association tracts (Mori, 1992).

Moreover, AgCC can be associated with a wide range of conditions including CNS anomalies (e.g., hydrocephalus, interhemispheric cyst, gyral abnormalities, alteration in anterior commissure size; Gupta & Lilford, 1995). Of note, it seems that complete AgCC with associated CNS abnormalities is more frequent than complete AgCC without associated CNS abnormalities (Neal, Filippi, & Mayeux, 2015). Additionally, AgCC can also be associated with neurological conditions, such as epilepsy, macro or microcephaly, hearing and vision

impairments (Gupta & Lilford, 1995; Kamnasaran, 2005; Paul et al., 2007; D'Antonio et al., 2016), extra-cerebral malformations (e.g., eyes, kidney, heart), viral infection (e.g., rubella, influenza), toxic syndrome (e.g., foetal alcohol syndrome), and metabolic diseases (e.g., nonketotic hyperglycinemia; Hetts, Sherr, Chao, Gobuty, & Barkovich, 2006; Moutard et al., 2003) . In addition, various genetic conditions are associated with AgCC (see section below, Aetiology of AgCC).

Consistent with the variability in presentation of this brain malformation, cognitive difficulties observed in the AgCC population range from mild, with many individuals attending mainstream school and having a conventional career (Caillé et al., 1999), to severe, with individuals attending special developmental school and requiring assistance in daily living activities (D'Antonio et al., 2016; Graham et al., 2008; Graham et al., 2003). Several studies report that isolated and primary AgCC appears to carry the best prognosis with up to 85% chance of a normal outcome (Blum, André, Droullé, Husson, & Leheup, 1990; Pilu et al., 1993; Vergani et al., 1994). The comparison between complete and partial AgCC reveals conflicting data, and no clear conclusions have been drawn to date (Moutard et al., 2003; Paul et al., 2007). These various anatomical differences could explain partly the cognitive and behavioural heterogeneity within the AgCC population. In addition, the underlying disruptions in brain development and cerebral connectivity that lead to AgCC may also alter intrahemispheric connectivity. Therefore, it is possible that AgCC individuals have additional cognitive deficits that are caused by impairment of intrahemispheric connectivity (Hinkley et al., 2012). A review of the literature with detailed neuropsychological outcomes in individuals with AgCC is presented later in this Chapter.

Aetiology of agenesis of the corpus callosum

Cross-sectional cohort studies report that 50 to 70 % of cases with AgCC do not have an identified cause (Bedeschi et al., 2006; Chiappedi & Bejor, 2010; Schell-Apacik et al., 2008). Identified causes of AgCC include: environmental factors, metabolic factors and genetic factors.

Environmental factors include maternal alcohol use during pregnancy (Sowell, Mattson, et al., 2001), antenatal infections such as cytomegalovirus, toxoplasmosis, rubella and influenza (Palmer & Mowat, 2014), maternal phenylketonuria (Levy, Lobbregt, Barnes, & Poussaint,

1996) or maternal vascular or hypoxic insults (Palmer & Mowat, 2014). Of note, the prevalence of AgCC in children with foetal alcohol syndrome is almost 7% (Roebuck, Mattson, & Riley, 1998).

In addition to environmental factors, AgCC may result from metabolic factors, such as neonatal adrenoleucodystrophy, pyruvate dehydrogenase deficiency, fumarase deficiency or Smith-Lemli-Opitz syndrome (Palmer & Mowat, 2014).

It is finally recognised that genetic factors contribute to AgCC in the vast majority of cases (Bedeschi et al., 2006; Dobyns, 1996; Edwards et al., 2014; Paul et al., 2007; M. Taylor & David, 1998). The apparently sporadic nature of AgCC makes genetic studies difficult (Schell-Apacik et al., 2008; Sherr et al., 2005). Only 30 to 45 % of cases with AgCC have an identifiable genetic cause. Various recognised genetic conditions are systematically associated with AgCC, such as Aicardi syndrome; see Table 1 for a list of genetic conditions systematically associated with AgCC (Siffredi et al., 2013).

Table 1. Genetic conditions systematically related to AgCC, based on the POSSUM Library (reproduced from Siffredi et al., 2013; p. 40).

Recognised syndromes
Acrocallosal syndrome
Aicardi syndrome
Braddock-Carey syndrome
Curatolo-Pessagno syndrome
Curry-Jones syndrome
Da-Silva syndrome
Fetal akinesia syndrome, X-linked
FG syndrome
Fine-Lubinsky syndrome
Lin-Gettig syndrome
MASA syndrome (Mental retardation, Aphasia, Shuffling gait, Adductus thumbs)
Say-Poznanski syndrome
Toriello-Carey syndrome
Warburg micro syndrome

Combined congenital conditions
Agenesis corpus callosum, cataract, immunodeficiency
Agenesis of corpus callosum, camptodactyly, obesity
Agenesis of corpus callosum, colobomata, facial dysmorphism
Agenesis of corpus callosum, mental retardation, osseous lesions
Agenesis of corpus callosum, pyloric stenosis, Hirschsprung
Agenesis of corpus callosum, sensorimotor neuropathy
Agenesis of the corpus callosum
Congenital bowing, camptodactyly, talipes, agenesis of the corpus callosum
Congenital lymphedema, agenesis of corpus callosum
Craniotelencephalic dysplasia
Dysgenesis corpus callosum, microcephaly, mental retardation
Endocrine-cerebroosteodysplasia
Focal dermal hypoplasia, morning glory anomaly, Polymicrogyria
Frontofacial dysostosis, alopecia, hypogonadism
Left ventricular noncompaction, partial agenesis of corpus callosum, developmental delay
Lethal skeletal dysplasia, Sharony-Borochowitz type
Neuronal migration disorder, agenesis of corpus callosum, 'morning glory' anomaly
Phalangeal hypoplasia, mental retardation, agenesis of corpus callosum, brain stem anomalies, ectopic grey matter
Poly/asplenia, agenesis of corpus callosum, caudal deficiency
Sakoda complex, anophthalmia/microphthalmia, cortical dysgenesis
Severe 1st arch defect, bony fusion, brain defect
X-linked lissencephaly
X-linked lissencephaly, ambiguous genitalia
X-linked M.R. (mental retardation), agenesis of corpus callosum, urogenital anomalies
X-linked mental retardation, agenesis of the corpus callosum, coloboma, micrognathia

Single-gene abnormalities (as a result of a single mutated gene), including autosomal-dominant, autosomal-recessive and X-linked inheritance causes of AgCC have been described (Edwards et al., 2014; Palmer & Mowat, 2014). Of the 30 to 45% of identified genetic causes,

20 to 35% are caused by single-gene abnormality (Bedeschi et al., 2006; Schell-Apacik et al., 2008). However, for a significant number of individuals with AgCC no inheritance pattern is found, which has led geneticists to hypothesize that AgCC may be caused for number of cases by de novo genetic changes (Sherr et al., 2005). In addition to single-gene forms, chromosomal abnormalities are reported in the literature (result of one or more chromosomes, or large segments of them, missing, duplicated, or otherwise altered; D'Antonio et al., 2016). This includes trisomies (18, 13, mosaic 8) and karyotypically visible rearrangements and submiscroscopic copy number variants (Glass et al., 2008; Palmer & Mowat, 2014; Sajan et al., 2013) . In fact, improvements of molecular and cytogenetic technology, especially microarray comparative genomic hybridization have led to a rapid increase in the use and identification of multiple rare copy-number variations. O'Driscoll and colleagues (2010) used a genotype-to-phenotype diagnostic approach from 374 patients with AgCC and structural chromosome rearrangements from the Californian Birth Defects Monitoring Program. They identified 12 genomic loci consistently associated with AgCC and at least 30 other recurrent loci that may also contain genes that cause or contribute to this condition. Two of the most notable copy number variants associated with AgCC were rearrangements of 8p and a deletion at 1q4 (Palmer & Mowat, 2014). Firstly, rearrangements (deletion or duplication) of 8p were found in 59 out of 374 individuals with AgCC. Secondly, deletion (or a translocation breakpoint) at 1q4 was found in 35 patients with AgCC. These findings also supported several AgCC causative loci in the regions 1q42, q43, and q44.

Finally, the genetic aetiology of AgCC might be, for many individuals, polygenic and/or other reflect complex interactions (Paul et al., 2007). For instance, genetic conditions associated with AgCC can be classified by the stage in development that is primarily affected: disorders of neuronal and/or glial proliferation, neuronal migration and/or specification, midline patterning, axonal growth and/or guidance, and post-guidance development (Edwards et al., 2014).

Candidate for compensatory mechanisms in agenesis of the corpus callosum

The importance of developmental neural plasticity is evident when comparing individuals with developmental absence of the CC present at birth to individuals with acquired absence of the CC during adulthood. Traditionally, patients having undergone a corpus callosotomy (surgical disconnection of the cerebral hemisphere consisting "to cut" the fibres of the CC to address severe intractable epilepsy, also called "split-brain" patients) present impairment in

interhemispheric integration affecting motor control, spatial orientation, vision, hearing, and language. In contrast, individuals with AgCC show very little evidence of interhemispheric disconnection, and do not present these typical disconnection deficits (Jea et al., 2008; Lassonde, 1994; Lassonde & Jeeves, 1994). This suggests that the timing of the insult or the malformation is one critical factor for anatomical and/or functional plasticity in determining neuropsychological outcomes. Brain plasticity is an intrinsic property of the CNS, reflecting the capacity to modify its structure and networks to respond in a dynamic manner to the environment and experience. This phenomenon is linked to processes of brain development and functions across the lifespan (V. Anderson, Spencer-Smith, & Wood, 2011). Indeed, clinicopathological observations suggest that the immature brain is capable of major structural and functional reorganisation (Tovar-Moll et al., 2007). After insult or malformation in the immature brain, neural and functional plasticity as well as developmental processes coexist and contribute to long-term functional outcome (V. Anderson et al., 2011; Spencer-Smith & Anderson, 2011). As the CC is the major commissural fibre bundle in the human brain, studying AgCC provides a unique window to understand brain plasticity. A number of potential candidates for compensatory mechanisms in AgCC have been suggested.

Firstly, enlargement (hyperplasia) of the anterior commissure is relatively common in AgCC and was proposed as a compensatory mechanism in individuals with this brain malformation (Figure 6; W. S. Brown, Jeeves, Dietrich, & Burnison, 1999; Fischer, Ryan, & Dobyns, 1992; Hannay, Dennis, Kramer, Blaser, & Fletcher, 2009; Paul et al., 2007) . Enlargement of the anterior commissure was found in about 10% of individuals with AgCC, and it was absent in 60% (Loeser & Alvord, 1968). A recent study found that the anterior commissure was enlarged in 7%, small in 25%, and absent in about 33% of the cases (Hetts et al., 2006). In the case of complete AgCC, it has been suggested that the fibres of the anterior commissure might connect visual and auditory cortices instead of the posterior body and splenium (Barr & Corballis, 2002; Fischer et al., 1992). Fischer and colleagues (1992) investigated visual, auditory and tactile interhemispheric transfer in two 8-year-old boys with complete AgCC. Patient 1 showed complete absence of anterior commissure, whereas Patient 2 showed enlargement of this same structure. The results showed degradation in transfer of visual information to the left hemisphere in Patient 1, but no degradation of auditory and tactile interhemispheric transfer. Results for the visual, auditory and tactile interhemispheric transfer tasks were normal in Patient 2. Similarly, Barr and Corbalis (2002) tested interhemispheric visual integration in two individuals with AgCC. The patient whose anterior commissure was

within normal limits was much worse at the interhemispheric visual integration task than the other patient, whose anterior commissure was greatly enlarged, who showed no evidence of interhemispheric disconnection. These findings suggest that the intactness of the anterior commissure is an important mechanism of functional compensation in AgCC, however, other mechanisms might play a role.

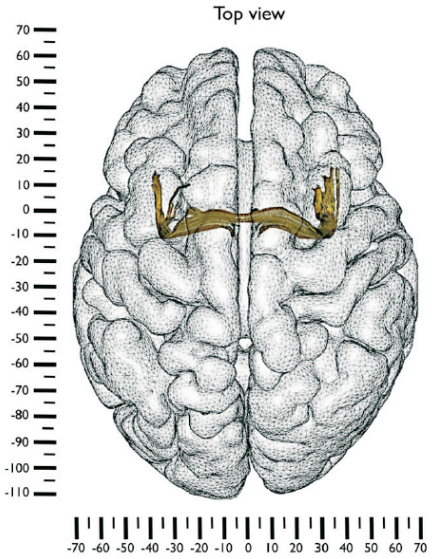

Figure 6. Fibres of the anterior commissure (reproduced from Catani & Thiebaut de Schotten, 2008; p. 1118) . The anterior commissure connects the anterior and temporal lobes, including the amygdala (Catani & Thiebaut de Schotten, 2008). It extends from one hemisphere to the other and is located at the base of the fornix (Paul et al., 2007; Raybaud, 2010). It contains approximately 50000 axons in humans and there is evidence that its average area is approximately 1% that of the CC (Foxman, Oppenheim, Petito, & Gazzaniga, 1986; Paul et al., 2007).

Secondly, enlargement of the hippocampal commissure might also be an indicator of CC fibres using the hippocampal commissure as an alternative interhemispheric conduit (Hannay et al., 2009). A recent study of prenatal ultrasound in 41 foetuses with complete AgCC between 19 and 30 weeks of gestation found that hippocampal commissure was visible in 66% of cases and absent or not clearly recognizable in the remaining 34% (Contro et al., 2015). The hippocampal commissure is part of the fornix and, in typically developing brain, crosses the midline under the caudal body and rostal splenium of the CC, and connects the hippocampi (Raybaud, 2010). However, the hippocampal commissure is quite small usually difficult to visualize on MRI (Rauch & Jinkins, 1994). As the hippocampal commissure

carries fibres from the hippocampus and not from the neocortical areas of the brain like the CC, Rauch and Jinkins (1994) considered that it is unlikely that the hippocampal commissure might be enlarged by aberrant CC fibres. Also, as noted by Barkovich (2000), an enlarged hippocampal commissure may be mistaken for the splenium of the CC in humans on a sagittal view, but can be seen to connect the fornices on the coronal view. However, the association between structural properties of the hippocampal commissure and functional outcomes have never been investigated so far.

Thirdly, and mentioned previously, Probst bundles were first described by Probst (1901; Figure 7). These longitudinal bundles of Probst are thought to contain fibres intended for the CC or the misrouted callosal axons that run parallel to the interhemispheric fissure (Paul et al., 2007). They have been reported in cases of complete and partial AgCC (Barkovich, 1996; Barkovich & Kjos, 1988; Edwards et al., 2014; Pirola et al., 1998; Rakic & Yakovlev, 1968). In the study of Loeser and Alvord (1968), Probst bundles were present on both sides in 60% of 10 autopsy cases of complete AgCC. Recent DTI studies also showed high percentages of presence of Probst bundles in individuals with complete and partial AgCC: from 100% (in 11 individuals with complete and partial AgCC) to 90% (in 20 complete and partial acallosal foetus; Kasprian et al., 2013; J. P. Owen, Li, Ziv, et al., 2013; Tovar-Moll et al., 2007) . Of particular interest is the so-called 'sigmoid bundle', an heterotopic commissural tract within the Probst bundles, that appears to connect the frontal lobe with the contralateral occipito-parietal cortex (Figure 8; Edwards et al., 2014; Paul et al., 2007) . Whereas the Probst bundles are topographically organized and have an ipsilateral U-connectivity, the sigmoid bundle is a long, heterotopic commissural tract (J. P. Owen, Li, Ziv, et al., 2013). The sigmoid bundle has been identified in partial AgCC only, and might potentially represent a pathologic plasticity, which conserves a topographical organisation confined to the ipsilateral cortex (Tovar-Moll et al., 2007; Wahl et al., 2009). The Probst and sigmoid bundles have been posited to be anatomical structures that aid in intra and interhemispheric transfer during cognition, although this has yet to be shown (Lassonde, Sauerwein, Chicoine, & Geoffroy, 1991; Lessard, Lepore, Villemagne, & Lassonde, 2002). Moreover, the association the presence of the Probst or sigmoid bundles and functional outcomes have never been investigated so far.

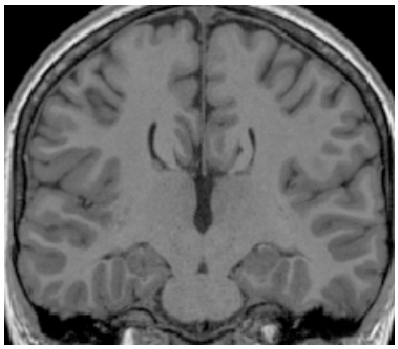

Figure 7. Coronal T1-weighted MRI presenting complete AgCC. The lateral ventricles form a bull's-horn appearance and are indented medially by the Probst bundles (arrows). Image taken from the AgCC Study of the Murdoch Children's Research Institute.

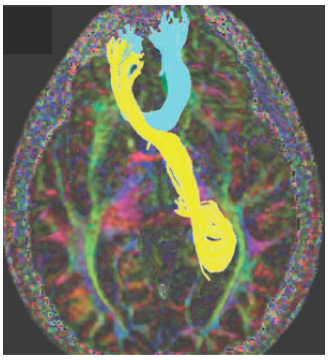

Figure 8. Diffusion tensor imaging tractography of an individual with partial AgCC. In yellow, the sigmoid bundles (reproduced from Wahl et al., 2009; p. 286).

Fourthly, strengthening of the ipsilateral and/or subcortical pathways has been suggested as a compensatory mechanism (Risse, LeDoux, Springer, Wilson, & Gazzaniga, 1978). There is some evidence of subcortical transfer from callosotomy studies (Funnell et al., 2000; Gazzaniga, Holtzman, & Smylie, 1987; Gazzaniga, Kutas, Vanpetten, & Fendrich, 1989), but this has never been investigated in individuals with AgCC.

Finally, the degree of intactness of the CC in AgCC has also been proposed as a compensatory mechanism. In comparison to complete AgCC, partial AgCC allows white matter fibres to cross the midline, and therefore an increased number of interhemispheric functional connections might be present (Huber-Okrainec, Blaser, & Dennis, 2005).

Of note, the posterior commissure is an exclusively subcortical, mesodiencephalic bundle that makes direct connections with the nucleus of Darkschewitsch and the red nucleus, as well as

with the habenular nuclei (Keene, 1938). The posterior commissure has never been considered as a potential pathway in the AgCC literature.

1.3. Neuropsychological Outcomes in Agenesis of the Corpus Callosum

A recent systematic review explored neuropsychological outcomes of AgCC in children and adults (Siffredi et al., 2013). Our study constitutes the first step in understanding functional outcomes in individuals with AgCC. We also highlighted number of limitations in the AgCC literature, including small sample sizes (64% of articles included in this review counted three or fewer participants), the lack of important medical and neurological details, and the lack of essential methodological information reported (e.g. recruitment procedure, age of participants). Results of previous research are presented below, including the results from the systematic review of Siffredi and colleagues (2013) as well as more recent studies. These studies report on neuropsychological functions of interest for this thesis, including WM, general intellectual, academic, and socio-emotional functions; as well as cognitive functions that are not in the focus of this thesis, such as visuo-spatial skills, language or processing speed.

Working memory

The investigation of WM abilities in children with AgCC constitutes one of the main focus of this thesis. Only two adult case studies have examined WM abilities in AgCC and results are contradictory. While impairments were reported using a 2-back task in an adult with partial AgCC associated with brain abnormalities (Simon, Walterfang, Petralli, & Velakoulis, 2008), performances in the average range were reported in an adult with complete AgCC and severe traumatic brain injury using an auditory-verbal and a visual WM task (Reddy, Jamuna, & Hemchand, 2010). WM (definition, models, links to other cognitive functions and neural substrates) will be addressed more fully in the following chapter.

General intellectual function

General intellectual or general cognitive abilities refer to the ability to understand, interpret and reason on visual and/or verbal information (Semrud-Clikeman & Teeter Ellison, 2009).

Based on findings of a systematic review (Siffredi et al., 2013), the overall mean Intellectual Quotient (IQ) for 110 individuals with AgCC (41 articles; age range 3 months to 73 years) was 82.2 (SD=24.05, n=110), which corresponds to the 'Low Average' range, and was more than one standard deviation below the mean score for the general population (M=100, SD=15). Studies included in the systematic review used 14 different measures to assess general intellectual function (e.g. Wechsler Preschool and Primary Scale of Intelligence WPPSI; Wechsler, 1967 or Wechsler Intelligence Scale for Children WISC; Wechsler, 2003) . The overall mean IQ for individuals with AgCC differed significantly from the test normative mean for the general population, t (109) = -1.762, $p < 0.001$. There was a wide variability in IQ scores, ranging from 'Extremely Low' to 'Superior', but the overall distribution was skewed toward the lower end of the normal population for the AgCC group (Figure 9). In this sample, 24% of individuals with AgCC showed isolated AgCC, 45% showed associated brain anomalies on MRI and this information was not reported in 31% of cases. AgCC was associated with a genetic syndrome in 10% of the cases, epilepsy was diagnosed in 13%, and traumatic brain injury in 4% of individuals of the sample.

The systematic review from Siffredi and colleagues (2013) compared mean IQ scores for children (0 to 11 years at assessment), adolescents (12 to 20 years) and adults (>21 years). Looking across age groups, the mean IQ score for children was 76.35 (SD = 30.12, n = 48), within the 'Borderline' range; for adolescents, it was 85.56 (SD = 18.8, n = 20), within the 'Low Average' range; and for adults it was 88.22 (SD = 15.18, n = 41), in the 'Low Average' range. The adult mean IQ score was significantly higher than children.

Finally, Verbal and Performance IQs were reported in 58 individuals aged 6 to 73 years (24 studies; Siffredi et al, 2013). Mean Verbal IQ was 89.23 (SD = 17.66, n = 58), in the 'Low Average' range, and varied from 'Extremely Low' to 'Very Superior', while the mean Performance IQ was 91.7 (SD = 15.06, n = 58), and was in the 'Average' range, varying from 'Extremely Low' to 'High Average'. There was no significant difference between the mean Verbal IQ and Performance IQ.

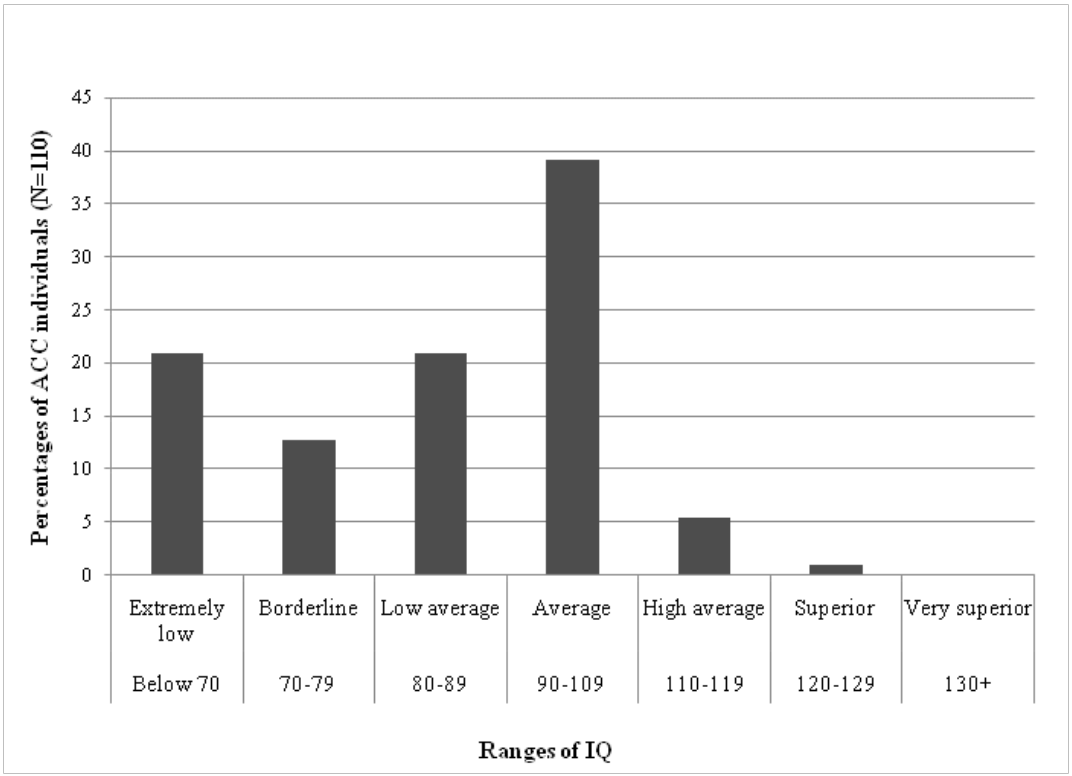

Figure 9. Rates of general intellectual function (IQ) in 110 individuals with AgCC (reproduced from Siffredi et al., 2013; p. 47).

Academic abilities

Three major domains of academic performance have been examined in individuals with AgCC: reading, spelling and mathematics.

For reading, performance within the normal range has been reported for both decoding and comprehension in children and adolescents with AgCC; in three 8-year-old children with complete AgCC and associated brain anomalies (Fischer et al., 1992; Stickles, Schilmoeller, & Schilmoeller, 2002), in a 14-year-old adolescent with complete AgCC and brain anomalies (David, 1992), in an 11-year-old boy with partial AgCC and mild traumatic brain injury (Panos, Porter, Panos, Gaines, & Erdberg, 2001), in 17 children and adolescents with complete AgCC (Moutard et al., 2003), and in adolescents and adults with complete and partial AgCC (n =6; W. S. Brown et al., 1999) . Only Finlay et al. (2000) described reading difficulties in a mother and her two daughters with complete AgCC.

Regarding spelling abilities, conflicting results have been reported in 12 individuals with AgCC included in the systematic review (Siffredi et al., 2013). Across childhood and adulthood, average performance was found in 75% of individuals with AgCC (W. S. Brown et al., 1999; Fischer et al., 1992; Panos et al., 2001); whereas 25% of the studies reported difficulties (W. S. Brown & Paul, 2000; Stickles et al., 2002).

Impairments in mathematics were commonly reported in children and adults with AgCC. Significant difficulties were reported in an 8-year-old with complete isolated AgCC (Stickles et al., 2002), and in a 10-year-old with partial isolated AgCC (Lamonica et al., 2009) and partial AgCC and mild traumatic brain injury (Panos et al., 2001). During adolescence and adulthood, marked mathematical impairments were also reported in four individuals aged 14 to 27 years of age with complete and partial AgCC (W. S. Brown et al., 1999). Only one case study reported intact arithmetic skills in an adult individual with AgCC (David, 1992).

In summary, reading and spelling skills appear to be relatively preserved in most individuals with AgCC, with 10% and 25% of impairment respectively. However, difficulties in mathematics have commonly been reported, with 86% of individuals demonstrating impairments (Siffredi et al., 2013).

Executive functions

Executive function is an umbrella term traditionally used to represent a collection of higher-level processes involved in the top-down control of cognitive processes that facilitate goal-directed behaviour (Lezak, 1995; A. Miyake, Friedman, Emerson, Witzki, & Howerter, 2001). A total of four studies included in the systematic review have examined executive functions in AgCC patients (n = 5; Siffredi et al., 2013). The Wisconsin Card Sorting Test (WCST; Berg, 1948; Grant & Berg, 1948) has been used to evaluate a myriad of executive skills, including the ability to form concept, to generate an organisational strategy, to use examiner feedback, to shift strategy, and be flexible to the challenging demands of a task (Semrud-Clikeman & Teeter Ellison, 2009). In children, conflicting results are reported with impairment in an 8-year-old with complete AgCC and associated brain anomalies (Fischer et al., 1992), but abilities in the average range in two boys (11- and 8-year-old) with isolated partial AgCC and with complete AgCC and associated brain anomalies (Fischer et al., 1992; Panos et al., 2001).

Similarly, findings are discordant in adults with impairment in an individual with partial AgCC associated with brain abnormalities (Simon et al., 2008), but intact scores in a patient with complete AgCC and severe traumatic brain injury (Reddy et al., 2010). Verbal fluency tests are used to evaluate several executive skills, such as word retrieval, the capacity to generate new ideas, and to generate a strategy. Once again, results are discordant with impairment in an individual with partial AgCC associated with brain abnormalities (Simon et al., 2008), but average scores in an adult with complete AgCC and severe traumatic brain injury (Reddy et al., 2010). This last individual also performed in the average range on a Tower of London task (Shallice, 1982), suggesting intact planning skills.

Cohort studies have recently been published showing more reliable results. Performance in the average range for the Tower Test, the Problem-Solving Test, and the Colour-Word Naming and Interference Test of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) were found in a cohort of 18 adults with partial and complete AgCC (Hinkley et al., 2012). In 40 adults with complete and partial AgCC (full-scale IQ above 80), a study from Brown and colleagues (2012) showed significant difficulties in the Iowa gambling task (Bechara, Damasio, Damasio, & Anderson, 1994). Individuals with AgCC showed difficulties in inferring game contingencies and forming a coherent selection strategy.

To sum up, a number of studies with stronger methodological design and using a structural framework reporting on executive functions has been published the last few years. Studies indicated that executive impairments are likely to occur in individuals with AgCC.

Visual and spatial skills

Visual perception, as well as integration of visuo-spatial perception and motor skills, are referred to as visuo-spatial reasoning skills in this section (Semrud-Clikeman & Teeter Ellison, 2009). There is considerable variability observed in the literature for visual and spatial skills in individuals with AgCC. Intact visual perception, visuo-motor integration or visuo-spatial perceptual skills were reported in two children with complete AgCC diagnosed following a traumatic brain injury (Fischer et al., 1992), and in two adults with complete AgCC and associated neurological abnormalities (Jäncke, Wunderlich, Schlaug, & Steinmetz,

1997). In contrast, impairments were observed in an 11-year-old boy with partial AgCC and mild traumatic brain injury (Panos et al., 2001), in a 14-year-old child with complete AgCC associated with brain malformations (David, 1992), and in a 10-year-old child with isolated partial AgCC (notable graphic spatial disorganisation, Lamonica et al., 2009 . The limited number of studies reporting on visual and spatial reasoning skills suggests that individuals with AgCC may experience difficulties in this cognitive domain, particularly during childhood.

Language

Language is a higher cognitive function that includes speaking (expressive language) and understanding (receptive language), as well as the ability to name objects (Semrud-Clikeman & Teeter Ellison, 2009). Language has been examined in nine studies (n=42), as highlighted by our systematic review (Siffredi et al., 2013). The ability to name objects (vocabulary tasks) was in the average range in 17 children and adolescents with complete AgCC (Moutard et al., 2003), and in an 8-year-old boy with complete AgCC and associated brain anomalies (Stickles et al., 2002). Only one study reported impairment on a picture naming task in an 8-year-old girl with complete AgCC and Turner syndrome (El Abd et al., 1997). Marked expressive and receptive language impairments were observed during childhood: in a 2-year-old with complete AgCC (Lawson-Yuen, Berend, Soul, & Irons, 2006), in an 8-year-old with complete AgCC and associated brain malformations (El Abd et al., 1997), and in a 10-year-old with partial AgCC (Lamonica et al., 2009). A follow-up study from 8 to 22 year-old of a patient with complete AgCC and additional brain anomalies showed expressive and receptive language skills in the borderline to average range, with relatively stable performances over time and specific difficulties in formal language forms (Stickles et al., 2002).

In adults, only one study, conducted in a 45-year-old patient with complete AgCC and associated brain anomalies, reported intact receptive language abilities (Kessler, Huber, Pawlik, Heiss, & Markowitsch, 1991). Finally, several studies reported difficulty in pragmatic abilities. Huber-Okrainec and colleagues (2005) showed that children and adolescents with partial AgCC and spina-bifida meningomyelocele (n = 8) performed significantly worse than the control group (n = 11) on idioms comprehension tasks, with less accurate results and slower response. In accordance with previous authors, Brown and colleagues (2000) reported

difficulties in proverbs generation in two young adults with complete AgCC and associated brain anomalies.

In summary, children with AgCC appeared to be more at risk of expressive and receptive language impairment compared to adults. Vocabulary skills appeared relatively preserved in most AgCC individuals, whereas difficulties in pragmatic language skills were commonly reported, with 100% of individuals with AgCC reported in the literature who demonstrated impairments in this domain.

Attention

Attention is a multifaceted construct (P. J. Anderson, 2008). This construct has not been systematically studied in individuals with AgCC; and usually only one of its components has been evaluated. The systematic review reported results of eight studies (n = 11; Siffredi et al., 2013) . General attentional deficits, evaluated using a parent-rated questionnaire, were reported: in a 10-year-old with partial isolated AgCC (Lamonica et al., 2009) and in a 8-year-old with complete AgCC and associated brain anomalies (El Abd et al., 1997). However, intact general attention skills were observed in two children aged 11 and 12 years with complete and partial AgCC using teacher-rated questionnaires (Párraga, Párraga, & Jensen, 2003), and in four adults with complete AgCC: two associated with brain anomalies (W. S. Brown & Paul, 2000), one associated with complex partial seizures (Jäncke et al., 1997), and one associated with severe traumatic brain injury (Reddy et al., 2010). Sustained attention difficulties and impulsivity were reported in an 8-year-old boy with complete AgCC associated with several brain anomalies (Fischer et al., 1992), and disinhibition were observed in a 11-year-old boy with partial AgCC diagnosed following a mild traumatic brain injury (Panos et al., 2001).

In summary, the number of studies with strong methodological design reporting on attentional skills is limited. However, the literature suggests that individuals with AgCC might present attentional difficulties.

Learning and memory

Memory and learning go hand in hand: learning is acquiring information while memory is retrieving this information for later use (Gazzaniga, Ivry, & Mangun, 2002). In this section we

initially explore short-term memory before looking at long-term memory in individuals with AgCC.

According to the review of Siffredi and colleagues (2013), adult AgCC studies have reported inconsistent findings for short-term memory. Performance in the average range in verbal immediate recall was observed in a case of isolated complete AgCC (Jäncke et al., 1997), while impairments were observed in an individual with partial AgCC and associated brain anomalies (Simon et al., 2008). The mean scores for immediate recall of word pairs and thematic information from stories in 28 individuals aged 16 to 55 (21 complete AgCC and nine partial) were also below average using the Wechsler Memory Scale-Third Edition (WMS-III; Paul, Erickson, Hartman, & Brown, 2016; Wechsler, 1997). Marked difficulties in visual-motor short-term memory (design learning task, Reddy et al., 2010) as well as intact performance (Corsi block tapping task; Corsi, 1972; Kessler, 1991) have been reported in two adults with complete AgCC. In the previous sample of 28 individuals with AgCC, immediate recall for faces and abstract figures was comparable to intellectual functioning matched controls (Paul et al., 2016).

Long-term explicit memory in verbal modality was studied in five children and five adults with AgCC across seven studies (Finlay et al., 2000; Fischer et al., 1992; Kessler et al., 1991; Midorikawa, Kawamura, & Takaya, 2006; Panos et al., 2001; Reddy et al., 2010; Simon et al., 2008). Impairments were found in 60% of the cases in this systematic review. Additionally, two recent studies exploring verbal learning and memory. Erickson and colleagues (2014) used the California Verbal Learning Test (CVLT-II; Donders, 2008) in twenty-six adults with complete and partial AgCC and general intellectual function in the average range (Erickson, Paul, & Brown, 2014). Individuals with AgCC performed significantly below healthy controls, confirming impairments in short and long delayed free recall and cued recall for verbal learning. Previously mentioned, Paul and colleagues (2016) evaluate delayed verbal recall in 28 individuals with AgCC aged 16 to 55. While recall for word pairs was significantly low compared to the control group, there was no difference for thematic stories recall. Performances in long-term visual and visuo-spatial explicit memory were in the average or low average range in a cohort of children and adolescents with complete AgCC (n = 17; Moutard et al., 2003) , in a child with partial AgCC (Panos et al., 2001), and an adult with complete AgCC (Reddy et al., 2010). Only one study completed in two children with complete AgCC and associated brain abnormalities reported mild impairment in visual long-

term memory (Fischer et al., 1992). Overall long-term memory impairments for spatial and visuo-spatial modalities were found in only 10% of cases in the systematic review. The recent study from Paul and colleagues (2016) previously mentioned found that delayed recall for faces was low compared to the healthy control, but there was no group difference for abstract figure.

Overall, short-term memory (verbal and visuo-spatial) as well as verbal long-term memory seem to be impaired in most individuals with AgCC. Better performance have been observed for long-term visual or visuo-spatial memory and learning. It seems that memory and learning performance in individuals with AgCC also depend on the material used (e.g., word pairs, stories, faces, abstract figure, Corsi test).

Information processing speed

There are three main levels of processing speed (Carroll, 1993). In the systematic review, seven articles examined different levels of information processing speed in individuals with AgCC (n = 11; Siffredi et al., 2013). The most basic level of processing speed, psychomotor speed, is the ability to rapidly and fluently perform motor movements independent of cognitive control (Carroll, 1993). Discordant results were reported for this basic level of processing speed with average performance in an 11-year-old with partial AgCC (Panos et al., 2001), but impaired capacity in an adult aged 25 years with complete AgCC who was diagnosed following severe traumatic brain injury (Reddy et al., 2010). Processing speed is certainly reduced after severe traumatic brain injury, thereby this finding may not be due to AgCC in those cases (Vicki Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005; Madigan, DeLuca, Diamond, Tramontano, & Averill, 2000). The second level of processing speed refers to the ability to react and/or make decisions quickly in response to simple stimuli (Carroll, 1993). In tasks evaluating motor response to visual stimuli, reaction times were not different than healthy controls in four individuals with complete AgCC, associated brain anomalies, and epilepsy in two patients (de Guise et al., 1999), as well as in one 45-year-old patient with complete AgCC and mild brain anomalies (Kessler et al., 1991). However, two case studies described significant slowness in motor reaction time to visual stimuli: one with isolated complete AgCC (Midorikawa et al., 2006) and the other with partial AgCC and associated brain abnormalities (Simon et al., 2008).

Cognitive information processing is the highest level of processing speed (Carroll, 1993). It is the ability to automatically and fluently perform relatively easy or over-learned cognitive tasks, especially when high mental efficiency is required (i.e., attention and focused concentration). In a case study, Reddy and colleagues (2010) reported cognitive processing speed in the average range in an adult with complete AgCC and severe traumatic brain injury (Digit Symbol Substitution Test) . In contrast, slow reaction times in three adults with complete AgCC and associated brain malformation were observed in a visual search task (Dell'Acqua et al., 2005). Similarly, a recent cohort study of 36 adults with partial and complete AgCC showed significantly reduced processing speed in a Colour-Word Naming task, and in the Trail-Making Test from the D-KEKS (Marco et al., 2012).

In summary, individuals with AgCC might present with slowness in basic information processing speed. However, higher level of cognitive information processing speed seems to be particularly at risk of impairment.

Social communication, socio-emotional skills, and autism spectrum disorder in agenesis of the corpus callosum

Some studies suggest that individuals with AgCC present difficulties in communicative and socio-emotional functioning. Buchanan, Watherhouse and West (1980) were among the pioneers to study emotional processing in individuals with AgCC. These authors reported an adult case study of AgCC with normal general cognitive skills but reduced verbal expression of emotion. With the findings of previous study with commissurotomised patients (Hoppe & Bogen, 1977), the authors made a parallel between hemispheric disconnection and alexithymia. However, this parallel was not confirmed in more recent studies.

A number of studies describe difficulties affecting various social skills in individuals with AgCC. During adulthood, Brown and colleagues (2005) found that 16 individuals with complete AgCC and IQ in the average range performed significantly worse than control participants on a narrative joke subtest of a humour test. Similarly, Paul and colleagues (2003) showed significant impairments in 10 young males with complete AgCC and normal general intellectual functions on recognition of proverb meaning (Gorham Proverbs Test; Gorham, 1956) and comprehension on non-literal items (Formulaic and Novel Language Comprehension Test, FANL-C; Kempler & Van Lancker, 1996) . The Thematic Apperception

Test (TAT; Murray, 1943) was administered to five individuals with complete AgCC and one with partial AgCC and normal IQ (Paul, Schieffer, & Brown, 2004), as well as in 22 individuals with isolated complete AgCC and normal IQ (Turk, Brown, Symington, & Paul, 2010). These studies found that individuals with complete AgCC exhibited significant difficulties in understanding complex social scenes and generating appropriate narratives, and used fewer words pertaining to emotional and social processes. However, the individual with partial AgCC showed performance comparable to the control group (Paul et al., 2004). Likewise, Symington and colleagues (2010) found poor performance in 11 individuals with complete AgCC and IQ within the average range (compared to controls) on the Thames Awareness of Social Inference Test (TASIT; McDonald, Flanagan, Rollins, & Kinch, 2003) suggesting difficulties in integrating social information from multiple sources, such as paralinguistic cues and nonliteral language. In 19 adults with isolated AgCC (15 complete and four partial), Rehmel et al. (2016) found performance significantly lower than the control group at the Gorham Proverb Test (Gorham, 1956) and at the free-responses Proverbs subtest of the Delis-Kaplan Executive Function System (D-KEFS, Delis et al., 2001). However, interestingly, group differences in proverb comprehension on the Gorham test were considerably reduced when covarying with a measure of non-literal language comprehension, but had little effect on the D-KEFS group differences.

During adolescence, Brown and Paul (2000), using the Proverbs Test (Gorham, 1956), the Thematic Apperception Test (Murray, 1943), and the Rorschach Inkblot Test (Rorschach, 1942), found significant poor performance in a 16- and an 18-year-old with complete AgCC and normal IQ on social insight, proverb interpretation, social logic, self-perception, and interpretation of ambiguous stimuli. Only one case study was reported in children. An 8-year-old with complete AgCC and Turner syndrome showed difficulties with presupposition (taking the listener perspective into account), shared knowledge, and conversational breakdown and repair (Abd et al., 1997). The author also noted impaired abilities to read non-verbal cues such as body language and facial expression and some lack of awareness of social conventions.

A recent study reported impairments in visual emotional recognition for faces in nine adults with complete AgCC (Bridgman et al., 2014). Findings showed lower accuracy for fear and anger compared to disgusted, happy, sad, and surprised faces, and these impairments were directly associated with diminished attention to the eye region as measured by eye-tracking.

These findings did not differ when taking into account full-scale IQ or presence of autism spectrum symptoms. Additionally, a study reported difficulties with emotional prosody in 10 individuals with complete AgCC and normal IQ (Paul et al., 2003). However, another study from Brown and colleagues (2005) showed no difference on a prosody test in 13 children with AgCC and normal IQ compared with a control group.

Finally, some authors have made links between AgCC and ASD. In a large cohort of AgCC (n = 189), Doherty and colleagues (2006) found that 8.5% had received a diagnosis of autism (vs. 1% of their siblings). However, numbers of individuals with AgCC without a diagnosis of ASD might still present autistic symptoms. Indeed, in 106 individuals with AgCC, Lau and colleagues (2013) found that 45% of children, 35% of adolescents, and 18% of adults exceeded the predetermined autism-screening cut-off. In 22 individuals with AgCC, Paul and colleagues (2014) found that only three met full criteria for an ASD diagnosis, however, three more met the Austism Diagnostic Observation Schedule (ADOS) criteria for an ASD and had a clinical diagnosis of ASD but did not meet ASD criteria on parent report. Another study from Booth and colleagues (2011) found that half of a cohort of 10 children with AgCC from 6 to 17 years of age were classified as being above or near to the cut-off criteria for an ASD diagnosis on at least two of three standardised parental questionnaires (Childhood Autism Spectrum Test - Scott, Baron-Cohen, Bolton, & Brayne, 2002; Social Communication Questionnaire - Rutter, Bailey, & Lord, 2003; and the Children's Communication Checklist - Bishop, 1998) . This subgroup of five children with AgCC and ASD symptoms included both partial and complete AgCC, and had lower general intellectual abilities than those without ASD symptoms.

1.4. Neuroimaging Studies in agenesis of the corpus callosum

Structural properties and functional connectivity in agenesis of the corpus callosum

Structural and functional connectivity in AgCC has been recently studied using DTI, resting-state fMRI, as well as electroencephalography.

To my knowledge, Tovar-moll and colleagues (2007) were the first authors to study white-matter connectivity in eight individuals with AgCC (three complete and five partial) and three with callosal hypoplasia. Using DTI, they revealed the presence of at least two long abnormal tracts in patients with AgCC: the Probst bundles and a so far unknown sigmoid bundle. They also found that in the presence of a callosal remnant or a hypoplastic CC, fibres connect the expected neocortical regions in a topographical way similar to typical brain development. Despite an important variability in the network topology of AgCC, the presence of Probst bundles in the AgCC connectome was consistently found in 11 individuals with AgCC, seven complete and four partial. In another study, the remarkable diversity of callosal fibre connectivity was confirmed in six individuals with partial AgCC, with not only homotopic connections but also heterotopic connections in four of the participants (Wahl et al., 2009). However, the observed homotopic connections did not necessarily correlate with the position or size of the residual callosum. In addition, congruent results showed that whether global connectivity was abnormally reduced in AgCC, local connectivity was increased (in 11 adults with complete and partial AgCC; J.P. Owen, Li, Ziv, et al., 2013) and in 10 children with complete AgCC (Meoded, Katipally, Bosemani, Huisman, & Poretti, 2015). Interestingly, a recent study demonstrated that despite the lack of callosal fibres and colpocephaly observed in AgCC, all major white matter bundles were identified with a relatively normal morphology, and preserved microstructure (i.e., fractional anisotropy, mean diffusivity) and asymmetries (Bénézit et al., 2015). This study was completed in seven children aged between 9 and 13 years (three complete, three partial and one hypoplasia).

Using DTI in 20 foetuses with AgCC (18 complete and two partial) during the second and third semester of gestation, globally altered connectivity network structure was observed compared to normal (Jakab et al., 2015). Atypical organisation of macroconnectome, dominated by increased connectivity, was found in AgCC foetus. In 16 foetuses with complete and partial AgCC, Kaspria and colleagues (2013) showed that Probst bundles and sigmoid bundles can be visualized as early as 20 and 22 gestational weeks during early stages of pre-myelination.

Using resting-state fMRI, two studies of complete and partial AgCC demonstrate a qualitative organisation of resting-state networks very similar to control participants (J. P. Owen, Li, Yang, et al., 2013; Tyszka, Kennedy, Adolphs, & Paul, 2011). However, some individuals with AgCC show reduction in interhemispheric functional connectivity of the precuneus, the

posterior cingulate cortex, and the insular-opercular regions (J. P. Owen, Li, Yang, et al., 2013; Rane, Kose, Gore, & Heckers, 2013). Two recent studies used the combined methods of DTI and resting-state fMRI in four adults with AgCC, in two with complete and two with partial AgCC (Tovar-Moll et al., 2014), and in one with complete AgCC (Rane et al., 2013). Compensatory pathways connecting the homotopic posterior parietal cortical areas (Brodmann areas 39 and surroundings) via the posterior and anterior commissures were found for tactile and visuo-tactile recognition and naming abilities. Finally, Hinkley and colleagues (2012) studied functional connectivity and related cognitive impairments using resting-state electroencephalography in 18 adults with AgCC (nine complete, nine partial) . They found reduced alpha band global connectivity in the dorsolateral prefrontal cortex (DLPFC), posterior parietal and parieto-occipital cortices. Performance in verbal processing speed was significantly correlated with resting-state functional connectivity of the left medial and superior temporal lobe, whereas performance on the Tower of London (D. Delis et al., 2001) was strongly correlated with connectivity in the DLPFC in individuals with AgCC.

Considering structural differences in individuals with AgCC, cortical thickness has been studied in five adults with complete AgCC compared to a group of healthy controls (Beaule et al., 2015). Findings suggested relatively limited effects of AgCC on cortical morphology, except few areas showing significant and consistent alterations in primary sensory and motor areas (primary visual cortex, primary somatosensory cortex and primary motor cortex).

Functional MRI studies in agenesis of the corpus callosum

Functional MRI studies have investigated sensory-motor, language and emotional functions in individuals with AgCC; but to my knowledge, WM has never been investigated. Firstly, motor, tactile and auditory activations have been studied in complete AgCC. Bilateral activation similar to neurologically intact participants was found for motor (Lum et al., 2011; Quigley et al., 2003), tactile (Duquette, Rainville, Alary, Lassonde, & Lepore, 2008; Lum et al., 2011), and auditory stimulation (Paiement et al., 2010). However, Quigley and colleagues (2003) found reduced interhemispheric functional connectivity in the motor and auditory cortices in three individuals with AgCC compared to healthy participants in finger-tapping and text listening tasks. Similarly, Paiement and colleagues (2010) reported reduced auditory activations in two of five participants with AgCC.

Secondly, language related brain activity has been of interest in the AgCC literature, especially in the study of lateralisation of language processes. Case studies using a variety of techniques (fMRI, positron emission tomography) and measures (verb generation, speech production and perception, auditory sentence tasks and Wada Test) found bilateral language representations in individuals with AgCC (Alsaadi & Shahrour, 2015; Kessler et al., 1991; Komaba et al., 1998; Riecker et al., 2007). An fMRI study completed in six adults with complete AgCC using a syntactic decision task (receptive language) found bilateral pattern of activation in frontal region, including Broca's area, but left-lateralized activation in temporal regions similar to healthy controls (Pelletier et al., 2011). Results also showed increased variability in the AgCC group compared to the control group. Finally, McIlroy and colleagues (in preparation) completed a verb generation paradigm in seventeen children and adolescents with AgCC (ten complete, seven partial, from 8 to 22 years of age. These authors found bilateral symmetric activation in language area in the AgCC cohort in comparison to left-lateralized activations in the typically developing group. They showed that this atypical language lateralization in AgCC was not accounted for by handedness or the extent of AgCC (complete or partial). Of note, a recent study using magnetoencephalographic imaging during auditory or visually driven language tasks in 25 individuals with AgCC corroborates these findings (Hinkley et al., 2016).

Thirdly, brain activity during the processing of emotionally laden information (pictures of faces, scenes) has been studied in a 23-year-old woman with partial AgCC and schizophrenia in comparison to a control group composed of patients with solely schizophrenia (Lungu & Stip, 2012). Although visual cortex activations in response to visual stimuli regardless of their emotional content was comparable between the individual with AgCC and the control group, there was a very large, non-specific and non-lateralized cerebral activation in the AgCC patient compared to the control group when the emotional content of the stimuli was considered.

Limitations of current neuroimaging studies in agenesis of the corpus callosum

Altogether, the number of imaging studies conducted in individuals with AgCC is sparse. The first studies examine neural correlates, and more particularly lateralisation, of language functions. Most recently (over the last ten years), researchers investigated neural correlate of different sensory-motor functions using fMRI, as well as structural and functional

connectivity using DWI and resting-state fMRI. Small sample size is also a recurrent methodological limitation in AgCC studies. In addition, association between functional brain organisation and higher cognitive functions (other than language) in individuals with AgCC has only been made with executive functions using resting state electroencephalography and with emotional processes in a single case study using fMRI. Moreover, association between structural organisation and higher cognitive functions in individuals with AgCC has never been made. Studying association between structural and functional properties with higher cognitive functions could help identify neural makers of cognitive outcomes. This could be then used to inform prognosis. This could also contribute to better determining why some children with AgCC are asymptomatic whilst others have cognitive and neurodevelopmental difficulties.

1.5. Summary of the Chapter

AgCC is a heterogeneous condition that can have different aetiologies and being associated with various neurological conditions. In some individuals, incidental finding of AgCC have been found. Therefore, it is possible that the current literature is biased toward individuals with sufficient clinical need for a scan to be requested, and AgCC to be diagnosed. Nowadays, routine ultrasound screening is becoming largely used in developed countries and an increased number of individuals with AgCC can be diagnosed prenatally. The two case studies reporting on WM abilities in individuals with AgCC showed contradictory results. It is therefore impossible to draw conclusion for this cognitive function of interest. Based on the literature, intellectual abilities in individuals with AgCC are generally within the low average to average range. Individuals with AgCC are at risk of impairments across a wide range of neuropsychological and social domains. Difficulties in mathematics and pragmatic language skills are commonly reported and include impairments in humour and proverb comprehension, understanding complex social scene and integration of social information. Individuals with AgCC are also at risk of impairments in other domains, particularly during childhood, such as expressive and receptive language, visual and spatial skills, attention and executive functions, information processing speed as well as a range of learning and memory skills. However, reading, spelling, vocabulary skills as well as visuo-spatial long-term memory ability appear to be relatively preserved in most AgCC individuals. Finally, important overlap between AgCC and ASD has been observed. However, as previously

mentioned, individuals with AgCC represent a heterogeneous group and this may result in the contradictory results observed in the current literature in regards to neuropsychological and social outcomes. It is important to consider the breadth of factors that might influence neurodevelopmental outcomes, such as associated brain anomalies and comorbid neurological and genetic conditions. It seems that isolated and primary AgCC carry the best outcomes in terms of prognosis. Unfortunately, in the current literature, methodological limitations, such as very small sample size and the lack of medical information on patients with AgCC, restricted our ability to determine exactly how factors, for instance associated brain anomalies, modulate the impact of AgCC on neuropsychological functions.

CHAPTER 2: Working Memory

2.1. Introduction

Definition

Traditionally, researchers have classified two distinct human memory systems: short-term memory and long-term memory (Peterson & Peterson, 1959). In short-term memory, the memory traces are lost within a few seconds. If this information is reinforced (by active rehearsal), it may be transferred into long-term memory and retained for much longer periods (Baddeley, 1996a).

WM is the term used to refer to the capacity to store and manipulate information over brief periods of time (Baddeley, 1986; Baddeley, Allen, & Hitch, 2011; Just & Carpenter, 1992). It is related but distinguishable from short-term memory. Short-term memory is only specialised for temporary storage of information (Gathercole & Alloway, 2006), whereas WM is composed of at least two task components involving storage of information and the processing of the same or a different information (Logie & Duff, 2007). Therefore, WM is a mental workspace that can be flexibly used to support everyday cognitive activities involving multiple steps with intermediate results that need to be kept in mind temporarily to accomplish the task successfully. It provides a pivotal interface between perception, attention, memory and action (Vergauwe, Barrouillet, & Camos, 2009). However, WM is a capacity-limited cognitive system. In the course of an ongoing cognitive activity, critical loss of information can be due to an excess of demands in storage and/or processing (Gathercole & Alloway, 2006; Portrat, Camos, & Barrouillet, 2009). Finally, WM function overlaps with other competencies, such as attentional focus and inhibition of irrelevant information (M. Osaka & Osaka, 2007).

During cognitive development and in adulthood, WM is crucially required for any higher cognitive brain functions and recognised to play an essential role in elementary and complex cognition (Barrouillet et al., 2008; Gathercole & Alloway, 2006; Akira Miyake & Shah, 1999). In fact, it has been labelled the “workbench of cognition” (Klatzky, 1980) or “the hub

of cognition" (Haberlandt, 1997). Since 1980's, WM has become a central construct in cognitive psychology and more recently in cognitive neurosciences (Akira Miyake & Shah, 1999; Naoyuki Osaka, Logie, & D'Esposito, 2007).

From a developmental point of view, WM capacity develops dramatically across childhood and early adulthood (Gathercole, 1999; Klingberg, 2006; Klingberg et al., 2002). This can be measured by the increase in the amount of information that can be retained and transformed in complex memory span tasks (Gathercole, Alloway, Willis, & Adams, 2006). Developmental studies showed that as early as 8 to 12 month-old, infants are correctly retaining objects in a short-term memory task, called short delayed match-to-sample task (Diamond, 1990). Different trajectories of WM development for visuo-spatial and verbal modalities have been reported in the literature (Koppenol-Gonzalez, Bouwmeester, & Vermunt, 2012). However, the increase in WM capacity for both modalities from about 6 years of age seems to be linear, and continues to around 16 years of age when a level close or similar to that of adults is reached (Fry & Hale, 2000; Huizinga, Dolan, & van der Molen, 2006; Luciana, Conklin, Hooper, & Yarger, 2005; Pickering, 2001; Vuontela et al., 2009; Westerberg, Hirvikoski, Forssberg, & Klingberg, 2004; Zald & Iacono, 1998). Active rehearsal or active refreshment is an important component during maintenance to efficiently retain information in WM. The transition from passive maintenance into active rehearsal seems to emerge around 7 years of age (Camos & Barrouillet, 2011). A recent study showed that spontaneous rehearsal might emerge before, at least from 5 year-old (Miller, McCulloch, & Jarrold, 2015). Additionally, the ability to recode visual information into verbal form is associated with age-related improvements in WM (Kemps, De Rammelaere, & Desmet, 2000; Pickering, 2001). Around 7 years of age, children gradually recode visual information in phonological form, and thereby benefit from more efficient and effective strategies to process information in WM (Hitch, Halliday, Dodd, & Littler, 1989; Hitch, Halliday, & Littler, 1989; Kemps et al., 2000; Pickering, Gathercole, Hall, & Lloyd, 2001). Importantly, these changes in WM capacity are also thought to play a crucial role in a wide range of cognitive skills (Klingberg et al., 2002), see section 2.3.

Experimental paradigms of working memory

Numerous experimental designs have been created to investigate WM processes and capacity. In experimental settings, the demand for controlled attention or executive control during WM

can be increased in different ways: a) by requiring the participants to manipulate the stored information; b) by introducing a dual-task requirement (Conway, Kane, & Engle, 2003; Engle, Tuholski, Laughlin, & Conway, 1999); or c) by including distractions or interference (Gray, Chabris, & Braver, 2003). In this section, four examples of experimental design of WM are presented.

Complex span tasks require participants to either manipulate the stored information or to complete a dual-task. Daneman and Carpenter (1980b) developed the first complex memory span task: a reading span, which has become a well-established measure of WM capacity. Compared to simple span tasks, in which participants have to recall a list of stimuli after a brief retention interval, complex span tasks require the additional accomplishment of a (related or unrelated) secondary task, such as evaluating equations (Figure 10a; Schmiedek, Hildebrandt, Lovden, Lindenberger, & Wilhelm, 2009) . Complex span tasks have been used widely in behavioural experimental and clinical setting at all ages (Alloway, 2012; Shelton, Elliott, Hill, Calamia, & Gouvier, 2009; Unsworth, Redick, Heitz, Broadway, & Engle, 2009). Complex span tasks have also been used occasionally in neuroimaging studies completed in adults (Faraco et al., 2011), but to my knowledge, never in developmental sample.

The Brown-Peterson pre-load paradigm was developed at the end of the 1950s (J. Brown, 1958; Peterson & Peterson, 1959). In the original task, participants were asked to complete the dual-task of maintaining and recalling a string of letters or words with a distracting task (i.e., counting backward) interposed between the exposure to the last stimulus to recall and the time of recall (Figure 10b). The distracting task is supposed to prevent attention to the memoranda or rehearsal. Thus, this type of task invokes retroactive interference where the processing of later materials may block the recall of earlier learning (Baddeley, 1996b; Rai & Harris, 2013; Vergauwe & Cowan, 2014). This paradigm allows studying functional dissociation of the encoding, maintenance and retrieval processes of WM. The Brown-Peterson task has been widely used in both clinical and behavioural experimental studies of children and adult populations (Bherer, Belleville, & Peretz, 2001; Floden, Stuss, & Craik, 2000; Rai & Harris, 2013; Randolph, Gold, Carpenter, Goldberg, & Weinberger, 1992).

The Sternberg Item Recognition Paradigm, created in the late 1960's (Sternberg, 1966), has been used to study the neural architecture of verbal WM brain network in adults (Manoach et al., 1997), as well as in children (Klingberg et al., 2002; O'Hare, Lu, Houston, Bookheimer, &

Sowell, 2008; Olesen, Nagy, Westerberg, & Klingberg, 2003; Spencer-Smith, Ritter, Murner-Lavanchy, et al., 2013; van den Bosch et al., 2014), see Table 2 for a review of the literature. This classical paradigm requires participants to memorise a list of different items and then decide, as quickly as possible without making errors, whether a probe was a member of the list held in short-term memory (Figure 10c). Classical findings showed that response times increase linearly with the size of the list to memorise. Therefore, the delay of response is assumed to reflect the time it takes to retrieve a single item from short-term memory (Vergauwe & Cowan, 2014). Thus, this task requires the maintenance of information in short-term memory, but not the simultaneous maintenance and manipulation of information as the theoretical construct of WM specifies (Baddeley et al., 2011; Barrouillet & Camos, 2015).

More recently, the N-back task has become one of the most popular experimental paradigms for functional neuroimaging studies of WM (Gevins & Cutillo, 1993; A. M. Owen, McMillan, Laird, & Bullmore, 2005) and has been widely used with developmental samples (Figure 10d; Kwon, Reiss, & Menon, 2002; Libertus, Brannon, & Pelphrey, 2009; Schweinsburg, Nagel, & Tapert, 2005; M. J. Taylor, Donner, & Pang, 2012; Thomas et al., 1999; Thomason et al., 2009). A sequence of stimuli is presented to the participant, the task consisting of indicating when the current stimulus matches the one from *n* steps earlier in the sequence (where *n* is a pre-specified integer, usually 1, 2, or 3). As difficulty level increases, the number of interfering stimuli between the target and the relevant stimulus increases, requiring the utilisation of different mental strategies at each level (e.g., 0-back: recognition; 1-back: maintenance; 2-back: maintenance and monitoring; Vogan, Morgan, Powell, Smith, & Taylor 2015) . This paradigm is assumed to place great demands on a number of key processes within WM, including on-line monitoring, updating, and manipulation of remembered information. However, empirical evidence shows that the n-back task correlates weakly with WM span tasks, suggesting that it is unlikely that these two types of tasks reflect a single construct, thus questioning the empirical validity of using n-back tasks (continuous-recognition or updating measures) as a WM task (Kane, Conway, Miura, & Colflesh, 2007; Wilhelm, Hildebrandt, & Oberauer, 2013).

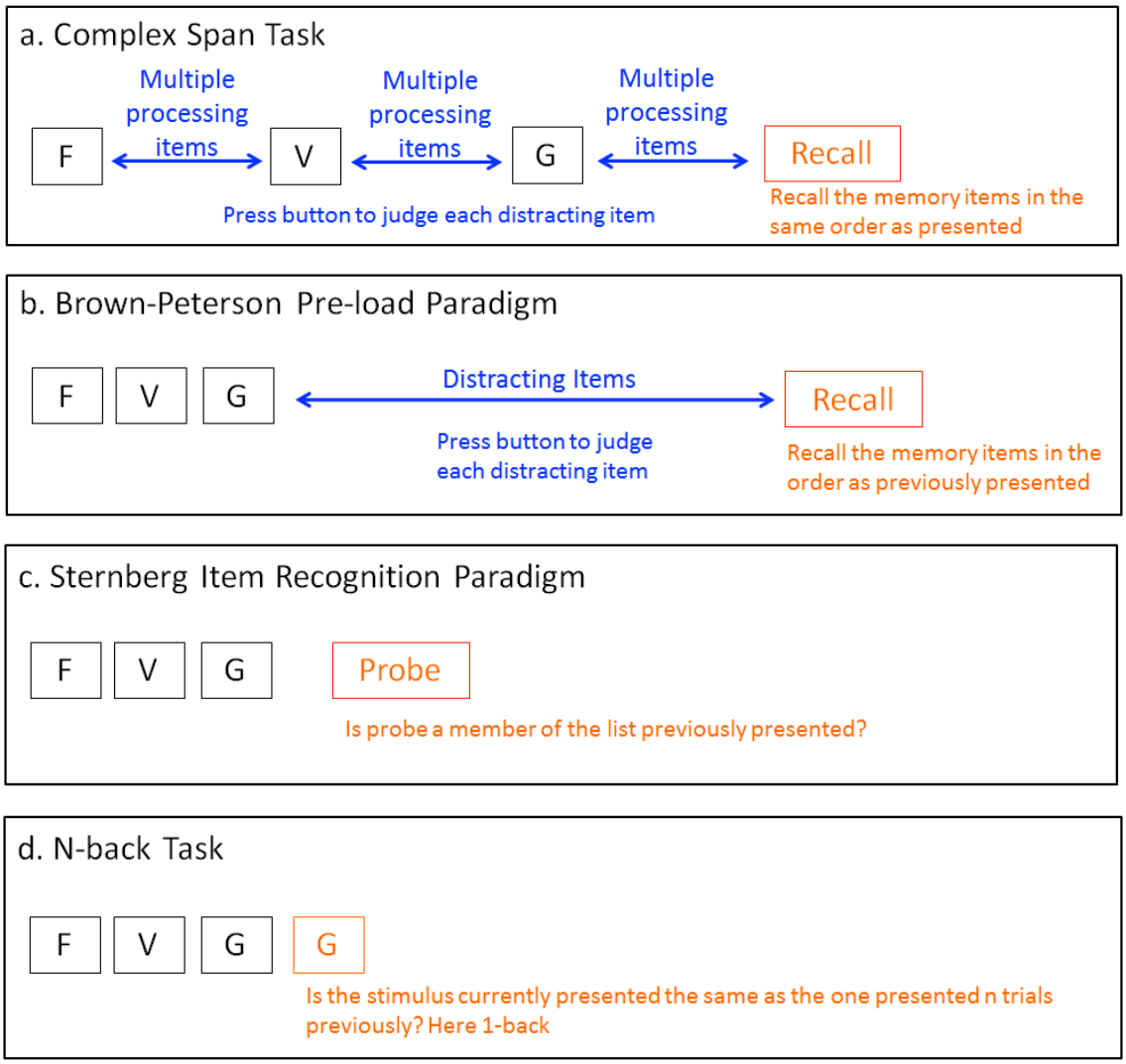

Figure 10. Schematic presentation of the original version of different WM paradigms: the complex span task, the Brown-Peterson pre-load paradigm, the Sternberg Item Recognition Paradigm and the N-Back task (adapted from A. M. Owen et al., 2005; Vergauwe & Cowan, 2014; p. 2).

2.3. Association between Working Memory and Higher-Level Cognition during Development

As previously mentioned, studies in children and adolescents show that WM capacity plays a crucial role in many complex cognitive activities, and predicts academic performance and achievement. Therefore, it is reasonable to think that WM capacity also plays a crucial role in cognitions functions in atypically developing children and adolescents, such as children and

adolescent with AgCC. Association between WM capacity and higher cognitive functions during childhood are presented in this section.

General intellectual function

General intellectual function (defined by diverse measures and constructs, such as intelligence, fluid intelligence, reasoning ability or the general factor of intelligence "g") is a complex cognitive ability that allows humans to flexibly adapt their thinking to new problems or situations (Colom, Rubio, Shih, & Santacreu, 2006; de Abreu, Conway, & Gathercole, 2010). Considerable overlaps between performance on tests of WM and tasks assessing reasoning and general intellectual function have been found in children and adults. Correlations between these two constructs are all positive and range from r = .20 to r = .80 in the literature (Barrouillet, 1996; de Abreu et al., 2010; Engle, Tuholski, et al., 1999; Fry & Hale, 2000; Hornung, Brunner, Reuter, & Martin, 2011; Kyllonen & Christal, 1990; Rabinowitz, Howe, & Saunders, 2002). Although researchers generally agree on the existence of such a relationship, the underlying nature of the association remains an issue of controversy. The relationship between WM and reasoning skills raises two opposing theories. Some argue that WM is so highly correlated with fluid intelligence that they could be considered as isomorphic properties (Colom, Rebollo, Palacios, Juan-Espinosa, & Kyllonen, 2004; Hambrick & Engle, 2002). Alternatively, others claim that WM shares psychometric properties with reasoning activities but these two constructs remain dissociable (Alloway, Gathercole, Willis, & Adams, 2004; Conway, Cowan, Bunting, Therriault, & Minkoff, 2002). Indeed, in children and adolescents, methods of assessing general reasoning skills are strongly influenced by WM (Jurden, 1995), and WM is now an integral part of one of many widely used IQ assessment batteries (Wechsler, 2003).

Academic abilities

Associations between WM and academic achievement in children and adolescents have been extensively investigated. In typically developing children, longitudinal studies show a strong association between WM skills and children's abilities in key academic domains, such as reading, mathematics and science, at all school ages. In a longitudinal study, Alloway and Alloway (2010) investigated WM skills at the very beginning of formal education (4 to 5 years of age). They found that WM skills were linked to learning outcomes 6 years later,

including reading and numerical skills, independently of IQ. In another study, teacher ratings of children's skills in the areas of reading, writing, speaking and listening, mathematics, and personal and social development have been collected at the time of school entry. Results showed that writing abilities were linked specifically with performance on complex memory span tests (Alloway et al., 2005).

In school-aged children and adolescents, national scholastic evaluations have often been used to investigate literacy, mathematical and science skills. Numerous studies demonstrate a strong link between complex memory span tasks and all domains of scholastic evaluations from 7 to 11 years of age (Gathercole, Brown, & Pickering, 2003; Gathercole & Pickering, 2000; Gathercole, Pickering, Ambridge, & Wearing, 2004; Geary, Hoard, & Hamson, 1999; Jarvis & Gathercole, 2003; Lepine, Barrouillet, & Camos, 2005; St Clair-Thompson & Gathercole, 2006). Gathercole and colleagues (2004) found that a strong link persisted at age 14 years between complex WM tasks and attainment in both mathematics and science, while ability in literacy assessments showed no strong association with WM skills. Other studies using a wide range of academic evaluations and WM tasks confirmed this association between WM and reading comprehension (Alloway, Gathercole, Kirkwood, & Elliott, 2009; Daneman & Carpenter, 1980a; Engle, Cantor, & Carullo, 1992; Seigneuric, Ehrlich, Oakhill, & Yuill, 2000), as well as with mathematical and numerical skills (Barrouillet & Lepine, 2005; Bull, Johnston, & Roy, 1999; Bull & Scerif, 2001; De Smedt et al., 2009; Gathercole, Tiffany, Briscoe, & Thorn, 2005; Meyer, Salimpoor, Wu, Geary, & Menon, 2010). Regarding reading achievement, WM has been shown to predict reading comprehension in children and adolescent independently of verbal ability (Cain, Oakhill, & Bryant, 2004), vocabulary (Leather & Henry, 1994), and verbal short-term memory (Leather & Henry, 1994; Swanson, 2003). Regarding mathematics, it has been shown that WM predicts a wide range of numerical and mathematical skills including, problem solving (Passolunghi & Siegel, 2001; Swanson & Beebe-Frankenberger, 2004), number transcoding (Camos, 2008), and the use of direct retrieval for single-digit additions (Barrouillet & Lepine, 2005). It is interesting to note that the association between WM and reading as well as mathematics is not mediated by IQ (Bull et al., 1999; Geary et al., 1999).

Evidence also suggests that children and adolescents with learning disability have significantly impaired performance on complex memory span tasks (Gathercole & Alloway, 2006; Swanson, 1993, 1994; Swanson, Xinhua, & Jerman, 2009). In children with reading

disability, an association has been found between reading skills and complex span tasks, including comprehension and reading fluency (Nation, Adams, Bowyer-Crane, & Snowling, 1999; Swanson & Jerman, 2007; S. Wang & Gathercole, 2013). In children with mathematical disability, a similar association has been found with performance on complex span tasks and general mathematical skills, including mathematical computation, problem solving and addition (Geary, Hoard, Byrd-Craven, & DeSoto, 2004; McLean & Hitch, 1999; Passolunghi & Siegel, 2001; Wilson & Swanson, 2001). Some researchers have reported that the association between mathematical skills and WM is specific to visuo-spatial complex span tasks (McLean & Hitch, 1999; Passolunghi & Mammarella, 2012). Moreover, this association between learning disability and complex span tasks holds true during adulthood (Swanson, 1993; Wilson & Swanson, 2001). Importantly, the link between WM and academic achievement in children and adolescents with learning disability is independent of IQ, verbal ability, short-term memory and phonological awareness (Gathercole, Alloway, Willis, & Adams, 2006).

Executive functions

As stressed by Anderson (2008), executive function is not a unitary process, but rather a construct composed of multiple interrelated higher-level cognitive skills. A developmental framework developed by Anderson (2008) conceptualised executive functions as an overall control system, which comprises four distinct domains: attentional control, cognitive flexibility, goal setting, and information processing. WM is part of the "cognitive flexibility" domain, considered the principal component of executive functions in this framework. The degree to which WM difficulties extend to other executive functions in children and adolescents is not well understood at present. Some studies have distinguished WM from executive functions. Results showed that WM abilities and inhibition as well as shifting skills were unrelated in children of 10 to 12 years of age (St Clair-Thompson, 2011; St Clair-Thompson & Gathercole, 2006). These findings are consistent with the previous evidence found in adults (A. Miyake et al., 2001). In contrast, some studies reported that WM difficulties extend to other executive functions. Using behavioural ratings of executive functions (Behavior Rating Inventory of Executive Function, BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) in children of 5 to 10 years of age, Gathercole and colleagues (2008) found that WM difficulties were associated with executive function difficulties in daily life, such as monitoring activities and generating new solutions to problems. Thus, it appears that WM and

executive difficulties could co-occur in children and adolescents, however, the relationship between WM and executive functions needs further exploration.

Language

Human language is a complex and multifaceted cognitive capacity (Glasser & Rilling, 2008). WM seems to play an important role in several language processes in children and in adults. In typically developing children, Baddeley and Hitch's phonological loop has been associated with native language acquisition. A series of studies have shown a correlation between vocabulary acquisition and knowledge with the phonological loop tasks in children from 4 to 13 years of age (Avons, Wragg, Cupples, & Lovegrove, 1998; Gathercole & Baddeley, 1989; Gathercole, Hitch, Service, & Martin, 1997; Gathercole, Willis, Emslie, & Baddeley, 1992) as well as in second language acquisition (Service & Kohonen, 1995). Researchers have also shown that spoken language comprehension in children from 6 years and older is related to performance on complex memory span tasks (Engle et al., 1992; Nation et al., 1999). In children and adolescents, a body of evidence suggests that young people with SLI demonstrate severe impairment in verbal complex span tasks (Archibald & Gathercole, 2007; Montgomery, 2003). Together the existing literature suggests that WM, especially in the verbal modality, plays a role in expressive and receptive language ability but how these are linked remains unclear.

Conclusion

Developmental studies show that WM is a building block for the development of higher cognitive functions and learning, including general intellectual function, executive functions, language and academic performance. Impairment in WM abilities can have an important impact on cognitive development and learning in childhood. WM abilities have been studied in different clinical samples with atypical development. However, despite its central role during development, WM abilities have never been studies in children with AgCC so far.

2.4. Models of Working Memory

Several WM models have been proposed, reflecting the diversity of perspectives on the nature, structure and function of WM (J. R. Anderson, Reder, & Lebiere, 1996; Baddeley, 1996a; Barrouillet, Bernardin, & Camos, 2004; Barrouillet & Camos, 2001; Cowan, 1988). However, despite a variety of theoretical approaches, Towse and colleagues (2007) stressed that it is not easy to discern a developmental model of WM. A source of controversy in the WM literature has been to consider WM as a unitary versus a non-unitary concept (Akira Miyake & Shah, 1999). These different models and the distinction between unitary and non-unitary models might help us to better understand organisation of WM in children and adolescents with AgCC.

Non-unitary models

Some researchers fractionate WM in several specialised components and subsystems. The most influential model of WM, called the "multiple-component model", has an inherent non-unitary nature. This model, originally developed by Baddeley and Hitch (1974), has been revised several times (Baddeley, 1986, 1992, 1996a, 1998a, 1998b, 2000, 2007; Baddeley & Hitch, 1974). In this model, WM is conceptualised as a cognitive system comprising several specialised components, which can be further fractionated (Figure 11). The "central executive system" offers the mechanism for attentional-controlling processes in WM. It regulates the distribution of limited attentional resources and coordinates the control of encoding and retrieval strategies, as well as the mental manipulation of material held in two subsidiary slave systems. The different components of this model are described further below.

The two slave systems, the "phonological loop" and the "visuo-spatial sketch pad", are memory storage buffers with limited capacity that are responsible for immediate registration and rehearsal of language-based or visuo-spatial information respectively. The distinction between two domain-specific slave systems is motivated, in part, by findings using dual-task paradigms in which performance of two simultaneous tasks requiring the use of verbal and spatial information was nearly as efficient as performance of each task individually. In contrast, simultaneously carrying out two tasks that use the same informational modality results in less efficient performance than performing the tasks individually (Thomason et al., 2009).

The phonological loop was originally developed to account for four memory phenomena: a) the word length effect, which consists of poor recall for lists of long words compared to lists of short words; b) the phonological similarity effect (or acoustic confusion effect) consisting of poor recall for lists of similar-sounding words compared to lists of dissimilar-sounding words; c) the irrelevant speech effect revealed by poor recall in the presence of irrelevant auditory stimuli; and d) the concurrent articulation effect consisting of poor recall if a person is required to concurrently articulate irrelevant information while completing a memory span task (Baddeley, 1986, 1992). The phonological loop is further fractionated into a passive phonological store and an active rehearsal system, the articulatory loop. Similarly, the visuo-spatial sketchpad has been fractionated into a passive visual cache and an active spatially-based rehearsal system called the inner scribe.
Finally, the "episodic buffer" is a workspace for the temporary storage of multidimensional information that allows the binding of information from the slave systems to create a unitary episode, event or representation.

The multiple-component model offers a useful framework for a wide range of empirical findings on WM. It has been supported by evidence from studies of children and adolescents (Alloway, Gathercole, & Pickering, 2006; Alloway et al., 2004; Gathercole, 1998), adult participants, neuropsychological patients (Baddeley, 1996a; Vallar & Pagano, 2002), as well as neuroimaging studies (Smith & Jonides, 1997). Furthermore, this WM model can also be applied to the study of atypical development in children and adolescents (Jarrold, 2000). It provides a potential framework for describing, explaining and predicting deficits in WM functioning that might be seen in individuals with neurodevelopmental disorders, such as children with AgCC. Firstly, by characterising specific types of WM difficulties (i.e., breakdown or dysfunction in one of the components), we can also suggest ways to improve specific WM components. Further, as WM has been shown to be important in the development of other cognitive abilities, it may be possible to predict how broader problems in cognitive functioning arise in the context of specific WM impairments. Therefore, this model has an important predictive power, especially in the study of learning disabilities (Baddeley, Gathercole, & Papagno, 1998; Hanley, Young, & Pearson, 1991). However, in the study of atypical development, this model also shows some weaknesses (Jarrold, 2000). In particular, there is a lack of specification and details in the development and functioning of the working of these components. When studying atypical development, developmental

factors need to be consider as competences and abilities that are not only delayed, but rather deviated from what we would expect in typical development (Jarrold, 2000).

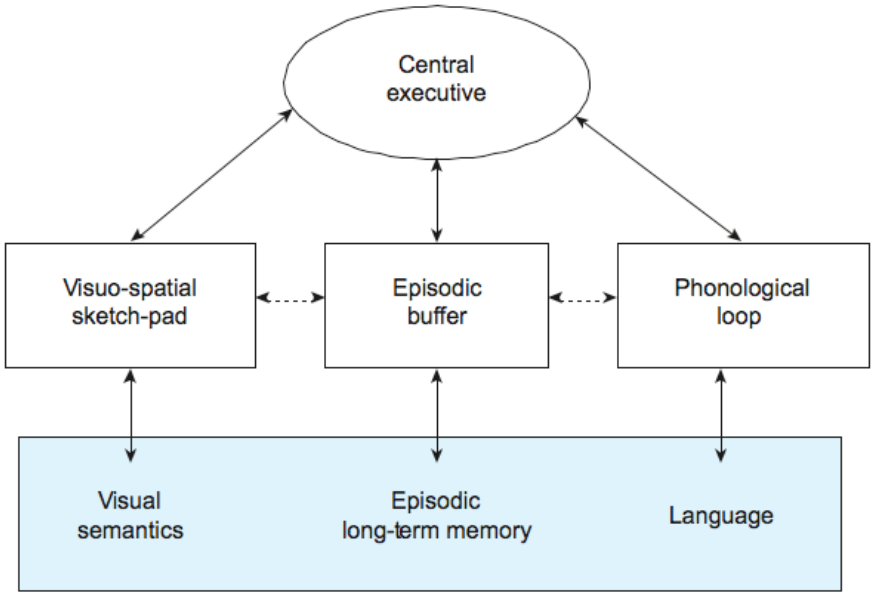

Figure 11. The multi-component model of WM (reproduced from Baddeley, 2012; p. 16).

The non-unitary view of WM has also been adopted by other authors. Barrouillet and colleagues developed a time-based resource-sharing (TBRS) model, which proposes a new conception of the relationships between processing and storage (Barrouillet et al., 2004; Barrouillet, Bernardin, Portrat, Vergauwe, & Camos, 2007; Barrouillet & Camos, 2015; Barrouillet, Portrat, & Camos, 2011). This model was initially inspired and conceived based on developmental studies (Barrouillet & Camos, 2001) and is based on four main assumptions. First, the two main processes of WM, processing and storage of information, are assumed to rely on the same resource, which is attention. Attention is viewed as a limited resource that should be shared between processing and storage functions. Second, a processing limitation in cognition, also called the central bottleneck, constrains central processes: when the bottleneck is occupied by some processing episode, it is not available for processes related to the maintenance of memory items. As a consequence, processing and maintenance take place serially. Third, as soon the focus of attention is switched away from maintenance to processing, the activation of memory traces suffers from a time-related decay. Therefore, memory traces of the items to be maintained fade away if not reactivated before complete disappearance. Fourth, a rapid and incessant switching of attention from processing to maintenance occurs in order to constantly reactivate memory traces.

The TBRS model assumes that the cognitive load involved in an activity is a function of the proportion of time during which this activity occupies attention. Thus, activities that capture attention for a long period of time prevent the possibility of refreshing memory traces, which leads to a detrimental effect on maintenance of information. Whereas maintenance of visuo-spatial information relies only on attention, maintenance of verbal information relies not only on attention but also on a verbal-specific system independent from attention, corresponding to an articulatory rehearsal system comparable to the phonological loop in Baddeley and Hitch's model (Camos, Lagner, & Barrouillet, 2009). Only a limited amount of information can be maintained in this phonological loop without attentional involvement, such that when the capacity of this process is exceeded, attention-based mechanisms are needed to maintain relevant information (Vergauwe, Camos, & Barrouillet, 2014). Assumptions of the TBRS model have been supported by evidence in adults (Barrouillet et al., 2007) as well as in children (Portrat et al., 2009).

The non-unitary approach of WM has gained support from brain imaging studies. The PFC appears to play a role in executive control involved in the active maintenance of task-relevant information (D'Esposito, 2007; Stuss & Alexander, 2007). For the TBRS model, bilateral inferior frontal gyri, in particular the right inferior-frontal junction appears to play a crucial role for domain-general contribution to time-based resource sharing (Vergauwe, Hartstra, Barrouillet, & Brass, 2015). It appears that different WM modalities are underpinned by different specialised brain regions; however, findings are not consistent. Some studies support involvement of bilateral DLPFC regions for spatial WM information, and involvement of bilateral ventrolateral prefrontal cortex (VLPFC) regions for WM non-spatial information (Belger et al., 1998; Sala, Rama, & Courtney, 2003). Others document that the left and right prefrontal areas contribute differently to visuo-spatial and verbal WM, with DLPFC activation more lateralised to the right hemisphere during visuo-spatial WM, and to the left hemisphere during verbal WM (Reuter-Lorenz et al., 2000; Thomason et al., 2009).

The phonological loop, as conceptualised by Baddeley and used in the TBRS, has also found support in neuroimaging studies. Verbal WM tasks have been found to engage bilateral Broca's area, a set of regions known to be involved in phonological processing (Awh et al., 1996; Paulesu, Frith, & Frackowiak, 1993). It also seems that higher-order association cortices, such as the PFC and parietal cortex, interact with posterior sensory regions, such as

language or phonological-related regions, to facilitate maintenance of a sensory percept (D'Esposito, 2007). Using a delayed recognition paradigm with faces, bilateral functional activations in the fusiform face area, a visual region selective for viewing face, were found to correlate with bilateral activation in the prefrontal and parietal cortices (Druzgal & D'Esposito, 2003). Similar results were found in response to delayed cued recall paradigm using written words (Fiebach, Rissman, & D'Esposito, 2006). Left inferior temporal regions, corresponding to language-related visual association areas, exhibit increased functional connectivity with the left PFC.

To summarise, non-unitary view of WM has been supported by a few neuroimaging studies. Frontal and parietal regions seem to be largely involved in executive and attentional control engaged during WM task. However, specialised regions for the different WM modalities have been found but findings are inconsistent.

Unitary models

In contrast to the multi-component and the TBRS models, some researchers emphasise the unitary nature of WM, focusing on the central component of WM (Barrouillet et al., 2004; Daneman & Carpenter, 1980b).

The "embedded processes model" proposed by Cowan (Cowan, 1999) suggests that the "contents of WM" are not maintained within dedicated storage buffers, but are a subset of information within the focus of attention at a given time (Figure 12). This model contains three hierarchical facilities: (1) long-term memory; (2) the subset of working long-term memory that is currently activated; (3) the subset of activated memory that is the focus of attention and awareness. The direction of the attentional focus is controlled by the central executive, that is, a domain-general processing capacity (Cowan 1999). The focus of attention is capacity-limited and similarly activation is time-limited. If information exceeds the capacity, the earlier items in the focus have a higher chance of being deactivated and displaced from the focus of attention (Haarmann & Usher, 2001). In this model, task-relevant representations have different levels of activation that can be higher or lower. They may be in the focus of attention; some may be in an especially active state, ready to enter the focus as needed; and some may have the appropriate contextual coding in long-term memory that

allows it to be made available quickly. The concept of "activated memory" is based on any modality and any form of representation. In this sense, the model is unitary (Cowan, 1999).

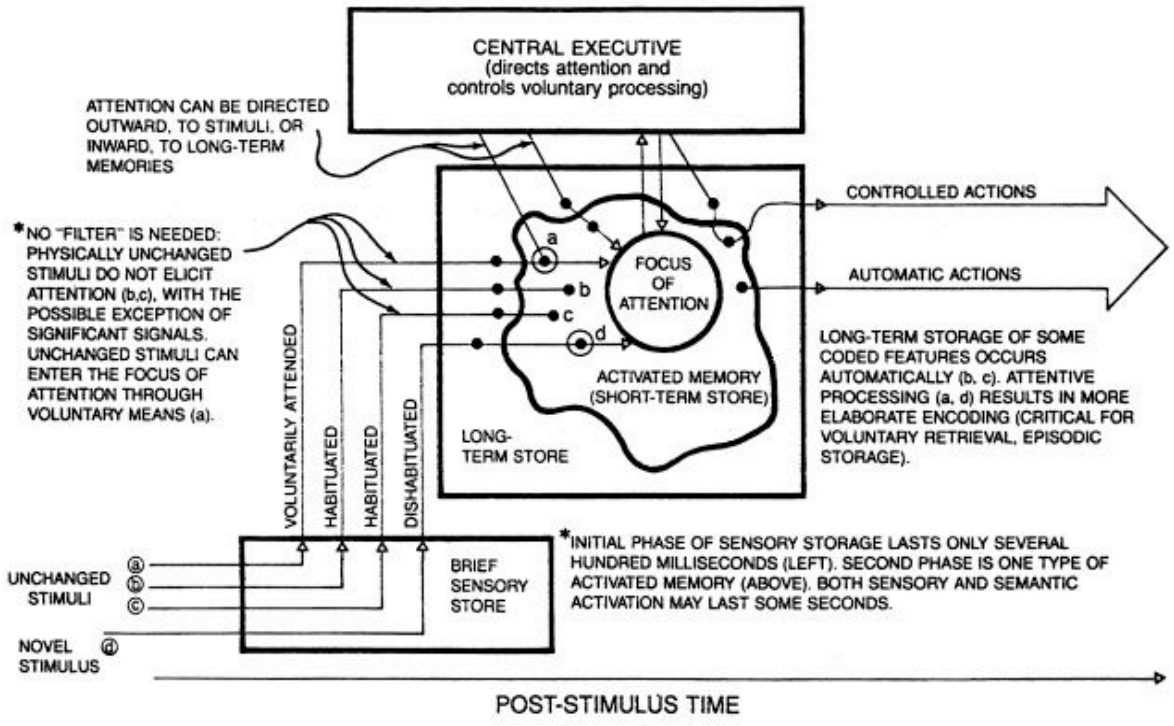

Figure 12. The embedded processes model (reproduced from Cowan, 1999; p.66).

As a second example, the model of Engle, Kane, and Tuholski defines WM as "the capacity for controlled and sustained attention in the face of interference or distraction" (Engle, Kane, & Tuholski, 1999; p.103) . This model proposes two different features: (1) a domain-free, limited capacity controlled attention; (2) domain-specific codes and maintenance, such as the phonological loop but the number of such codes is very large. This model is unitary in the sense that WM capacity or capacity to sustain attention is domain free. It also suggests that individual differences in capacity for controlled processing are general and possibly the mechanism for general fluid intelligence.

Considering the unitary view of WM in neural terms, temporary retention of task-relevant information is processes by a unitary system consisting of activation of the neural structures that represent the information being maintained or stored (D'Esposito, 2007). For example,

the temporary retention of a face would require activation of cortical areas that are involved in the perceptual processing of face. However, each of the authors mentioned above has a different view. Based on the literature, Cowan proposes that each of the components of his model is underpinned by a specific neural substrate. The inferior parietal might be critical for the focus of attention, and the prefrontal cortex for the central executive. In addition, associative cortex is supposed to play a role in memory activation and the hippocampus for the storage with attention. In contrast, Engle, Kane, and Tuholski argue that the DLPFC and associated structures mediate the controlled processing functions of WM. These authors suggest that domain specific codes might be mediated by the structures appropriate to the domain. As an example, speech-based codes would be mediated by speech centres in the brain.

Conclusion

Non-unitary and unitary models propose different approaches of WM. Considering neural correlates of WM, all these models suggest both an integration of WM information across hemispheres. Apart from the involvement of specific unitary system that are usually lateralised (e.g., language-related system), all these models predict the involvement of executive and attentional network, with frontal and parietal areas, that are not restricted to one hemisphere but rather a network of left and right-lateralised regions. Indeed, in addition to the importance of prefrontal, including the DLPFC and the VLPFC, and parietal regions, between and within hemispheric modulations of these regions have been consistently reported in fMRI studies of WM (Figure 13; Hillary et al., 2011; Koshino et al., 2005; Schlösser, Wagner, & Sauer, 2006) . We have seen that between hemispheric connectivity is mainly carried out by the major commissure in the brain, the CC (Richards et al., 2004). But what happen to WM functioning and capacity when the CC fails to develop and transfer of information between the two hemispheres are largely restricted?

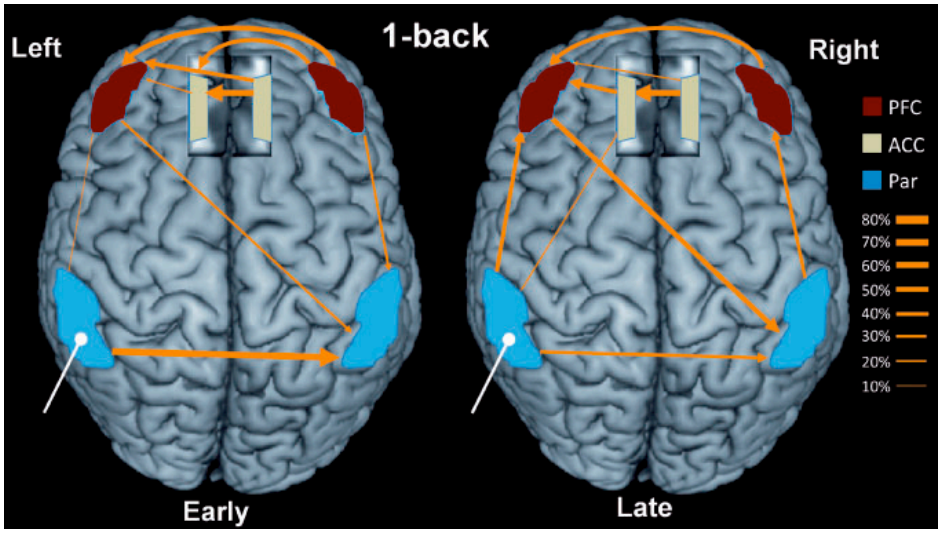

Figure 13. Between and within hemispheric connectivity in healthy individuals for 'early' and 'late' effects during a 1-back task (visual sequential letter task). Line thickness indicates frequency of connections. ACC = anterior cingulate cortex; Par = parietal; PFC = prefrontal cortex (reproduced from Hillary et al., 2011; p. 11).

2.5. Biological Underpinnings of Working Memory during Development

Neural underpinnings of WM have important similarities between adults and children. Here we review the literature of functional MRI studies on WM completed in typically developing children and adolescents before making links with structural maturation processes linked to development of WM abilities.

Functional MRI studies of working memory during childhood

As previously described, developmental behavioural studies have documented an increase in WM ability from childhood to adulthood (Chelonis, Daniels-Shaw, Blake, & Paule, 2000; Conklin, Luciana, Hooper, & Yarger, 2007; Gathercole, Pickering, Ambridge, et al., 2004; Hitch, Towse, & Hutton, 2001; Kemps et al., 2000). In brain imaging of typical and atypical cognitive development, the confounding effect of age and task performance on blood oxygen level-dependent (BOLD) activation poses a challenge. At issue is whether changes in brain activity reflect changes in functional maturation of the CNS, independent of behavioural changes or whether they reflect changes in task performance, increasing with age (Kwon et

al., 2002; Schweinsburg et al., 2005). When behavioural performance during fMRI scan varies between two groups, differences in brain activity are difficult to interpret. Two approaches are employed in developmental neuroimaging studies. The first approach is to simplify cognitive tasks so that all children can perform them to obtain a ceiling effect (Klingberg et al., 2002). Although this approach eliminates performance as a confounding factor, the simplified tasks may not capture critical cognitive operations that are evoked during WM (Kwon et al., 2002). The second approach is to group participants and attribute tasks of different levels of difficulty based on individual performance levels (Thomas et al., 1999). However, this approach poses difficulties in selection of performance criteria and in interpretation of different tasks (Kwon et al., 2002).

A number of studies have investigated neural correlates of WM during childhood and adolescence. These studies are summarised in Table 2. Most of these are cross-sectional fMRI studies which report similar distributions of brain activation foci in children and adults.

In 1995, Casey and colleagues were the first to examined brain activation during the performance of a verbal WM task among six children aged 9–11 years. These early results mirrored those observed in adults performing an identical version of the task (J. D. Cohen et al., 1994) with activation of inferior and middle frontal gyri. More recent studies explored further brain activations during different verbal WM tasks. Using an fMRI Sternberg item recognition task, O'Hare and colleagues (2008) examined developmental differences in 12 children (7-10 years), 10 adolescents (11-15 years), and eight young adults (20-28 years) ; Van der Brosh and colleagues (2014) studied the development of brain connectivity related to verbal WM in 10 children (9-12), 12 adolescents (13-16) and 13 young adults (17-19) ; and finally, Vogan and colleagues (2016) explored developmental changes in brain activity related to verbal WM in 24 children, aged from 9 to 15, using a verbal n-back task. In these three studies, it was found that verbal WM was underpinned by a fronto-parietal network across all age groups.

The same core fronto-parietal network was found in response to viso-spatial WM task in children and adolescent studies. Thomas and colleagues (1999) reported right DLPFC, right superior frontal gyrus, right superior parietal lobule, and bilateral inferior parietal cortex activations during a visuo-spatial WM task in six children (8–10 years) and six adults (19–26 years) . Nelson and colleagues (2000) replicated these findings in nine children aged 8–11 years performing a visuo-spatial WM task, with activations in right DLPFC, bilateral superior

frontal gyrus, right superior parietal lobule, and right inferior parietal cortex. Using a voxel-based approach, Kwon and colleagues (2002) showed linear changes in brain activation in right DLPFC, left VLPFC (including Broca's area), and bilateral posterior parietal cortex in response to visuo-spatial WM task. Similarly, the involvement of this fronto-parietal network in response to visuo-spatial WM was found by several authors: Schweinsburg and colleagues (2005) in 49 adolescents from 12 to 17 years of age; Scherf and colleages (2006) in nine children aged 10 to 13 years and 13 adolescents aged 14 to 17 compared to eight adults aged 18 to 47 years; Olsen and colleagues (2007) in comparing 13 13-year-olds and 11 adults; Vuontela and colleagues (2009) in nine children aged 11 to 13 years; Taylor and colleagues (2011) in 73 participants aged 6 to 34; Spencer-Smith and colleagues (2013) in 44 children aged 7 to 12; and finally Kharitonova and colleagues (2015) in 22 young children aged 5 to 8 years .

Two studies also explored the influence of verbal and visuo-spatial content of information on WM-related brain activations: Brahmbhatt and colleagues (2008) in 15 adolescents aged 14 to 17 and 15 adults, and Thomason and colleagues (2008) in 16 children aged 7 to 12 years and 16 adults aged 20 to 30 years. Both studies showed that children and adults recruited the same activation foci for verbal and visuo-spatial WM task, including frontal and parietal regions. As reported in some adult studies, they also found greater left-hemisphere activation for verbal content and greater right-hemisphere activation for visuo-spatial content in both groups.

In addition to this core WM network, fMRI studies investigating development of brain organisation of WM in children and adolescents also reported the involvement of the cerebellum during verbal (O'Hare et al., 2008; Thomason et al., 2009; van den Bosch et al., 2014) and visuo-spatial WM tasks (Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006; Scherf et al., 2006; Thomason et al., 2009). Premotor and motor areas were also found to be involved in verbal (van den Bosch et al., 2014) and visuo-spatial WM (Ciesielski et al., 2006; Kwon et al., 2002). The caudate nucleus has been associated to visuo-spatial WM (Ciesielski et al., 2006; Klingberg et al., 2002; Olesen et al., 2007; Thomason et al., 2009). Finally, the involvement of hippocampus and parahippocampus regions has only been reported in response to verbal WM task in children and adolescents (Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Thomason et al., 2009).

Functional MRI studies also reported quantitative changes in the set of core regions underpinning WM during childhood and adolescence, and the degree of engagement of these different regions may change with maturation (Berl, Vaidya, & Gaillard, 2006). Age-related increase in brain activation have been reported in frontal regions (Klingberg et al., 2002; Kwon et al., 2002; Scherf et al., 2006; Schweinsburg et al., 2005; M. J. Taylor et al., 2012; Thomason et al., 2009), parietal regions (Klingberg et al., 2002; Kwon et al., 2002; Scherf et al., 2006; Schweinsburg et al., 2005; Spencer-Smith, Ritter, Murner-Lavanchy, et al., 2013; M. J. Taylor et al., 2012), and PMC (Kwon et al., 2002). In addition, children demonstrate greater activation than adults in portions of the parahippocampal gyrus (Thomason et al., 2009). Kwon and colleagues (2002) suggested that age-related increases in this distributed fronto-parietal network are linked to the implementation of the phonological loop. According to these authors, almost all brain regions implicated in the phonological loop shows age-related increases in activation, including VLPFC, PMC, and parietal regions (left IPC and intraparietal sulcus). Moreover, age-related increases in brain activity have been associated with increases in WM capacity. Klingberg and colleagues (2002) found a positive correlation between age-related increases in visuo-spatial WM capacity and brain activity in the superior frontal and intraparietal cortices in 13 participants between 9-18 years of age. Only one study found that adolescents with better WM capacity tend to recruit fewer regions in the visuo-spatial WM network (49 adolescents aged 12 to 17 years; Nagel, Barlett, Schweinsburg, & Tapert, 2005).

Only three published fMRI studies to date have investigated the different processes involved in WM activity in children and adolescents, specifically encoding, manipulation and recall. Crone, Wendelken, Donohue, van Leijenhorst, and Bunge (2006) completed a visuo-spatial WM task in 14 children aged 8 to 12 years, 12 adolescents aged 13 to 17 years, and in 18 adults aged 18 to 25 years. Results showed maintenance-related activation in prefrontal (DLPFC and VLPFC) and parietal cortices across the three groups, whereas manipulation-related activation in DLPFC was only found in adolescents and adults but not in children. In 13 13-year-olds and 11 adults (19 to 25 years) completing a visuo-spatial WM task, Olesen and colleagues (2007) found similar activation foci across the two groups: a) during the maintenance phase in the DLPFC; b) during the manipulation phase, in the superior fontal sulcus and parietal cortex; c) during the recall phase, in the parietal cortex. Van den Bosch and colleagues (2014) investigated encoding and recognition activation during a Stenberg item recognition task in 10 children aged 9 to 12 years, 12 adolescents aged 13 to 16 years,

and 13 older adolescents aged 17 to 19 years. Similar activation foci was found for the encoding phase in the right prefrontal and parietal cortex, cerebellum, left motor area, and occipital lobe and for recognition phase in the left prefrontal and parietal cortex, anterior and posterior cingulate cortex, cerebellum, and right motor area.

To conclude, it appears that WM development in childhood and adolescence is associated with increased activation in the specialised WM network reported in the adult literature, i.e., frontal and parietal regions (Klingberg et al., 2002; Kwon et al., 2002; Nagel, Barlett, Schweinsburg, & Tapert, 2005; Olesen et al., 2007; Scherf et al., 2006; Schweinsburg et al., 2005; Spencer-Smith, Ritter, Murner-Lavanchy, et al., 2013). Greater activation across this network has also been associated with improvements in children and adolescents' WM capacity (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Klingberg et al., 2002). It appears that these brain areas become increasingly involved over childhood and adolescence in WM task and in the development of WM capacity. Therefore, the developing brain becomes more functionally specialised with age, with qualitative and quantitative changes in functional WM brain circuitry (Spencer-Smith, Ritter, Murner-Lavanchy, et al., 2013; M. J. Taylor et al., 2012).

Structural maturation processes in brain regions used for working memory

The gross architecture of the human brain is largely developed in late childhood (Caviness, Kennedy, Bates, & Makris, 1996). Throughout childhood and adolescence, the brain undergoes a multifaceted and regionally differentiated maturational process. Structural MRI studies have revealed two distinctly different maturational processes during childhood and adolescence, specifically white matter maturation and cortical thinning (Vestergaard et al., 2011). Both white and grey matter exhibit protracted trajectories of developmental changes that vary across different cerebral regions (Giedd, Blumenthal, Jeffries, Castellanos, et al., 1999; Paus et al., 2001; Sowell et al., 2004; Sowell, Trauner, Gamst, & Jernigan, 2002). Improvement of WM capacity during childhood and adolescence has been associated with these structural changes in brain regions implicated in WM processing during functional MRI.

White matter

They are several white matter maturation processes that coincide with increased of WM capacity, including synapse formation and pruning (i.e., elimination), and most importantly the myelinisation of axons (Klingberg, 2006).

Synapse production and pruning in regions underpinning WM is a possible contributor to the development of WM competencies. Early synapse formation seems to be mainly endogenously regulated (Bourgeois, Jastreboff, & Rakic, 1989), whereas late synapse formation can be influenced by environmental factors and occurs in relation to learning and memory (Kleim, Vij, Ballard, & Greenough, 1997; Olesen et al., 2003; Zito & Svoboda, 2002). An overproduction of connections and synapses occurs early in life, followed by a pruning of the connections that are not used (Bourgeois & Rakic, 1993; LaMantia & Rakic, 1990).

Myelin is a lipo proteinaceous membrane covering the axons in order to insulate them from the fluids in the CNS (Jacobson & Marcus, 2008). The principal purpose of the myelin is to help the axons to have faster information transfer, and allow a more precise timing in the communication between cortical areas (Nagy, Westerberg, & Klingberg, 2004). Microstructural properties of white matter can be investigated in vivo by DTI. DTI measures properties of the diffusion of water in the brain. Myelination of axons increases anisotropy (i.e., directionality, degree of elongation of the diffusion tensor), as shown in mice and human studies (Gulani, Webb, Duncan, & Lauterbur, 2001; Werring, Clark, Barker, Thompson, & Miller, 1999). Using DTI, the degree of anisotropy can be quantified as fractional anisotropy (FA). Increases in FA during childhood and adolescence can be attributed to maturation of myelination and thickening of axons as well as other properties of fibre organisation (Klingberg, 2006; Ostby, Tamnes, Fjell, & Walhovd, 2011). Myelinisation of axons is one of the most prolonged developmental processes in the human brain as it continues at least until 20 years of age (Benes, 1989; De Bellis et al., 2001; Giedd, Blumenthal, Jeffries, Rajapakse, et al., 1999). The prefrontal and intraparietal cortices, largely implicated in the functional network underlying WM function in children and adolescence, are among the last brain regions to myelinate (Fuster, 2008; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Yakovlev & Lecours, 1967).

Olesen and colleagues (2003) found a correlation between FA values in fronto-parietal white matter and BOLD response to a dot location n-back task, in 23 children aged 8 to 18 years, a correlation principally explained by age-related maturation of white and grey matter. Nagy and colleagues (2004) showed that development of WM capacity was positively correlated with FA in the left superior frontal and parietal cortices (n = 23) . They also found that FA value in the CC was significantly correlated with WM capacity, even after the effect of age was removed. It has been suggested by the authors that white matter maturation in the CC presumably improves the communication between the two frontal lobes. Vestergaard and colleagues (2011) extended the findings of Nagy and colleagues with a sample of 76 typically developing children between 7 and 13 years completing a spatial WM task. The results showed that increased FA in the left fronto-parietal network composed of the superior longitudinal fasciculus, the regional white matter underlying the DLPFC and the posterior parietal cortex, exhibits a significant association with better spatial WM performance in children between 7 and 13 years. These findings are consistent with a relationship between structural connectivity in this network and individual differences in spatial WM abilities, and were not attributable to age-related differences (adjusted for effects statistically attributable to age). Østby and colleagues (2011) corroborated these findings in 108 healthy participants aged 8–19 years with a forward and backward digit span task. Microstructural properties (FA) of the superior longitudinal fasciculus were related to verbal WM performance in both tasks. These findings confirm the importance of white matter maturation for verbal and visuo-spatial WM performance in development, especially in the fronto-parietal network. White matter maturation, in turn, may be affected by genetic pre-programming or by experience and learning (Nagy et al., 2004).

Grey matter

Increase of WM capacity and white matter maturation processes in development also coincide with changes in cortical grey matter thickness (Shaw et al., 2008). Several authors suggested that thinning of cortical grey matter could be attributable, in part, to increased proliferation of myelin into the periphery of the cortical neuropil, which would change the MR signal value from grey matter in the younger subjects to white matter in the older subjects (Courchesne et al., 2000; Sowell et al., 2004; Sowell, Thompson, Tessner, & Toga, 2001). To some extent, they suggested that, during typical brain development, grey matter is replaced by white matter, given that white matter volume increases and grey matter volume declines.

The study of Østby and colleagues (2011) previously mentioned showed that cortical thickness of both the supramarginal gyrus and rostral middle frontal cortex were negatively related to forward digit span performance (much more weaker association for digit span backward), independently of age. In a cross-sectional study of 98 healthy children and adolescents (8–19 years old), Tamnes and colleagues (2010) found that thinner cortices in bilateral parietal and frontal areas (around the central sulcus, and encompassing areas in the left IFG and right superior medial parietal areas) were associated with better WM updating performance, as measured by a variant of verbal n-back task (i.e., keep track task) . In a subsequent study using a longitudinal design in 79 children and adolescents from 8 to 22 years of age, Tamnes and colleagues (2013) found that the extent of improvement in verbal WM performance was related to the degree of bilateral volume decrease in three cortical regions, including the prefrontal cortex, posterior parietal regions, and central sulci. These associations were observed independently of gender, age, general intellectual abilities, and change in intellectual abilities.

Conclusion of structural changes during development

Darki and Klingberg (2014) used both cross-sectional and longitudinal designs in 89 children and young adults aged 6 to 25 years. Cross-sectional analysis showed a correlation between visuo-spatial WM abilities, BOLD contrast in both frontal and parietal regions, cortical thickness in the parietal cortex, and white matter structure of fronto-parietal and fronto-striatal tracts (both FA and volume). Nevertheless, longitudinal analysis showed that only white matter structure of fronto-parietal and fronto-striatal tracts correlated with WM capacity two years later. These results suggested that white matter integrity, specifically of fronto-parietal and fronto-striatal tracts, provides an important basis for the development of future WM capacity.

Taken together, these studies suggest that developmental improvements in WM functions are supported by the functional (BOLD signal) and structural (white matter microstructure and cortical thickness) maturation of specific brain regions involved in WM function, specifically the fronto-parietal network. However, gradual white matter maturation in the fronto-parietal network appears to be the most important association with improvement of WM capacity during childhood and adolescence.

2.6. Summary of the Chapter

Over the last 40 years, WM has become a central construct in cognitive psychology and more recently in cognitive neurosciences, including developmental cognitive neurosciences. It is considered to be a system devoted to the simultaneous storage and maintenance over short periods of time. A diversity of perspectives on the nature and structure of WM have led to as a myriad of WM models that can be classified into a unitary or a non-unitary view of WM, as well as the development of different WM paradigms. Something that all researchers seem to agree on is the essential role that plays WM in elementary and complex cognition, including general intellectual functioning, executive functions, language, and academic achievement, especially during cognitive development. Indeed, impairment in WM abilities can have dramatic impact on cognitive development and learning during childhood. Finally, the neural network of WM in children and adolescents seem to encompass fronto-parietal regions, similar to what have been found in adults. Structural maturation of white and grey matter in these brain regions during childhood is also associated with developmental improvement of WM capacity. In accordance with this fronto-parietal network, intrahemispheric but also interhemispheric communications, underpinned by the CC, appear crucial for WM functions in typically developing children and adults. Despite the crucial role of WM during cognitive development and the central role of the CC for WM brain functions, WM abilities and related functional brain organisation of WM have never been studies in children with AgCC so far.

Table 2. Functional MRI studies of WM BOLD activation in children and adolescents.

Study	Aim of the study	Sample size (N); [age range in years]	WM paradigm	Stimuli type	Monitoring type	Results
Casey et al. (1995)	Examine prefrontal activation in children during verbal WM task	N=6; [9-11]	N-back (0, 1, 2-back)	Letters	Identity	a) Similar activation foci in children and adults: inferior and middle fontal gyri b) Activation correlates with behavioural performance
Thomas et al. (1999)	Investigate brain activity during spatial WM in children and adults	N=6; [8-10] N=6; [19-26]	N-back (1, 2-back)	Coloured dots	Location	Similar activation foci in children and adults: right SFG, mid frontal, superior parietal and bilateral inferior parietal gyri
Nelson et al. (2000)	Examine functional anatomic organisation of WM in children	N=9; [8-11]	N-back (1, 2-back)	Coloured dots	Location	Similar activation foci in children and adults: middle and SFG, posterior parietal area, and ACC.
Klingberg (2002)	Identify changes in brain activity associated with the increase in WM capacity that occurs during childhood and early adulthood	N=14; [9-19]	Sternberg item location paradigm (three and five loads)	Dots	Location	a) Positive correlation between age-related increases in WM capacity and brain activity in the SFG and intraparietal cortex b) Positive correlation between WM capacity and WM activity in the left SFG and left intraparietal areas across all age group
Kwon et al. (2002)	Examine focal changes in WM-related brain activation with age using a voxel-based approach	N=34; [7-22]	2-back	Letter O	Location	a) Linear changes between age and brain activation in a distributed fronto-parietal network: bilateral DLPFC, left posterior VLPFC (including Broca's area), left PMC, and posterior parietal cortex b) Age was the most significant predictor of activation in these brain regions
Nagel et al. (2005)	Understand how neuropsychological test performance relate to brain activation patterns during WM fMRI tasks in adolescents	N=45; [12-17]	2-back	Abstract lines	Location	a) Better performance on WM tasks associated with fewer regions recruited in bilateral DLPF and intraparietal brain activation b) Performances on measures of executive functions, memory and speed of processing linked to increases and decreases in bilateral DLPF and intraparietal brain activation
Schweinsburg et al. (2005)	Examine neural substrates involved in SWM in a relatively large sample of normally developing teens	N=49; [12-17]	2-back	Abstract lines	Location	a) Activation foci in children and adults: frontal and parietal neural networks b) Age associated with WM brain response: - Positive association in left PFC and bilateral inferior posterior parietal regions - Negatively associated in bilateral SPC
Crone et al. (2006)	Study developmental improvements in manipulation, relative to pure maintenance using event-related functional	N=14; [8-12] N=12; [13-17] N=18; [18-25]	Verbal object naming WM task	Objects	Identity and order	a) For maintenance-related activation, similar patterns of activation in children and adults: PFC and parietal cortex b) For manipulation-related activation: - Adults, adolescents and children aged 8–12 recruit VLPFC - Children: fail to additionally recruit right DLPFC and SPL

Ciesielski et al. (2006)	Examining whether the neural networks engaged by the Categorical n-back task in children consist of the same brain regions as those in adults	N= 9; [5.11-6-6] N=10; [9.1; 10.5] N=10; [20-28]	Categorical 2-back	Complex objects (drawing of people, objects, animals)	Identity (category)	Age-related pattern of fMRI activation in adults and children: - Adults: reliance on the ventral prefrontal and inferior temporal networks - Children: reliance on the dorsal visual stream and premotor/striatal/cerebellar networks
Scherf et al. (2006)	Investigate both qualitative and quantitative changes in the functional neural circuitry that underlies developmental changes in visuo-spatial WM	N=9; [10-13] N=13; [14-17] N=8; [18-47]	Oculomotor delayed response	Dots	Location, reproduction by saccade	a) Similar activation foci for the three age groups: right DLPFC, right ACC, bilateral anterior insula, right STC, right basal ganglia, and right inferior occipital sulcus b) Quantitative changes across age groups in this set of core regions
Oleson et al. (2007)	Identify changes in brain activity related to each WM phases using an event-related fMRI design	N=13; [12-13] N=11; [19-25]	Sternberg item location paradigm (one load)	Dots	Location	a) Similar activation foci for the two groups (maintenance: DLPFC, manipulation: superior frontal sulcus and parietal cortex, recall: parietal cortex) b) In adults, stronger activation in the DLPFC during the maintenance phase
Brahmbhatt et al. (2008)	Assess age-related differences in the neural correlates of word and face WM tasks	N=15; [14-17] N=15; [24-27]	2-back	Words and faces	Identity	a)Activation related to WM in adolescents similar to adults based on structural ROIs: bilateral DLPFC, left VLPFC, left IFC, right middle frontal gyrus, medial presupplementary motor area, ACC, left IPC, right SPC, left thalamus, left PMC, right cerebellum, left fusiform gyrus. b) Similar age-related differences in left SPC for both word and face stimuli c) Age-related differences that differ according to stimulus: left IFC, left supramarginal gyrus, left rolandic sulcus, right cerebellum and left fusiform gyrus
O'Hare et al. (2008)	Investigate the contribution of cerebro-cerebellar networks to verbal WM in children and adolescents, and characterise developmental changes in the WM load-dependency of this network	N=30; [7-28]	Sternberg item recognition paradigm (three loads)	Letters	Identity	a) Similar cerebro-cerebellar verbal WM networks in children, adolescents and adults b) Neural substrates of linear load-dependency change with age: - In adolescents and adults: increased activation in frontal, parietal and cerebellar regions with increasing load - In children: only increased activation of left ventral PFC with increasing load
Thomason et al. (2008)	Studying the influence of two factors on the development of the brain organisation of WM in children, the content of information (verbal or spatial) and the amount of information (load)	N=16; [7-12] N=16; [20-30]	N-back tasks	Dots and letters	Location and identity	a) Similar activation foci in children and adults: -For both the verbal and spatial tasks: bilateral IFG, MFG, cingulate cortex, and parietal cortex - Greater left-hemisphere activation for verbal content and greater right hemisphere activation for spatial content b) For both tasks, adults exhibited greater activation than children in frontal, parietal, and temporal lobes, basal ganglia, and cerebellum. c) Children demonstrated greater activation than adults: - For verbal WM: in parahippocampal gyrus and right MFC

						- For visuo-spatial WM: several regions of the occipital lobe
Geier et al. (2009)	Characterize developmental changes in brain mechanisms supporting visuo-spatial WM across different delay periods.	N=13; [8-12] N=13; [13-17] N=17; [18-30]	Oculomotor delayed response task	Dots	Location, reproduction by saccade	a) All age groups recruited a common network of regions to support both delay trials, including frontal, parietal, occipital and insular regions b) Age-related differences were found in the recruitment of fronto-caudal areas and posterior parietal cortex. In addition, children and adolescents recruited a considerably more extensive distributed circuitry.
Libertus et al. (2009)	Examine and compare neural systems that children and adults engage to accomplish WM tasks involving different stimulus categories	N=15; [8-9] N=15; [20-35]	2-back	Digits, letters, and faces	Identity	a) Different brain activation foci in children and adults: - Digit condition: category-specific activation in adults only in intraparietal sulcus - Letter condition: category-specific activation in adults only in left occipital-temporal cortex. b) Similar brain-activity patterns between adults and children: - Face condition: activations in the lateral fusiform gyri
Vuontela et al. (2009)	Investigate whether attention and WM processing in children is segregated as suggested by domain-specific model	N=9; [11-13]	N-back (0, 2-back)	Coloured squares	Location and identity	a) During both tasks (spatial and non spatial WM), load related activation in PFC, posterior parietal and occipital cortices (in favour of domain-specific model)
Finn et al. (2010)	Investigate WM network change during adolescence and the involvement of the hippocampus using a longitudinal study design	N=10 Scan1 = [14-16] Scan2 = [17-19]	Delayed match-to-sample task	Letters	Identity	a) PFC involved during WM task in early and late adolescence b) Hippocampus and PFC are coactive in early adolescence irrespective of task demands or performance, in contrast to the pattern seen in late adolescents
Brahmbhatt et al. (2010)	Explore the relationship between WM demands and neural activity changes with age	N=17; [9-13] N=18; [18-23]	N-back (0, 1, 2-back)	Letters	Identity	a) Similar activation in children and adults for sustained activity (e.g., maintenance of information in WM) in left IFG, (BA47), right supramarginal gyrus (BA40), and bilateral SPL and for transient activity (e.g., updating, temporal coding) in right cerebellum, right ITG (BA20), and left precentral gyrus (BA44) b) Age-related difference in the 2-back task with children showing evidence for increased transient, but decreased sustained activity, in comparison to adults.
Jolles et al. (2010)	Investigate the involvement of DLPFC, VLPFC, and superior parietal cortex in the development of WM manipulation relative to maintenance functions under different loads	N=15; [11-13] N=15; [19-25]	Verbal object naming WM task	Objects	Identity and order	a) Similar frontoparietal activation in children and adults, including bilateral DLPFC, left VLPFC, left SPC, bilateral lateral occipital cortex, bilateral ACC, and bilateral supplementary motor area. b) Right DLPFC, left VLPFC engaged in manipulation for both groups c) Age-related behavioural improvements in WM and functional changes within right DLPFC for manipulation relative to maintenance trials (larger activation in adults than in children)
Taylor et al. (2011)	Study cognitive development of the frontal lobes using	N=28; [6-12] N=27; [13-	N-back (0, 1, 2-back)	Coloured patterns	Identity	a) Similar activation foci across the three age range b) Evidence of right hippocampal involvement during n-back task across

	magnetoencephalography (MEG) and functional MRI	19] N=18; [20-34]				age ranges c) Increased activation with age in bilateral SPC, bilateral SFC and MFC
Spencer-Smith et al. (2013)	Understand the influence of age, sex, and WM performance on the core brain regions underpinning the visuo-spatial WM network in childhood	N=44; [7-12]	Sternberg item location paradigm (three and four loads)	Dots	Location	a) Age-related increased of activation in parietal regions b) Girls and high WM performers showed more right-sided lateralization of parietal regions than boys and low WM performers
Van Der Brosh et al. (2014)	Study the development of brain connectivity related to verbal WM in typically developing children and adolescents	N=10; [9-12] N=12; [13-16] N=13; [17-19]	Sternberg item recognition paradigm (3 loads)	Digits	Identity	a) Similar activation foci between the three age groups but overall less activity in children in orbital frontal and ACC b) Neural substrates of linear load-dependency change with age: - In adolescents and adults: increased activation in left motor area and right cerebellum with increasing load - In children: increased activation in left PFC, left parietal lobe, and right cerebellum with reducing load
Kharitonova et al. (2015)	Investigate neural correlates of WM capacity in young children (5–8 years) and adults using a visual WM task with parametrically increasing loads	N=22 ; [5-8] N=20 ; [19-35]	Sternberg item recognition paradigm (4 loads)	Dots	Location	a) Both age groups increased the activation of frontoparietal networks with increasing WM loads, until WM capacity was reached b) In addition to fronto-parietal regions, activations in occipital areas in both groups
Vogan et al. (2016)	Explore developmental changes in brain activity related to verbal WM	N=24 ; [9-15] N=16 ; [20-25]	1-back	Letters	Identity	a) Children and adults activate similar fronto-parietal neural networks in response to verbal WM tasks b) However, the extent to which children and adults rely on these areas in response to increasing cognitive load evolves between childhood and adulthood: - Adults showed greater load-dependent changes than children in WM in the bilateral SPC, IFG and left MFG and right cerebellum - Adults also showed greater decreasing activation across WM load in the bilateral ACC, anterior medial PFG, right superior lateral temporal gyrus and left posterior cingulate cortex.

Note: prefrontal cortex=PFC, dorsolateral prefrontal cortex=DLPFC, ventrolateral prefrontal cortex=VLPFC, premotor cortex=PMC, anterior cingulate cortex=ACC, superior frontal gyrus=SFG, middle frontal gyrus=MFG, inferior frontal gyrus=IFG, superior parietal cortex=SPC, superior parietal lobule=SPL, inferior parietal cortex=IPC, superior temporal gyrus=STG, inferior temporal gyrus=ITG).

CHAPTER 3: Thesis Objectives

3.1. Rationale

Even though AgCC is among the most common brain malformations, it is a rare neurological condition. Overall, a small number of studies investigated neurobehavioural outcomes in individuals with AgCC. A review of the literature completed by our team in 2013 (Siffredi et al., 2013) reported that 47 publications investigated one or more neuropsychological functions in individuals with AgCC, including WM (two adult case studies), general intellectual abilities (41 studies), academic skills (nine studies) and executive functions (four studies). Since 2013, only four more studies reported on neurobehavioural functions in individuals with AgCC. Social and behavioural outcomes have been studied in about 12 studies overall, and links between AgCC and ASD were investigated in no more than five studies. Contradictory results were not rare in the literature, which makes it difficult to draw conclusions.

Similarly, neuroimaging studies in individuals with AgCC are sparse (about 20 overall). They mainly looked at structural brain features in individuals with AgCC and links with cognitive functions have only been made in studies investigating sensori-motor functions (four studies), language (five studies), executive (one study) and affective functions (one case study). Overall, functional brain organisation of higher cognitive functions, such as WM, in individuals with AgCC is poorly understood, particularly during childhood.

Another consequence of AgCC being a rare disease is the inherent property of small sample size in the AgCC literature. Siffredi and colleagues (2013) reported that 64% of articles included in their systematic review counted three of fewer participants. Additionally, published studies are characterised by a lack of information about medical details such as associated MRI findings and lack of strict recruitment procedure. This limits our ability to interpret the results and really understand what mechanisms underlie neurobehavioural difficulties. Another factor that increases the complexity of studying this population is that individuals with AgCC are highly heterogeneous. As developed in Chapter 1, factors of

heterogeneity include age at diagnosis, aetiology, neuroimaging profiles (e.g., complete or partial AgCC, different associated brain anomalies) and clinical sequelae.

In conclusion, there are significant gaps in our current understanding of the neurobehavioural outcomes as well as the risk and protective factors that contribute to these outcomes in children with AgCC. More particularly, despite the importance of the CC for WM and the crucial role of WM abilities for cognitive development during childhood, this cognitive function and its underlying functional brain organisation has not been investigated in children with AgCC.

3.2. Study Aims

The first aim of this thesis was to examine neurobehavioural outcomes in children and adolescents with AgCC, including WM abilities as well as general intellectual, academic, executive, social, and behavioural functions. To address the issue of small sample sizes in previous studies, a large cohort of school-age children participated in our investigation, following a strict inclusion criteria and recruitment process. Given the heterogeneity previously reported in this population, different factors that might contribute to the variability of neurobehavioural outcomes in children with AgCC were investigated, including: (a) age; (b) social risk factors, including demographic characteristics and family function; (c) neurological factors, such as the type of AgCC (complete or partial), anterior and posterior commissures properties, presence of associated CNS anomalies, history of seizure and presence of a recognised genetic condition. Finally, the impact of WM functions on academic outcomes in our cohort was also explored.

The second aim of the thesis was to investigate the functional brain organisation of WM in school-age children with AgCC using fMRI. This was achieved by comparing the neural substrates engaged during WM in children and adolescents with AgCC relative to a typically developing control group. For this purpose, a new WM paradigm based on the Brown-Peterson paradigm was developed, allowing us to assess different components of WM and the effects of stimulus material in relation to hemispheric dominance.

CHAPTER 4: Methods

This chapter presents a description of the general methods used for the three studies included in this thesis. Methods for each of the three studies are also described in the following chapters, as part of the published articles.

4.1. Participants

Agenesis of the corpus callosum cohort

The AgCC cohort was recruited as part of the "Agenesis of the corpus callosum project" at the Murdoch Children's Research Institute in Melbourne, Australia. This cohort constitutes a prospective cross-sectional study of school-age children diagnosed with AgCC and seen in the Radiology Department at The Royal Children's Hospital in Melbourne for MRI. Eligible children were ascertained by review of the radiology database at The Royal Children's Hospital. Keywords for database searches were "agenesis + corpus callosum" and "agenesis + callosal". There were two waves of recruitment (Figure 14). Wave 1: database searches performed in 2010 and 2011 for patients presenting between January 1998 and December 2008. Wave 2: database searches conducted in 2013 for patients presenting between January 2009 and July 2013.

Inclusion criteria were: 1) aged 8 years 0 months to 16 years and 11 months at the time of database searches; 2) documented evidence of AgCC on MRI conducted as part of routine clinical work-up; 3) English speaking; 4) functional ability to engage in the assessment procedure. All children with AgCC had normal or corrected-to normal vision and hearing.

For families of children who met inclusion criteria and who were patients seen at the Neurology Department at The Royal Children's Hospital in which Dr Richard Leventer is involved (paediatric neurologist, associate investigator on the study), contact was made by telephone or in person at a clinic visit by Dr Leventer or Ms Kate Pope (clinical research coordinator of the clinical genetics research). Families were informed about the research study and were invited to participate. It was made clear that refusal to participate in the

research would in no way affect their clinical care. For families of children who met inclusion criteria but were not directly known by Dr Leventer, contact was made through their primary physician. The physician was asked to either contact the family to inform them of the study, or to allow the study investigators to contact the family with permission from the patient/ parent/guardian. Details of the study and requests for written consent were mailed for families who gave their approval.

Children from Wave 1 participated in the study assessments between September 2009 and July 2011, and children from Wave 2 between September 2013 and February 2014. Seven children from Wave 1 completed follow-up assessments in Wave 2. One child included in the Wave 2 was recruited within the study age range, but assessed at 17 years and 1 month.

Typically developing control sample

We consciously tried to recruit a sample that would be comparable to the AgCC group from Wave 2 (n=14, including Wave 2 itself and follow-up from Wave 1) in terms of age and sex. A typically developing control group of 16 children and adolescents were recruited though advertisement in local schools and through staff at The Royal Children's Hospital between June 2013 and February 2014. Typically developing participants were aged 8 to 16 years at assessment (mean age= 12.19; SD=2.25), seven males and nine females, and all were English speaking. They had no documented history of a brain lesion, neurological disability or neurodevelopmental disorders. Typically developing children had normal or corrected-to normal vision and hearing. Assessments were conducted at the same time as Wave 2.

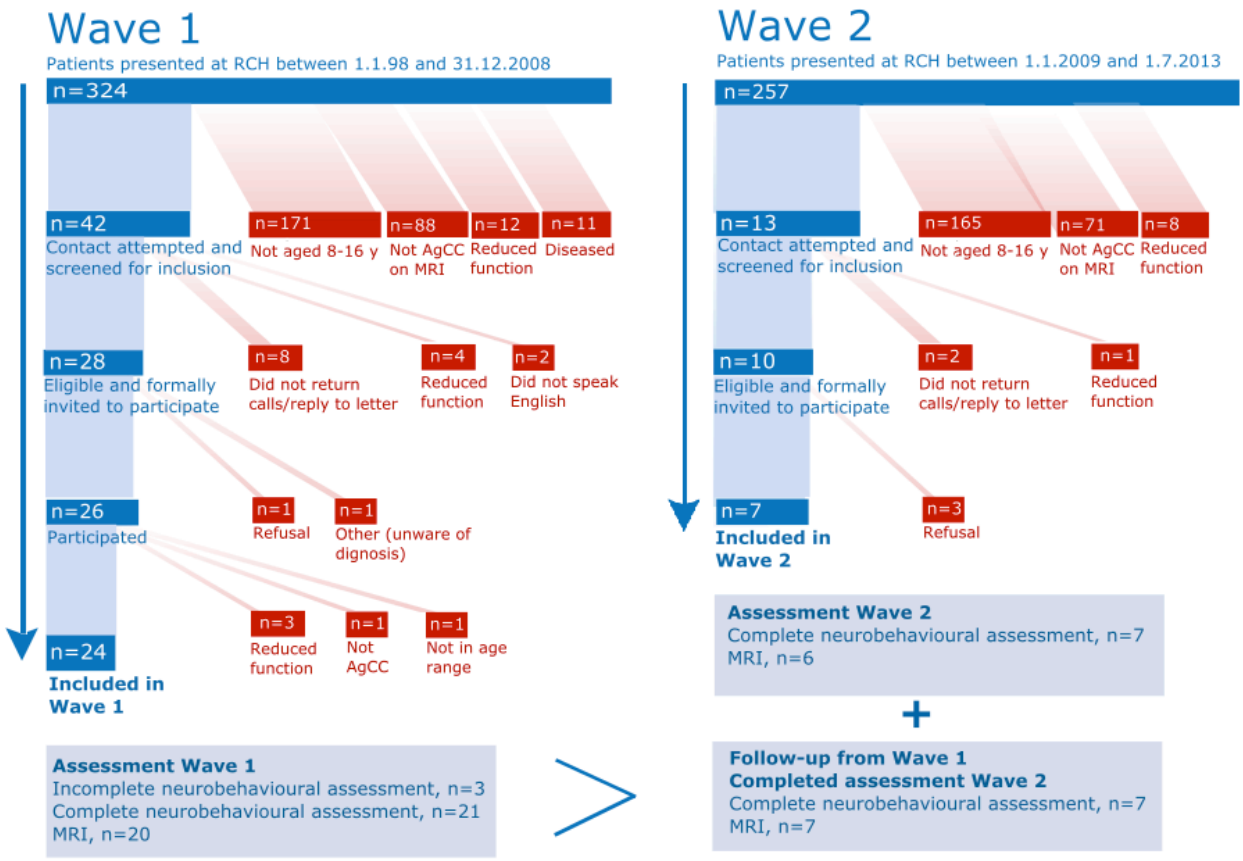

Figure 14. Flow of children and adolescents with AgCC for recruitment in Wave 1 and Wave 2.

Studies samples

Study 1 and 2

A total of 28 children with AgCC (73.7% of those eligible, n=38) aged 8 to 17 years (M=11.54, SD=2.35) were included in Studies 1 and 2. Of these, 21 children were from Wave 1 and 7 from Wave 2. Eleven were female and 18 were male, with 50% right-handed, 42.9% left-handed, and 7.1% were mixed. Half of the cohort presented with complete AgCC and the other half with partial AgCC. Isolated AgCC was present in 39.3% of cases, whereas AgCC was associated with other CNS anomalies in 60.7% of cases. AgCC was associated with seizure disorder in 21.4% of cases and associated with a recognised genetic condition in 21.4% of cases.

Study 3

Only typically developing children were included in Study 3. Participants were 16 children recruited during the Wave 2 period, aged 8 to 16 years at assessment (mean age= 12.19; SD=2.25), seven males and nine females, all were right-handed.

Study 4

Children with AgCC from Wave 2 and who completed the MRI scan (n=13) and the typically developing control group (n=16) participated in Study 4. Children with AgCC were all assessed during Wave 2, including follow-up of seven children recruited in Wave 1. Of the 13 AgCC children who completed the MRI scan, one was excluded due to technical difficulties, and three were excluded because of wrong calibration of functional MR images during acquisition. A sample of nine children with AgCC aged 9 to 17 years (mean age=12.31, SD=2.83), seven males, were finally included in Study 4. Six children had complete AgCC and three partial AgCC. The control group in this study was the same group of 16 typically developing children in Study 3.

4.2. Procedure and Ethical Considerations

This study was approved by the committee of The Royal Children's Hospital Human Ethics in Research. Written informed consent was obtained from the primary caregivers of the children and adolescents prior to participation in the study. All primary caregivers from the study were parent of their children. Consenting families were seen at an outpatient clinic at The Royal Children's hospital. Children were evaluated on an individual basis by a trained child psychologist. Children completed assessments lasting approximately 5 to 6 hours, including neuropsychological testing as well as mock and MRI scan if consent was obtained. Parents and teachers completed questionnaires. A database was created using EpiData, where all demographic and neurobehavioural data were entered.

4.3. Neurobehavioural Outcome Measures

A battery of standardised measures comprising both cognitive tasks completed by the child and behavioural questionnaires completed by parent and teacher were administered.

Following is a description of the measures relevant to this work drawn from a broader assessment protocol described in Appendix 1. All measures were age-standardised.

Working memory. Digit Span Forward and Backward subtests from the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV: Wechsler, 2003) was used to estimate verbal short term and WM capacity. A sequence of digits is read to the child who then immediately repeats the digits in the same order or in the reverse order. The sequence of digits presented increases in length across trials. The variable of interest is the number of correct trials. Standard scores have mean (M) = 10 and standard deviation (SD) = 3.

General intelligence. The 4-subtests version of the Wechsler Abbreviated Intelligence Scale (WASI: Wechsler, 1999) designed for individuals 6-80 years, or the WISC-IV (Wechsler, 2003) designed for individuals 6-16 years, was administered. The WASI and WISC-IV generate three summary scores: Verbal (Verbal IQ in the WASI or Verbal Comprehension Index (VCI) in the WISC-IV), Performance (Performance IQ in the WASI or Perceptual Reasoning Index (PRI) in the WISC-IV) and Full-Scale IQ. All standard scores have mean (M) = 100 and standard deviation (SD) = 15. Level of functional impairment was derived based on previous studies (V. Anderson et al., 2009), with standard scores between ≤-1SD to <-2 SD categorised as mild impairment, and scores ≤-2 SD categorised as moderate to severe impairment.

Academic performance. The Wide Range Achievement Test-4 (WRAT-4: Wilkinson and Robertson, 2006), designed for individuals 5–94 years, was administered to estimate single word reading, spelling and mathematics performance. The Reading and Spelling subtests involve the child reading or spelling single words, respectively. The Math Computation subtest requires the child to identify numbers and complete oral and written calculations and problems. All standard scores have mean (M) = 100 and standard deviation (SD) = 15. Level of functional impairment was determined consistent with cut points for general intelligence, with standard scores between ≤-1SD to <-2 SD categorised as mild impairment, and scores ≤-2 SD categorised as moderate to severe impairment.

Executive function in everyday life. The Behavioral Rating Inventory of Executive Function parent and teacher versions (BRIEF; Gioia et al., 2000), designed for individuals 5-18 years, provided an estimate of executive abilities in everyday life over the past 6 months. It

comprises 86 items that generate two summary index scales: Behavioural Regulation Index (BRI: based on inhibit, shift and emotional control subscales) and Metacognition Index (MCI: based on initiate, working memory, plan/organise, organisation of materials and monitor subscales). A Global Executive Composite that represents the child's overall executive functioning in daily life is generated using all indexes (GEC). All t-scores have mean (M) = 50 and standard deviation (SD) = 10, with higher t-scores reflecting increased difficulties in executive functioning. Level of functional impairment was determined consistent with cut points for general intelligence, with t-scores between ≤-1SD to <-2 SD categorised as mild impairment, and t-scores ≤-2 SD categorised as moderate to severe impairment.

Behavioural and emotional function. The Strengths and Difficulties Questionnaire parent and teacher versions (SDQ; Goodman, 1997), designed for individuals 4-17 years, estimated general behavioural and emotional functioning over the past 6 months. It comprises 25 items that are used to generate a summary Total Difficulties score (based on emotional symptoms, conduct symptoms, hyperactivity-inattention, peer problems subscales). Australian test norms were used to categorise scores of our AgCC cohort in the average or below average (≤-1 SD).

Social function. The Social Skills Improvement System parent, teacher and child versions (SSIS; Gresham and Elliott, 2008) estimated aspects of social functioning. Parent and teacher versions are designed for individuals 5-18 years; whereas youth rating scale is designed for individuals 11-18 years. The frequency of behaviours is rated as either "never", "sometimes" or "very often", and two scales are derived. The Social Skills scale is comprised of sub-domains exploring communication, cooperation, assertion, responsibility, empathy, engagement, and self-control. The Problem Behaviour scale is based on the sub-domains called externalising, bullying, hyperactivity/inattention, internalizing, autism spectrum. All scale scores have mean (M) = 100 and standard deviation (SD) = 15, with a higher score on the Social Skills scale indicating better social functioning and a lower score on the Problem Behaviour scale indicating better behavioural functioning (M= 100, SD= 15).

We used a conservative approach to address missing outcome data. Only behavioural ratings when informants provided responses and behavioural performance scores for children who completed the task were included in the analyses. Thus, the number of cases differs for each outcome.

4.4. Descriptive Information

In a structured interview, parents provided information on their child's medical and developmental history, as well as academic history and progress. They reported information on family situation, parental education and parental professional situation. The Social Risk Index (SRI; Roberts et al., 2008) was calculated based on information provided by parent structured interview and questionnaires. The SRI is a composite score comprising six aspects of social status: family structure, education of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home, and maternal age at birth. Scores range from 0-12, with higher scores representing higher socio-economical risk.

Handedness was measured using the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). It is a ten-item questionnaire assessing preferred hand for daily life activities. Right-handed was defined by a score between +40 and +100, left-handed was defined by a score between -40 to -100, and a score between -40 and +40 was defined as mixed. Additional standardised demographic measures were also collected but were not used in the context of this work (Appendix 2).

4.5. Neuroimaging

Scan procedure

Participation in MRI Scan. From Wave 1, 20 children with AgCC completed the study MRI and 4 provided consent to access previous clinical scans. From Wave 2, six additional children with AgCC completed the study MRI and one provided consent to access previous clinical scans. Seven children who completed the study MRI during Wave 1, also completed the follow-up study MRI during Wave 2. All typically developing children completed the study MRI at Wave 2.

Mock MRI. The mock MRI was performed with a trained therapist to introduce participants to the scanning environment, the MRI machine and acquisition process (e.g., loud noises, head coil with foam cushioning to minimise head movement, remaining still during sequences, movement of the machine during some sequences). At Wave 1, only three children with

AgCC who completed the study MRI scan did not participate in the mock MRI, mainly for time restraint. At Wave 2, all children from the AgCC and the typically developing groups completed the mock MRI scanner training protocol successfully.

MR Image Acquisition Procedure. The majority of participants were accompanied by a parent in the scanner room for the duration of the MRI scan. The researcher (MSS, AM or VS) and a radiographer observed the participant directly through a window and via a closed-circuit video monitor. Communication between the researcher/radiographer and participant occurred using an intercom system. To minimize head motion during scanning, a soft cloth was placed on the child's forehead, then taped to the head tray, and foam pads were inserted around the head. Participants had within reach an emergency button whilst in the scanner and were encouraged to press the button if they required assistance during the acquisition sequences.

Functional MRI Paradigm. Participants were prepared for the fMRI paradigm through training outside (5 new trials for each of the three conditions described below) and inside the scanner (again 5 new trials for each of the three conditions) as well as careful instructions inside the scanner before starting fMRI acquisition. All participants demonstrated understanding of the task before being placed in the scanner. The paradigm was projected onto a screen at the foot of the MRI bed, and participants viewed the images from a mirror attached to the head coil. Responses were provided using an MRI compatible response box with four response buttons. The response box was placed centrally on the child's stomach and responses were provided by pressing the left-most button with the left thumb or the right-most button with the right thumb.

Image acquisition

Images were acquired on a 3T Siemens Magnetom Trio scanner (Siemens, Erlangen, Germany) at The Royal Children's Hospital. The scanner was equipped with the Syngo MR B17 software release, and a 32-channel receive-only head coil was used.

Structural Images. T1-weighted MP-RAGE sequence (Magnetisation Prepared Rapid Gradient Echo) were obtained using the following parameters: TR=1900 ms, TE=2.71 ms, TI=900 ms, FA=9°, FoV=256mm, voxel size=0.7 x 0.7 x 0.7 mm.

Functional Images. Images were acquired using a T2*-weighted gradient-echo-planar imaging (EPI) sequence with 32 interleaved slices with 5% gap, voxel size=2.6 x 2.6 x 3 mm, TR=2400ms, TE=35ms, FA=90°, FoV=240mm.

Structural MRI qualitative coding

Structural MR images were qualitatively reviewed by a paediatric neurologist with expertise in brain malformations (Dr Richard Leventer). A specially modified protocol (V. Anderson et al., 2009; Leventer et al., 1999) was employed to characterise AgCC and associated CNS anomalies. This protocol was developed based on factors thought to be important for neurodevelopmental outcomes in children with AgCC (Appendix 3). Participants were classified as having partial AgCC if any remnant of the CC was identified on structural MR images. Anterior and posterior commissures were classified as absent, reduced, normal or enlarged. Probst bundles and colpocephaly were classified as present or absent. Associated CNS anomalies were documented (Appendix 4).

fMRI WM paradigm

MRI is based on the principles of nuclear magnetic resonance, a spectroscopic technique used by scientists to obtain microscopic chemical and physical information about molecules (Hornak, 2008). In cortical regions, an increase in neural activity is couple with an increase in the local blood flow to deal with the larger demand for oxygen and other substrates. fMRI detects these changes in blood oxygen level–dependent (BOLD) in the MRI signal occurring when there are changes in neuronal activity following a change in brain state that might be produced, for example, by a stimulus or a task (Gore, 2003).

In our study, participants completed a modified version of the Brown-Peterson paradigm (J. Brown, 1958; Peterson & Peterson, 1959). The fMRI paradigm was presented visually during fMRI using E-prime2 (Psychology Software Tools, PST, Pittsburgh). The task required a combination of verbal storage and maintenance during either verbal (within-domain) or visual (cross-domain) concurrent tasks. A mixed block and event-related design allowed us to separately examine specific processes of WM in this task. Each active trial consisted of three parts (Figure 15): 1) an encoding period during which participants were presented with a series of single upper-case letters for further recall displayed sequentially in the middle of the screen at a rate of one letter per second; 2) a retention delay of 6 seconds filled with a

concurrent task requiring to process either verbal or non-verbal stimuli involving within- or cross-domain interference respectively (see below); and finally 3) a letter retrieval period of 3 seconds during which participants were presented with one single upper-case letter among one (paradigm with two letters to remember) or two (paradigm with three letters to be remembered) dashes with a question mark in the middle of the screen. Participants had to indicate as quickly and as accurately as possible whether this letter matched the letter previously seen in that serial position, by pressing the green key [left side] for yes (same letters and same order) or the red key [right side] if not.

The within-domain concurrent task was a lexical decision task. Two successive letter-strings were presented for 3 seconds each and required simple motor responses (i.e., press as quickly and as accurately as possible the green key if the letter-string was a word or the red one if it was a non-word). The cross-domain concurrent task was a face decision task with two successive pictures presented for 3 seconds each, requiring similar motor responses (i.e., press as quickly and as accurately as possible the green key if a real face was presented or the red key if it was a scrambled face). In addition, there was a baseline condition (no-concurrent task) in which participants had to encode a single letter and recognise this letter after a short empty delay of 1 second. For the experimental and baseline conditions, a randomised inter-trial interval of 2000, 2500, or 3000 milliseconds was presented before the next trial.

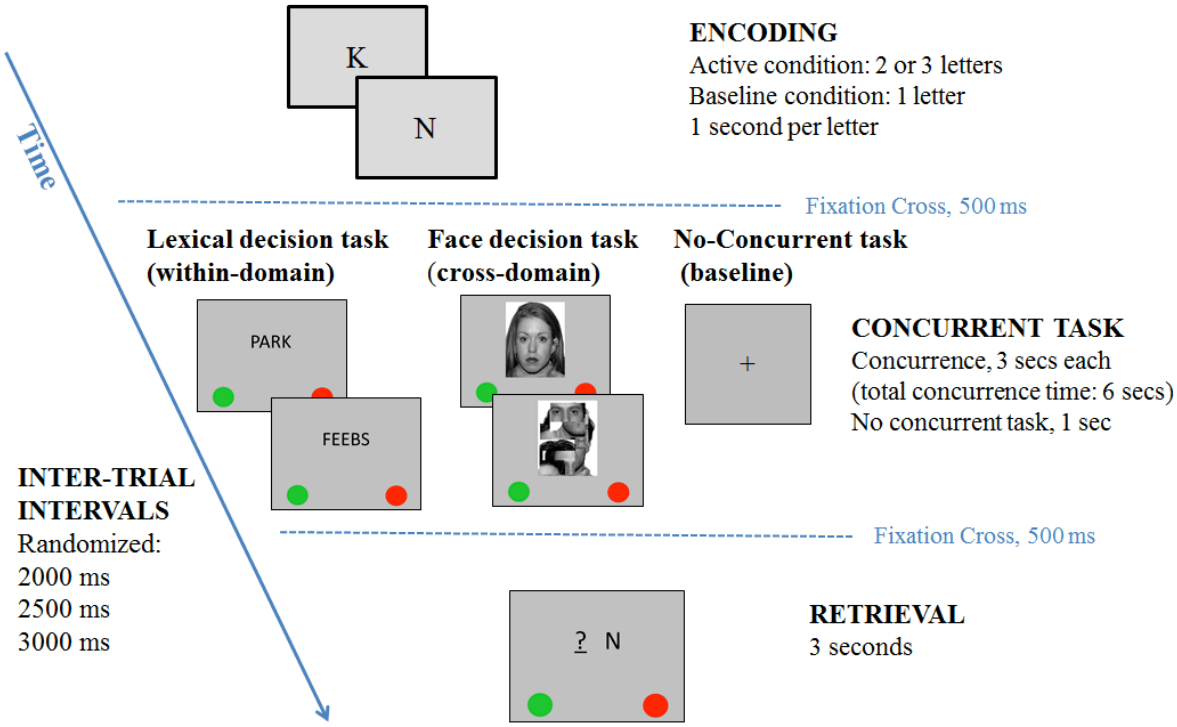

Figure 15. Modified version of Brown-Peterson paradigm using within- and cross-domain concurrent tasks.

Because a challenge to brain imaging studies of cognitive development is that differences in both age and task performance may influence activation patterns, the memory load was tailored to each participant. At issue is whether changes in neural activity reflect changes in functional maturation of the central nervous system, independently of behavioural efficiency, or whether they reflect changes in task performance consequent upon increasing age (Kwon et al., 2002; Schweinsburg et al., 2005). Therefore, in our paradigm, task difficulty was adapted to each participant by adapting the number of verbal items to remember, while keeping the protocol similar to avoid other issues related to differences in the timing and sampling of brain activity measures. Based on pilot testing conducted outside the scanner, children with a backward digit span of five or more were presented with three letters to be remembered, whereas children with a backward digit span lower than 5 had only two letters to remember. As a result, in the AgCC group, seven participants completed the 2-letters paradigm (age range=9-17.08, M=12.21, SD=2.78), and two completed the 3-letters paradigm (age range=9.67-15.58, M=12.63, SD=4.18); in the typically developing group, 10 participants

completed the 2-letters paradigm (age range=8.33-16.42, M=11.97, SD=2.63), and six completed the 3-letters paradigm (age range=10.92-15.08, M=12.57, SD=1.58).

Three types of block of 10 trials each were created: two experimental blocks, one including the within-domain concurrent task and the other including the cross-domain concurrent task, plus a baseline blocks. The order of presentation of these three blocks was counterbalanced across participants and repeated twice for a total of six blocks of 10 trials. Within each block, half of the probes were positive (i.e., 5 trials required a "yes" response), and position of positive and negative probes were randomised within each blocks.

For the encoding phase, all consonants of the English alphabet were used as memory items except W, which is three-syllabic. Series of two or three letters were created for within-domain and cross-domain blocks in such a way that each letter appeared with the same frequency in both blocks. Children were asked to maintain the letters in order of appearance. For the lexical decision task (within-domain concurrent task), words were selected from the "Oxford Wordlist", which is an Australian database of high frequency words in young children's writing and reading development (Bayetto, Lo Bianco, & Scull, 2007). Among the 307 most frequently used words, only nouns were selected considering any gender, any location (urban or rural), any socioeconomic status, any text type (e.g., description, discussion, narrative) and appearing during the first three years of school (40% were within 1 to 100 most frequently used words; 35% were within 101 to 200 most frequently used words; 25% were within 201-307 most frequently used words). Non-words with orthographically existing onsets and bodies were selected from the "ACR Nonword database" (Rastle, Harrington, & Coltheart, 2002). Three to eight letter-strings (words and non-words) were displayed centrally on the screen. Words and non-words were equally often presented. For the face decision task (cross-domain concurrence), 10 males and 10 females with a neutral expression were selected from the NimStim database (Tottenham et al., 2009), and converted into greyscale using Matlab R2013a (The MathWorks, 2012); scrambled faces were created from the original faces using Matlab (size of square = 300, iterations = 2). Faces and scrambled faces were equally often presented. For the letter retrieval period, one single upper-case letter was presented among one (paradigm with 2 letters to remember) or two (paradigm with 3 letters to be remembered) dashes with a question mark. The dash with the question mark represented the letters in the encoding serial position. Participants had to decide if the single letter matched with the letter that was presented in that serial position during the

encoding period. This was done to make sure that participants memorised both item and order information.

4.6. Data Analyses

Studies 1 and 2

Statistical analyses were performed using SPSS 22.0 (IBM, Released 2013). To describe functioning of the AgCC cohort in general intellectual, academic, social and behavioural domains, as well as WM abilities, mean standard scores and ratings as well as mean differences compared with test norms are reported for each outcome. One-sample t-tests or Wilcoxon signed-rank test in the case of violation of normality were used to test differences between group means and test norms. Mean differences between outcomes within each domain, e.g., Performance IQ vs Verbal IQ, were examined using paired-sample t-test or Wicoxon signed-rank test when violation of normality was detected. To examine the association between neurobehavioural outcomes with age, environmental and neurological factors, hierarchical regressions were computed for both adjusted and unadjusted analyses for gender known to be associated with functional outcomes. Factors used as predictors were: 1) age at assessment; 2) Social Risk Index score; 3) intactness of the CC (complete vs partial AgCC); 4) presence of associated CNS anomalies (AgCC as an isolated condition or associated with CNS anomalies); 5) intactness of the anterior commissure (coded as absent, small, normal or enlarged size); 6) intactness of the posterior commissure (coded as absent, small, normal or enlarged size); 7) presence of a seizure disorder; 8) presence of a recognised genetic condition. Backward hierarchical regressions were used as an exploratory model building method, and the default stepping criteria of $p<.05$ was used for inclusion and for removal of variables in the models. To address Type II Error, Bonferroni correction for multiple comparisons was applied to the resulting regression models: α altered = α original 0.05 / 8 comparisons = 0.006.

For Study 2, further analyses were performed in order to examine the impact of WM capacity on academic functions in children with AgCC, in addition to individual and neurological factors already considered in Study 1. Academic functioning were considered including Reading, Spelling and Math Computation. Factors used as predictors were factors already

considered previously: 1) age at assessment; 2) Social Risk Index score; 3) intactness of the CC (complete vs partial AgCC); 4) presence of associated CNS anomalies (AgCC as an isolated condition or associated with CNS anomalies); 5) intactness of the anterior commissure (coded as absent, small, normal or enlarged size); 6) intactness of the posterior commissure (coded as absent, small, normal or enlarged size); 7) presence of a seizure disorder; 8) presence of a recognised genetic condition; as well as additional factors including, 9) short term memory as measured by the Digit Span Forward; 10) WM as measured by the Digit Span Backwards; 11) Performance IQ. Backward hierarchical regressions were used as an exploratory model building method, and the default stepping criteria of $p<.05$ was used for inclusion and for removal of variables in the models. To address Type II Error, Bonferroni correction for multiple comparisons was applied to the resulting regression model: α altered = α original 0.05 / 11 comparisons = 0.005.

Study 3

fMRI WM paradigm – Behavioural data

Statistical analyses were performed using SPSS Statistics V22.0 (IBM, Released 2013). Separate repeated measures analyses of variance (ANOVA) were conducted on accuracy measures (percent correct) for the concurrent tasks (lexical and face decision tasks) and the WM retrieval task with the type of concurrent task (within- or cross-domain) as within-subject factor. If the assumption of normality was violated, as assessed by inspection of histograms and results of the Shapiro-Wilk test, a related-sample Wilcoxon-signed rank test was used to confirm results of the repeated-measures ANOVA. Independent-sample t tests were used to explore sex differences in accuracy. If the assumption of homogeneity of variance was violated, as assessed by significance of Levene's test, a Kruskal-Wallis test was used to confirm results of the independent t test. Pearson's correlation was used to study the relationship between age and accuracy.

fMRI WM paradigm – Neuroimaging data

fMRI data were preprocessed and analysed using SPM8 (Wellcome Department of Imaging Neuroscience, University College London, UK) implemented in Matlab R2014a. The images of each subject were corrected for slice acquisition timing, and spatially realigned to eliminate movement artefacts. No participant moved more than 1 voxel size (3 mm) in any direction and therefore no participant was excluded from further processing. To allow for inter-subject

comparison, data were normalized using the MNI brain template (Montreal Neurologic Institute) and resampled to 1.9 x 1.9 x 3 mm. These functional images were finally smoothed using a Gaussian filter of full width at half maximum=8 mm to increase signal-to-noise ratio.

Statistical analyses were performed using a two-step process, taking into account the intra-individual and inter-individual variance (Friston, Frith, Frackowiak, & Turner, 1995). First level single subject statistics were assessed by a voxel-based statistics according to the General Linear Model implemented in SPM8. The onsets of each event of interest (encoding in active condition, encoding in baseline condition, lexical decision task (within-domain concurrent task), face decision task (cross-domain concurrent task), retrieval after within-domain concurrence, retrieval after cross-domain concurrence, and retrieval baseline) were convolved with the canonical hemodynamic response function (HRF) and used as regressors in the individual design matrix. All six movement parameters (translation: x, y and z; rotation: pitch, roll and yaw) were included as covariates of no interest in the model. The individual statistical images from each condition were then entered in a group analysis at the second level using a flexible factorial design. In this random-effects model, independence and unequal variance between subjects and conditions were assumed, allowing for violation of sphericity, as implemented in SPM8. Considering a possible impact of gender on brain-activation, we also added this binary variable as a covariate in the flexible factorial design (Nagel et al., 2005; Schweinsburg et al., 2005; Spencer-Smith, Ritter, Murner-Lavanchy, et al., 2013). In line with guidelines used in neuroimaging studies of complex cognitive functions (Lieberman & Cunningham, 2009), whole-brain analysis was conducted with a significance threshold of $p<.001$ at the voxel level, uncorrected for multiple comparisons, and a minimum extent threshold of 20 voxels. Anatomical location of activations was verified using SPM Anatomy toolbox (Eickhoff et al., 2005).

We performed exploratory analyses to examine age- and retrieval accuracy-related changes in brain activation during the WM task. The most relevant clusters of activation identified at the group level were used to define functional regions of interest (ROIs) using the marsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002). First, we investigated specific age- and retrieval accuracy-related activation using comparisons between the active and baseline conditions. Beta values were calculated for each participant and each ROI using SPM8, and Pearson's correlation coefficients were computed to evaluate any age- and accuracy-related changes in these beta value using SPSS (IBM, Released 2013). Secondly, for contrasts

comparing different WM processes (encoding vs retrieval, within-domain concurrence vs cross-domain concurrence, retrieval following within-domain concurrence vs retrieval following cross-domain concurrence), we performed a multiple regression analyses with age and retrieval accuracy as covariates of interest for each of the relevant ROIs. For these regressions, a significant threshold of $p<.001$ uncorrected for multiple comparisons with a minimum extent threshold of 20 voxels was used.

Study 4

fMRI WM paradigm – Behavioural data

Statistical analyses were completed using SPSS (IBM, Released 2013). The assumption of normality was violated for accuracy measure in all conditions in the two groups, as assessed by inspection of histograms and results of the Shapiro-Wilk test (from $p<.001$ to $p=.003$). Therefore, Wilcoxon signed-rank tests were used to test significant difference between within and cross-domain concurrent tasks and the following retrieval. Kruskal-Wallis tests were used to explore group difference in accuracy for the different conditions. Linear regressions were used to examine the effect of the concurrent task on retrieval in the two groups. Regression plots involving various residual values were inspected to establish the validity of regression assumption including homoscedasticity, normality distributed errors and independence of errors.

fMRI WM paradigm – Neuroimaging data

fMRI data were preprocessed and analysed using SPM8 (Wellcome Department of Imaging Neuroscience, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in Matlab R2014a. Images of each subject were spatially realigned to eliminate movement artefacts, and corrected for slice acquisition timing. No child moved more than 1 voxel size (3 mm) in any direction and therefore no child was excluded from further processing. As already noted by Tyszka and colleagues (2011), morphological differences between typically developing and AgCC individuals are minimal on the lateral cortical surfaces, but are pronounced around the midline and ventricles due to the absence of the CC, and the presence of Probst bundles, mesial cortical reorganisation and colpocephaly (Tyszka et al., 2011). Therefore, we created a customised template using the DARTEL algorithm to account for the fact that standard neuroanatomical templates may be inappropriate for our clinical population (Ashburner,

2007). We followed the procedure defined by Salami and colleagues (Salami, Pudas, & Nyberg, 2014), similar to the procedure used in Tyszka and colleagues (2011). First, individuals' T1-weighted images were segmented into grey and white matter using a new segment algorithm in SPM8. Secondly, a group-specific template (across all participants, n=25) was created using exponentiated lie algebra in DARTEL. Grey and white matter tissue class images were imported using the normalisation parameter yielded during the segmentation step followed by resampling to isotropic voxels (1.5 x 1.5 x 1.5 mm). Then, the imported images went through and interactive procedure that began by producing an initial template as a mean of grey and white matter across all participants. Deformation from the initial template to each individual's grey and white matter images was computed and the inverse of the deformation was applied to each individual's grey and white matter images. A second template was created as the mean of the deformed individuals' grey and white matter images across all participants, and this procedure was repeated until a sixth template was created, Figure 16. Finally, the realigned and resliced fMRI images and the flow field grey matter image (created in the previous step) were nonlinearly normalised to the sample-specific template for each individual independently (using a voxel size of 1.9 x 1.9 x 3 mm); and affine-aligned into MNI template (Montreal Neurologic Institute). These functional images were finally smoothed using a Gaussian filter of full width at half maximum=8 mm to increase signal-to-noise ratio. For all the preprocessing steps (from data retrieval to smoothing), functional images of participants were carefully checked. Of note, another template was also created using the procedure used by Tyszka and colleagues (2007). However, we found that the quality of the template was better using DARTEL.

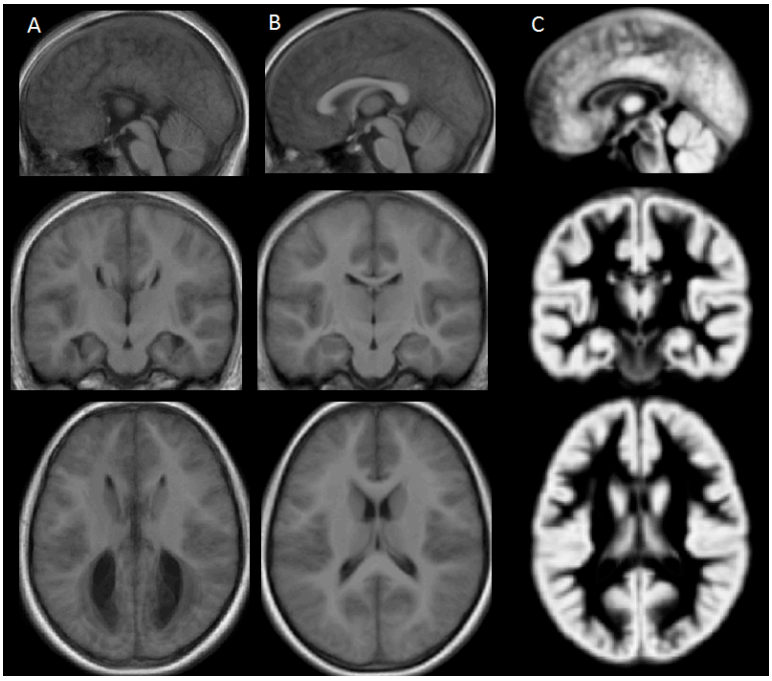

Figure 16. (a) Mean T1-weighted image of the AgCC group; (b) Mean T1-weighted image of the typically developing group; (c) Customised template created using DARTEL based on structural images from both AgCC and typically developing groups (6 iterations).

Statistical analyses were performed using a two-step process, taking into account the intra-individual and inter-individual variance (Friston et al., 1995). First level single subject statistics were assessed by a voxel-based statistics according to the General Linear Model implemented in SPM8. The onsets of each event of interest, i.e., verbal encoding, lexical decision task (within-domain concurrent task), face decision task (cross-domain concurrent task), retrieval following within-domain concurrent task, retrieval following cross-domain concurrent task, were convolved with the canonical hemodynamic response function (HRF) and used as regressors in the individual design matrix. All six movement parameters (translation: x, y and z; rotation: pitch, roll and yaw) were included as covariates of no interest in the model. The individual statistical images from each condition were then entered group-averaged at the second level using a flexible factorial design, with a main-effect of subject and an interaction of conditions and groups. In this random-effects model, we modelled independent levels for subject and group, but dependent levels for conditions. For the three factors, we modelled unequal variances, which allows for violation of sphericity, as implemented in SPM8. In line with guidelines used in neuroimaging studies of complex cognitive functions (Lieberman & Cunningham, 2009), whole-brain analysis was conducted with a significance threshold of $p<0.001$ at the voxel level, uncorrected for multiple

comparisons, and a minimum extent threshold of 20 voxels. Conjunction analysis was performed to define regions commonly activated in both groups (Friston, 1999). Between group contrasts were conducted to define regions differentially activated in the two groups. We used inclusive masks of within group contrast with an uncorrected mask p-value of 0.05 and a significance threshold of $p<0.001$ at the voxel level, uncorrected for multiple comparisons, and a minimum extent threshold of 20 voxels. Anatomical location of activations was verified using SPM Anatomy toolbox (Eickhoff et al., 2005) and xjView (Cui, 2007). In addition, results in AgCC were reviewed individually to make sure that the locations of group activations corroborate activations at the individual level.

A series of multiple regressions with retrieval accuracy as covariate and the factor group as regressor were computed for the whole brain in the AgCC and the typically developing groups during encoding, retrieval following within-domain concurrent tasks and following cross-domain concurrent tasks. Similarly, multiple regressions were used to explore any association between brain activity and IQ, as well as brain activity and WM capacity measured by digit span backward. In the AgCC group, multiple regressions were used to investigate association between brain activity and handedness, as well as AgCC type (complete or partial AgCC). For these regressions, a significant threshold of $p<.001$, and a minimum extent threshold of 20 voxels was used.

CHAPTER 5: Neurobehavioural outcomes in school-age children with agenesis of the corpus callosum

5.1. Study 1 – Cognitive, Academic, Executive, Social and Behavioural Outcomes in School-Age Children with Agenesis of the Corpus Callosum

A neuropsychological profile for agenesis of the corpus callosum? Cognitive, academic, executive, social and behavioural functioning in school-age children

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Complete transcript of the article in press in *Journal of the International Neuropsychological Society* in November 2017.

Declaration for a thesis with publication

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PhD and MPhil students may include a primary research publication in their thesis in lieu of a chapter if:

- The student contributed greater than 50% of the content in the publication and is the "primary author", ie. the student was responsible primarily for the planning, execution and preparation of the work for publication
- It has been peer-reviewed and accepted for publication
- The student has approval to include the publication in their thesis from their Advisory Committee
- It is a primary publication that reports on original research conducted by the student during their enrolment
- The initial draft of the work was written by the student and any subsequent editing in response to co-authors and editors reviews was performed by the student
- The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis

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A. PUBLICATION DETAILS *(to be completed by the student)*

Full title	A neuropsychological profile for agenesis of the corpus callosum? Cognitive, academic, executive, social and behavioral functioning in school-age children	
Authors	Vanessa Siffredi, Vicki Anderson, Alissandra McIlroy, Amanda G. Wood, Richard J. Leventer, Megan M. Spencer-Smith	
Student's contribution (%)	60 %	
Journal or book name	Journal of the International Neuropsychological Society	
Volume/page numbers		
Status	☒ Accepted and In press ☐ Published	Date accepted/ published November 2017

B. STUDENT'S DECLARATION

I declare that the publication above meets the requirements to be included in the thesis

Student's name	Student's signature	Date *(dd/mm/yy)*
Vanessa Siffredi		21.11.2017

C. PRINCIPAL SUPERVISOR'S DECLARATION

I declare that:

- the information above is accurate
- The advisory committee has met and agreed to the inclusion of this publication in the student's thesis
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity
- 'Co-Author Authorisation' forms for each co-author are attached.

Supervisor's name	Supervisor's signature	Date *(dd/mm/yy)*

Professor Vicki Anderson		21.11.2017

Co-author authorisation form

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A. PUBLICATION DETAILS *(to be completed by the student)*

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Student's contribution (%)	60%	
Journal or book name	Journal of the International Neuropsychological Society	
Volume/page numbers		
Status	☒ Accepted and In-press ☐ Published	Date accepted/published November 2017

B. CO-AUTHOR'S DECLARATION *(to be completed by the collaborator)*

I authorise the inclusion of this publication in the student's thesis and certify that:

- the declaration made by the student on the *Declaration for a thesis with publication form* correctly reflects the extent of the student's contribution to this work;
- the student contributed greater than 50% of the content of the publication and is the "primary author" ie. the student was responsible primarily for the planning, execution and preparation of the work for publication.

Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
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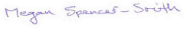
Amanda Wood		29/11/17

Richard Leventer	 Richard Leventer 2017.11.29 14:19:09 +11'00'	
Megan Spencer-Smith	 2017.11.28 11:13:15 +01'00'	

Abstract

Objective: Agenesis of the corpus callosum (AgCC), characterized by developmental absence of the corpus callosum, is one of the most common congenital brain malformations. To date, there are limited data on the neuropsychological consequences of AgCC and factors that modulate different outcomes, especially in children. This study aimed to describe general intellectual, academic, executive, social and behavioral functioning in a cohort of school-aged children presenting for clinical services to a hospital and diagnosed with AgCC. The influences of age, social risk and neurological factors were examined.

Method: 28 school-aged children (8 to 17 years) diagnosed with AgCC completed tests of general intelligence (IQ) and academic functioning. Executive, social and behavioral functioning in daily life, and social risk, were estimated from parent and teacher rated questionnaires. MRI findings reviewed by a pediatric neurologist confirmed diagnosis and identified brain characteristics. Clinical details including the presence of epilepsy and diagnosed genetic condition were obtained from medical records.

Results: In our cohort, ~50% of children experienced general intellectual, academic, executive, social and/or behavioral difficulties and ~20% were functioning at a level comparable to typically developing children. Social risk was important for understanding variability in neuropsychological outcomes. Brain anomalies and complete AgCC were associated with lower mathematics performance and poorer executive functioning.

Conclusions: This is the first comprehensive report of general intellectual, academic, executive social and behavioral consequences of AgCC in school-aged children. The findings have important clinical implications, suggesting that support to families and targeted intervention could promote positive neuropsychological functioning in children with AgCC who come to clinical attention.

Introduction

With over 190 million axons, the corpus callosum (CC) is the largest brain white matter pathway and connects homologous structures in the left and right cerebral hemispheres (Paul et al., 2007). Developmental absence of the CC, or Agenesis of the Corpus Callosum (AgCC), is amongst the most common brain malformations observed in humans, with an estimated prevalence of 1 to 7 per 4000 live births (Glass et al., 2008). Diagnosis is based on brain imaging including prenatal ultrasound and postnatal neuroimaging and can be complete or partial, see Figure 17. AgCC may occur as an isolated malformation or can be associated with other brain malformations or multiple congenital anomaly syndromes. It can result from environmental, metabolic or genetic causes (Edwards et al., 2014).

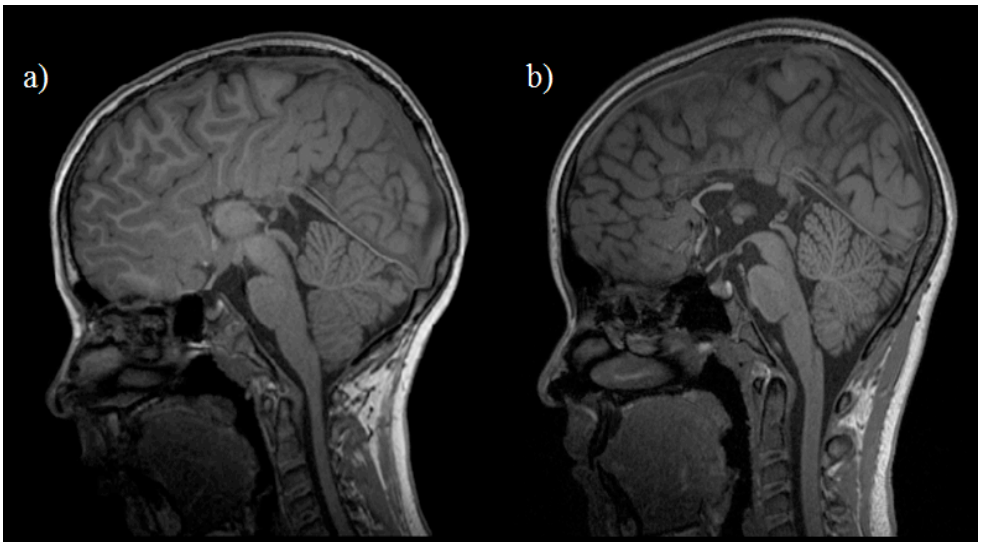


Figure 17. Midsagittal T1-weighted MRI of a) complete; and b) partial AgCC.

Consistent with the variability in presentation and etiology of this brain malformation, previous studies have reported cognitive abilities ranging from "normal", with children attending mainstream school and adults having a conventional career (Caillé et al., 1999), to severe cognitive difficulties, with individuals attending special developmental school and requiring assistance in daily living activities (Graham et al., 2008; Graham et al., 2003). Initial studies of individuals with AgCC reported a pattern of reduced performance across multiple cognitive domains (Chiarello, 1980; Lassonde & Jeeves, 1994; Sauerwein & Lassonde, 1994). However, these study samples collapsed across children and adults, and had specific selection criteria (e.g. IQ >70). Further, participants were not routinely diagnosed

based on MRI scan, which may have impacted diagnostic accuracy (e.g. diagnosis based on CT may lead to hypoplasia being incorrectly diagnosed as AgCC) (Sauerwein & Lassonde, 1994). In a systematic review of neuropsychological functioning in AgCC, where diagnosis was based on MRI (n=110 patients), intellectual functioning was described to be, on average, in the low average range for adults (IQ: Mean=88.2, SD=15.18, n=41) and significantly lower for children (IQ: Mean=76.4, SD=30.12, n=48; Siffredi, Anderson, Leventer, & Spencer-Smith, 2013). Qualitative examination highlighted that individuals (adults and children) with AgCC are at particular risk of impaired arithmetic skills, with 86% demonstrating impairments. In contrast, executive functions, reading and spelling skills were relatively preserved. Studies examining social functioning in individuals with AgCC report a range of impairments, such as reduced understanding of jokes and humor (W. S. Brown, Paul, et al., 2005), proverb and non-literal items (Paul et al., 2003), complex social scenes (W. S. Brown & Paul, 2000; Paul et al., 2004; Turk et al., 2010), integration of social information from multiple sources (e.g., paralinguistic cues, nonliteral language; Symington, Paul, Symington, Ono, & Brown, 2010), story-generation skills (Paul et al., 2004), and difficulties experiencing and thinking about complex but not basic emotions in the context of social interactions (L. B. Anderson, Paul, & Brown, 2017). Links between AgCC and autism spectrum disorder (ASD) symptoms have also been examined, but results have been mixed. In a convenience sample of 189 children and adults with AgCC, 8.5% met criteria for ASD diagnosis (vs. 1% of their siblings; Doherty, Tu, Schilmoeller, & Schilmoeller, 2006) while in a more recent convenience sample of 26 individuals with AgCC, eight (30.8%) were reported as having autism symptoms but only 3 of 22 (13.6%) met criteria for an ASD diagnosis (Paul et al., 2014).

Numerous factors are likely to influence neuropsychological development in children with AgCC, as outlined by Maureen Dennis and colleagues (2000, 2006) in their developmental framework. Age is important for understanding level of cognitive functioning, and in AgCC better general intellectual function have been observed in adults compared with children (Siffredi et al., 2013). Social factors, including demographic characteristics and family function, can influence a child's neuropsychological development (Hackman & Farah, 2009; Sirin, 2005). Neurological factors should also be considered in understanding neuropsychological outcomes in this atypically developing brain. In the context of AgCC, some of the neurological factors that might influence outcomes include clinical co-morbidities (e.g., additional central nervous system (CNS) anomalies) or the presence of seizures, and

associated genetic conditions (Dennis et al., 2006). Some genetic conditions, such as Aicardi syndrome, are uniformly associated with AgCC, and single gene disorders (e.g., Edwards et al., 2014; Palmer & Mowat, 2014) and multiple chromosomal abnormalities associated with AgCC have also been described (D'Antonio et al. 2016). Recently the first gene for isolated AgCC, DCC, was identified (Marsh et al., 2017). The genetic etiology may also be polygenic and/or reflect complex genetic interactions (Paul et al. 2007). Several studies suggest that isolated AgCC appears to carry the best prognosis, with up to 85% of individuals exhibiting average cognitive functioning (Pilu et al., 1993; Vergani et al., 1994). A number of potential candidates for compensation have been suggested, in particular enlargement of the anterior and posterior commissures, as well as the degree of AgCC (partial or complete). Enlargement (hyperplasia) of the anterior commissure, found in about 10% of individuals with AgCC (Hetts et al., 2006; Loeser & Alvord, 1968) and enlargement of posterior commissure might be indicators of CC fibers using these commissures as alternative interhemispheric conduits (Hannay et al., 2009). Similarly, the degree of AgCC (complete or partial) could differentially allow white matter fibers to cross the midline, and therefore increase the presence of interhemispheric functional connections (Huber-Okrainec et al., 2005).

Currently our understanding of the consequences of AgCC for school-age children on neuropsychological functioning and factors that modulate the consequences of AgCC on these functions is restricted by the inherent problem of small sample studies and conflicting results (Bedeschi et al., 2006; D'Antonio et al., 2016; Moutard et al., 2003; Shevell, 2002). The challenge of studying the high heterogeneity of this population has previously been addressed by focusing on individuals with isolated AgCC only, which does not reflect the AgCC population. A detailed MR-based study of 82 patients with AgCC showed that it was truly isolated in only 4% of patients, with most having additional brain abnormalities such as cortical malformations (Hetts et al., 2006). Clinicians therefore lack the necessary knowledge to provide the families of children with AgCC the information regarding prognosis or optimal intervention targets. This study aimed to describe general intellectual, academic, executive, social and behavioral functioning in a large cohort of school-aged children who presented for clinical services to a hospital and diagnosed with AgCC. The influence of age, social risk and neurological factors on neuropsychological functioning was examined. Patients included both those with isolated AgCC and AgCC associated with other brain malformations. This study represents a first step in providing an understanding of the neuropsychological profile of children with AgCC.

Methods

Sample

Our AgCC cohort was recruited as part of the "Paediatric Agenesis of the Corpus Callosum Project" at the Murdoch Children's Research Institute in Melbourne, Australia. Twenty-eight participants (85% of those eligible, n=33), aged 8 to 17 years (M=11.54, SD=2.35) were ascertained by review of the radiology database at The Royal Children's Hospital (RCH), see Figure 18 for participant flow. Inclusion criteria were: 1) aged 8.0 to 16.11 years at recruitment between September 2009 and February 2014; 2) evidence of AgCC on MRI; 3) English speaking; and 4) ability to engage in neuropsychological testing. 37% of children who were screened for inclusion in the study were excluded due to severe impairment and inability to engage in neuropsychological testing but otherwise met inclusion criteria.

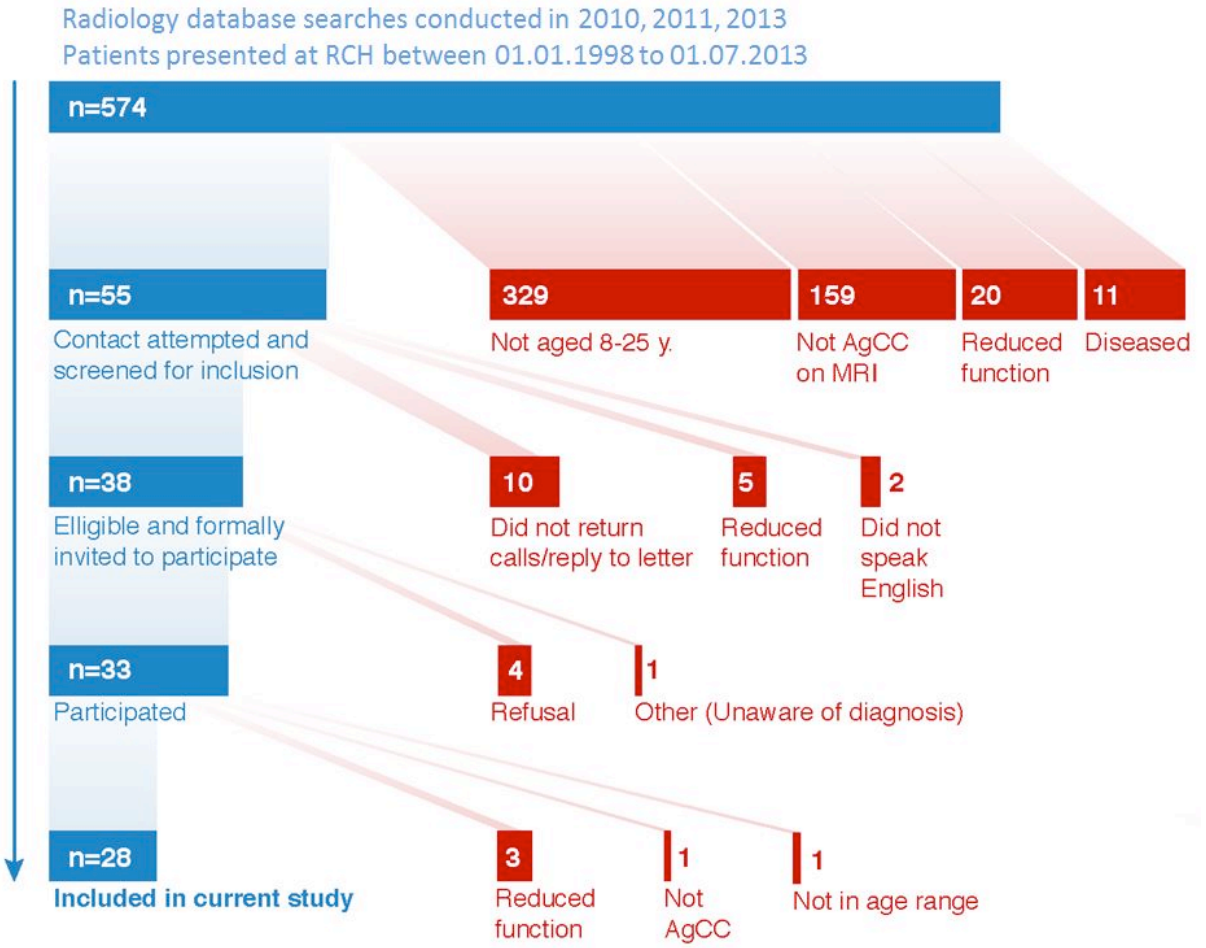


Figure 18. Flow chart of of study recruitment process.

Procedure

The RCH Human Research Ethics Committee approved the study. Caregivers, and when appropriate participants (based on age), provided informed written consent before participation. Participants completed a neuropsychological assessment and MRI, or gave consent to use previous clinical MRI scans. Caregivers and teachers completed questionnaires.

Measures

Neuropsychological functioning:

Child testing was conducted by a training child psychologist (MSS, AM, VS under supervision by VA) using standardized tests to estimate: *1) General intelligence:* Full Scale, Verbal and Performance IQ (M=100, SD=15) were generated from the four subtest version of the Wechsler Abbreviated Intelligence Scale (WASI: Wechsler, 1999, n=21, 75%) or the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV: Wechsler, 2003 n=7, 25%) based on 10 subtests. *2) Academic functioning:* The Wide Range Achievement Test 4 (WRAT-4: Wilkinson & Robertson, 2006) was administered to estimate: single Word Reading, Spelling and Math Computation (M=100, SD=15).

Parents and teachers completed age standardized questionnaires to estimate: *3) Executive function in everyday life:* The Behavioral Rating Inventory of Executive Function: parent form (BRIEF: Gioia, Isquith, Guy, & Kenworthy, 2000) estimates executive abilities in everyday life over the past 6 month. It generates two summary index scales: Behavioral Regulation Index (BRI: based on Inhibit, Shift and Emotional control subscales) and Metacognition Index (MCI: based on Initiate, Working memory, Plan/organize, Organization of materials and Monitor subscales); as well as a Global Executive Composite (GEC) based on both indices. Higher scores reflect increased difficulties in executive functioning (M=50, SD=10). *4) Behavior:* Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) generates a Total Difficulties score estimating general behavioral and emotional functioning over the past 6 months (based on the subscales Emotional Symptoms, Conduct Symptoms, Hyperactivity-Inattention and Peer Problems). Australian test norms were used (Mellor, 2005). *5) Social function:* Social Skills Improvement System (SSIS; Gresham & Elliott, 2008) estimated aspects of social functioning. It generates the Social Skills scale and the Problem Behavior scale, including the Autism Spectrum subscale that estimates ASD behaviors. A

higher score on the Social Skills scale indicates better social functioning and a lower score on the Problem Behavior scale indicates better behavioral functioning (M=100, SD=15).

Risk Factors:

1) Age at testing. *2) Social risk*: estimated using the Social Risk Index, a composite score based on information collected from a caregiver questionnaire: family structure, education of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home, and maternal age at birth. Scores range from 0-12, with higher scores representing higher socio-economical risk (Roberts et al., 2008). *3) Neurological factors*: Structural MR images acquired on 3T Siemens Magnetom Trio Scanner using a 32-channel head coil (TR=1900 ms, TE=2.71 ms, TI=900 ms, FA=9°, FoV=256mm and voxel size=0.7 x 0.7 x 0.7 mm) were qualitatively reviewed by a pediatric neurologist with expertise in brain malformations (RJL). A specially modified protocol (V. Anderson et al., 2009; Leventer et al., 1999) was employed to characterize AgCC and associated CNS anomalies: (a) AgCC type: AgCC was classified as partial = a section of the corpus callosum absent, or complete = the entire corpus callosum absent; (b) anterior and posterior commissures: were classified as absent, reduced, normal or enlarged; (c) CNS anomalies: additional to the AgCC were classified as absent or present (excluding common concomitant anatomical changes due to the absence (complete or partial) of the CC such as Probst bundles, cingulate gyrus alteration and colpocephaly; Booth, Wallace, & Happe, 2011; Lee, Kim, Cho, & Lee, 2004; Paul, 2011; Paul et al., 2007). Based on medical records and parent interview, (d) diagnosed genetic condition: classified as present or absent and (d) seizure disorder: classified as present or absent.

Developmental delay:

Caregivers completed a structured interview that elicited information on when the child reached developmental milestones and was used to estimate whether the child had a developmental delay. The child was classified as having a motor delay if they achieved the milestones of rolling after 6 months, crawling after 9 months, and walking after 15 months; and a speech delay if they achieved the milestone of speaking single words after 15 months and speaking sentences of 2 to 3 words after 24 months.

Statistical analyses

To examine differences between the AgCC group mean scores and test norms, one-sample t-test or Wilcoxon signed-rank test in the case of violation of normality was used. Mean differences in test scores within each functional domain were examined using paired-sample t-test or Wilcoxon signed-rank test. Based on previous studies reporting on individuals with AgCC and the developmental framework of Dennis (2000, 2006), backward hierarchical regressions were used as an exploratory model building method to examine associations between risk factors as predictors and neuropsychological functions as outcomes. The order in which predictors were entered into the model was guided by Dennis' framework: 1) age at testing; 2) social risk index; and 3) neurological factors, including AgCC type (complete vs partial), size of the anterior and of the posterior commissures (absent, reduced, normal or enlarged), additional CNS anomalies (present or absent), diagnosed genetic condition, presence of a seizure disorder. The default stepping criteria of $p<.05$ was used for inclusion and for removal of variables in the models. To address Type II Error, Bonferroni correction for multiple comparisons (Field, 2013) was applied to the resulting regression models: α altered = α original 0.05 / 8 comparisons = 0.006.

Results

Sample characteristics

Table 3 presents the characteristics of our pediatric AgCC cohort (n = 28), which included more males than females. Half of the cohort was right-handed, almost just as many were left-handed, and a small number showed mixed handedness. There were similar proportions of children with complete AgCC (n = 14) and partial AgCC (n = 14). There were fewer children with isolated AgCC (n = 11) and more children with AgCC associated with other CNS anomalies (n = 17) in our cohort. Table 3 highlights the heterogeneity in clinical presentation of children with AgCC. The supplementary table provides details of individuals' clinical characteristics.

Table 3. Characteristics of the Pediatric Agenesis of the Corpus Callosum Cohort.

Total n=28		**n**	**Percentage**
Sex	Female	10	35.7
	Male	18	64.3
Handedness[a]	Right	14	50
	Left	12	42.9
	Mixed	2	7.1
Neurological characteristics			
AgCC type	Complete AgCC	14	50
	Partial AgCC	14	50
CNS anomalies	None	11	39.3
	AgCC associated with other CNS anomalies	17	60.7
Associated conditions	Seizure disorder	4	14.3
	Diagnosed genetic condition	6	21.4
Age at AgCC diagnosis	Prenatal (ultrasound)	10	35.7
	First month of life	4	14.3
	Infancy (before 3 years)	9	32.1
	Early childhood (4 to 6 years)	1	3.6
	Middle childhood (7 to 9 years)	1	3.6
	Late childhood (10 to 12 years)	3	10.7
Developmental delays	Speech delay	9	32.1
	Motor delay	13	46.4
	Information missing	2	7.1
Schooling			
Kindergarten	Mainstream	24	85.7
	Special developmental	3	10.7
	No kindergarten	1	3.6
Primary School	Mainstream	19	67.9
	Special developmental	7	25
	Both mainstream and special developmental	2	7.1
High School (n=11)	Mainstream	6	54.4
	Special developmental	5	45.5
Educational progress in mainstream school			
Primary school (n=21)	Remedial classes/tutoring/aid	13	61.9
High school (n=6)	Remedial classes/tutoring/aid	3	50
Current school level	Achieving average or above	13	61.9
Interventional therapies	Speech	17	60.7
	Occupational	18	64.3
	Psychological	10	35.7

Note: [a]Handedness estimated by the Edinburgh Handedness Inventory (Groen, Whitehouse, Badcock, & Bishop, 2012; Oldfield, 1971).(Groen, Whitehouse, Badcock, & Bishop, 2012; Oldfield, 1971)(Groen, Whitehouse, Badcock, & Bishop, 2012; Oldfield, 1971) (Groen, Whitehouse, Badcock, & Bishop, 2012; Oldfield, 1971) Right-handed = +40 to +100, left-handed = -40 to -100, mixed handed = -40 to +40.
Abbreviations: AgCC agenesis of the corpus callosum. CNS central nervous system. WASI Wechsler Abbreviated Intelligence Scale. WISC-IV Wechsler Intelligence Scale for Children, 4th edition. WRAT-4 Wide Range Achievement Test 4. BRIEF Behavioral Rating Inventory of Executive Function. SDQ Strengths and Difficulties Questionnaire. SSIS Social Skills Improvement System.

AgCC neuropsychological functioning compared with normative expectations

Children with AgCC achieved poorer scores than the normative test mean on all neuropsychological measures, see Table 4. For general intellectual functioning, mean scores were in the borderline range for Full-Scale IQ and Verbal IQ, and higher, in the low average

range, for Performance IQ. The overall distribution for each IQ indices was skewed toward the lower end of population expectations. The majority of children (46.4 to 66.7%) were categorized with a mild impairment for intellectual functions. For academic functioning, mean scores were in the borderline range for Math Computation, and the low average range for Word Reading and Spelling. For Word Reading and Spelling, about half of the children performed in the average range or above, with impairments in Math Computation more frequent. For executive functioning in daily life, mean parent and teacher ratings on BRIEF indices were in the clinical range, with the exception of the parent rated Behavioral Regulation Index, which was in the borderline range. For behavioral functioning, mean ratings on the SDQ Total Difficulties score (parent and teacher) were above the average range (+1SD). For social functioning, mean parent and teacher ratings on the SISS scales were in the low average (parent ratings) to average (teacher ratings) range for the Social Skills scale, and in the average range for the Problem Behaviors scale. Of interest, a significant level of autism spectrum behaviors was reported in more than half of the sample by both parents (61.9%) and teachers (55.6%).

Table 4. Neuropsychological functioning of the Pediatric Agenesis of the Corpus Callosum Cohort: comparison with normative test means, and impairment rates.

	AgCC cohort		Normative Test M (SD)	Mean difference	One sample t or Wilcoxon signed-rank tests		Percentage impaired		
	n	M (SD) or Mdn			t (df) or Z	p value	Average or above	Mild	Moderate to severe
General intellectual functioning (WASI or WISC-IV)									
Full-Scale IQ	27	78.3 (15.21) Mdn=74	100 (15)	-21.7	Z=12.5	<.001	18.5	66.7	14.8
Verbal IQ	27	76.37 (13.45)	100 (15)	-23.63	t(26)=-9.13	<.001	29.6	48.2	22.2
Performance IQ	28	84 (18.19)	100 (15)	-16	t(27)=-4.65	<.001	39.3	46.4	14.3
Academic functioning (WRAT-4)									
Word Reading	25	89.04 (20.21)	100 (15)	-10.96	t(24)=-2.71	.012	56	24	20
Spelling	26	83.46 (18.27)	100 (15)	-16.54	t(25)=-4.62	<.001	46.2	30.7	23.1
Math Computation	27	76.04 (13.94)	100 (15)	-23.96	t(26)=-8.93	<.001	25.9	40.8	33.3
Executive functioning in daily life, parent ratings (BRIEF)									
Global Executive Composite	28	68.07 (11.91) Mdn=65	50 (10)	+18.07	Z=404	<.001	21.4	50	28.6
Behavior Regulation Index	28	64.82 (14.25) Mdn=61	50 (10)	+14.82	Z=343	<.001	42.9	28.5	28.6
Metacognition Index	28	68.29 (10.26)	50 (10)	+18.29	t(27)=9.4	<.001	17.9	50	32.1
Executive functioning in daily life, teacher ratings (BRIEF)									
Global Executive Composite	17	71.12 (13.6)	50 (10)	+21.12	t(16)=6.4	<.001	17.6	29.5	52.9
Behavior Regulation Index	17	67.41 (15.67)	50 (10)	+17.41	t(16)=4.58	<.001	29.4	23.5	47.1
Metacognition Index	17	71.12 (13.39)	50 (10)	+21.12	t(16)=6.5	<.001	23.5	17.7	58.8
							Average or above		**Below average**
Behavior, parent ratings (SDQ)									
Total score	25	Mdn=15	8.2 (6.1)	+6.32	Z=302	<.001	52		48
Behavior, teacher ratings (SDQ)									
Total score	16	13.25 (7.19)	6.5 (6)	+6.75	t(15)=3.76	.002	56.3		43.8
Social functioning, parent ratings (SSIS)									
Social Skills	22	86.95 (20.8)	100 (15)	-13.05	t(21)=-2.94	.008	59.1		40.9
Problem Behaviors	22	104 (14.71)	100 (15)	+4	t(21)=5.32	<.001	31.8		68.2
Autism Spectrum	22						38.1		61.9
Social functioning, teacher ratings (SSIS)									
Social Skills	18	90 (17.67)	100 (15)	-10	t(17)=-2.4	.028	94.4		5.6
Problem Behaviors	18	111 (11.77)	100 (15)	+11	t(17)=3.97	<.001	66.7		33.3

Autism Spectrum	18	44.4	55.6

Note: Average or above = scores > -1 standard deviation (SD) of the test mean, Mild impairment = scores ≤ -1 to < -2 SD, Moderate to severe impairment = scores ≤ -2 SD. The number of cases differs for each outcome as not all informants provided responses for each measure. WASI, WISC-IV, WRAT-4 higher scores reflect better performance. BRIEF and SDQ: lower scores reflect better functioning. SSIS: higher scores on the Social Skills scale indicates better functioning, while lower scores on the Problem Behavior scale indicates better functioning.

Abbreviations: WASI: Wechsler Abbreviated Intelligence Scale; WISC-IV: Wechsler Intelligence Scale for Children, 4th edition; WRAT-4: Wide Range Achievement Test 4; BRIEF: Behavioral Rating Inventory of Executive Function; SDQ: Strengths and Difficulties Questionnaire; SSIS: Social Skills Improvement System.

Pattern of functioning within neuropsychological domains

There were some significant within group comparisons for select neuropsychological domains examined. For general intellectual functioning, Performance IQ was significantly better than Verbal IQ, t(26)=3.245, p=.003. For academic functioning, Word Reading, t(24)=-5.221, p<.001, and Spelling t(25)=-3.063, p=.005 were significantly better than Math Computation. For executive functioning in daily life, the parent-rated Behavioral Regulation Index was better than Metacognition Index, t(27)=-2.093, p=.046.

Risk factors associated with neuropsychological functioning

Analyses revealed that some risk factors were important predictors for specific aspects of neuropsychological functioning, even after Bonferroni correction (p<.006), Table 5. For academic functioning, higher Social Risk Index and complete AgCC were associated with poorer Word Reading scores, together accounting for 36.2% of the variance, while higher Social Risk Index and additional CNS anomalies were associated with poorer Math Computation scores, accounting for 44.2% of the variance. For executive functioning in daily life, higher Social Risk Index, complete AgCC and older age at testing were associated with poorer parent ratings on the BRIEF Behavior Regulation Index and Global Executive Composite, accounting for 38.6% and 35.4% of the variance respectively, while higher Social Risk Index was associated with poorer parent ratings on the BRIEF Metacognition Index, accounting for 25.9% of the variance. For behavioral functioning, higher Social Risk Index was associated with poorer parent ratings on SDQ Total Difficulties, accounting for 55.5% of the variance, while additional CNS anomalies were associated with poorer teacher ratings on SDQ Total Difficulties, accounting for 45.3% of variance.

Table 5. Risk factors significantly associated with neuropsychological outcomes in children with AgCC.

	Risk Factor (Predictor)	B	Standard Error B	r^2	β	p
General intellectual functioning (WASI or WISC-IV)						
Full-Scale IQ	none					
Verbal IQ	none					
Performance IQ	none					
Academic functioning (WRAT-4)						
Word Reading	Social Risk Index*	-5.08	1.9		-.53	.006*
	AgCC type	16.27	6.9	.362	.41	.028
Spelling	Social Risk Index	-3.83	1.43	.221	-.47	.015
Math Computation	Social Risk Index*	-3.48	.97		-.55	.001*
	CNS anomalies	-11.81	4.33	.442	-.41	.012
Executive functioning in daily life, parent ratings (BRIEF)						
Behavior Regulation Index	Social Risk Index*	3.45	.95	.501	.53	.001*
	AgCC type*	-14.221	4.41		-.51	.004*
	Age at testing	2.432	.96		.4	.018
Metacognition Index	Social Risk Index*	2.53	.78	.259	.54	.002*
Global Executive Composite	Social Risk Index*	3.14	.77		.57	<.001*
	AgCC type*	-10.98	3.57		-.47	.005*
	Age at testing	2.1	.77	.534	.41	.012
Executive functioning in daily life, teacher ratings (BRIEF)						
Behavior Regulation Index	Seizure disorder	-22	8.05		-.61	.016
	CNS anomalies	-15.25	7.5	.385	-.46	.061
Metacognition Index	none					
Global Executive Composite	Seizure disorder	-18.5	7.12		-.44	.021
	CNS anomalies	-12.8	6.6	.361	-.6	.074
Behavior, parent ratings (SDQ)						
Total score	Social Risk Index*	2.28	.43	.555	.75	<.001*
Behavior, teacher ratings (SDQ)						
Total score	CNS anomalies*	-10.11	2.97	.453	-.67	.004*
Social functioning, parent ratings (SSIS)						
Social Skills	Social Risk Index	-3.81	1.38		-.434	.013
	Genetic disorder	19.15	7.76		.4	.024
Problem Behaviors	none					
Social functioning, teacher ratings (SSIS)						
Social Skills	CNS anomalies	18.5	7.85	.258	.51	.031
Problem Behaviors	none					

Notes: Sex had a significant impact on SSIS parent ratings and therefore sex was entered as a covariate in regression analyses. Risk factors that reached significance at the Bonferroni-corrected level ($p<.006$) are indicated with *.

Abbreviations: AgCC agenesis of the corpus callosum. CNS central nervous system. WASI Wechsler Abbreviated Intelligence Scale. WISC-IV Wechsler Intelligence Scale for Children, 4th edition. WRAT-4 Wide Range Achievement Test 4. BRIEF Behavioral Rating Inventory of Executive Function. SDQ Strengths and Difficulties Questionnaire. SSIS Social Skills Improvement System.

Backward hierarchical regressions examined risk factors as predictors of each outcome, including: age at testing, social risk index, AgCC type (complete vs partial), size of the anterior and of the posterior commissures (absent, reduced, normal or enlarged), additional CNS anomalies, diagnosed genetic condition, and seizure disorder.

Discussion

A major congenital brain malformation such as AgCC demonstrates the remarkable capacity of the brain for structural and functional plasticity during development. Indeed, individuals with AgCC do not exhibit the classic disconnection syndrome observed in "split-brain" patients, where absence of the CC is acquired through surgical resection for the treatment of epilepsy. Consequences of developmental absence of the CC remain imperfectly understood, largely reflecting the inherent problem of small sample studies and the important heterogeneity of this population in terms of neuroimaging profiles (complete or partial, isolated or associated AgCC), etiologies, neuropsychological difficulties, and clinical sequelae (Bedeschi et al., 2006; D'Antonio et al., 2016; Moutard et al., 2003; Shevell, 2002; Siffredi, Spencer-Smith, et al., 2017). This study provides the first comprehensive report of general intellectual, academic, executive, behavioral and social functioning in a cohort of school-age children presenting for clinical services to a hospital and diagnosed with AgCC confirmed on MRI.

Our pediatric cohort performed below normative test expectations across all neuropsychological domains studied. However, it is important to note that, despite major atypical brain development, around 20% performed at the average or above average level of functioning across all domains. Overall, general intellectual functioning in our AgCC cohort was in the borderline range, and more than one standard deviation below the average test mean for the general population. As often reported in previous AgCC studies, we observed a significant variability within our pediatric cohort, with Full-Scale IQ ranging from extremely low to superior. The distributions for both verbal and performance IQs were skewed toward the lower end of the normal distribution. Consistent with low general intellectual functioning in our cohort and previous child and adolescent AgCC studies (Siffredi et al., 2013), we observed high rates of parent-reported developmental delays, with 32% of children reported to have had speech delay and 46% motor delay. Our results reveal stronger visual-spatial than verbal abilities, a result that is specific to our cohort and might reflect the inherent heterogeneity of AgCC. For academic functioning, mathematical performance was most impaired, falling in the borderline range, with reading and spelling both in the low average range. This is consistent with previous studies showing high rates of mathematical impairment (Siffredi et al., 2013). In regards to educational placement, more children attended mainstream school in earlier school levels, while in later school levels it was more common

for children to attend special developmental school. Almost half of the children attending secondary school were attending special developmental school, while, in contrast, most of the remaining participants were reported by parents as performing at an average level at least in mainstream school (with or without the support of additional tutoring or aid). For executive functioning in daily life, children demonstrated more difficulties in metacognition (e.g., working memory, initiation) than behavioral regulation (e.g., inhibition, emotional control). Significant behavioral and social difficulties were observed in our cohort, consistent with previous studies. Furthermore, a high rate of ASD symptoms was observed, with more than half of parents and teachers reporting clinical levels of ASD in our cohort (Paul et al., 2014; Paul et al., 2004). Consistent with previous AgCC studies that have reported a higher proportion of left-handers than in the general population, ranging from 24% to 56% (e.g., Lábadi & Beke, 2017; Sauerwein & Lassonde, 1994; Chiarello, 1980), in our AgCC cohort almost half of the children were left-handed. This atypical clinical observation might reflect properties of this brain malformation. It is possible that processes associated with the early development of the corpus callosum and early development of lateralization of hemispheric function in general play a role in determining handedness.

In our cohort of children with AgCC, we found social risk was a key factor in understanding functioning across academic, executive and behavioral domains, but not intellectual or social functionin domains. In typically developing children, the association between high social risk and low achievement in academic functioning, in particular mathematics, as well as low executive and behavioral functioning has been well documented (Farah et al., 2006; Jordan & Levine, 2009; Sarsour et al., 2011). This importance of social risk for understanding variability in functional outcomes for children with AgCC is consistent with Dennis' developmental framework (2000, 2006) proposing factors likely to influence neuropsychological development. However, in contrast to this framework, we found little evidence that the child's age at testing or a wide range of neurological factors proposed in the literature to influence neuropsychological functioning, including AgCC type, size of the anterior and posterior commissures, additional CNS anomalies, diagnosed genetic condition or seizure disorder, were consistently associated with functioning across intellectual, academic, executive, behavioral and social domains. We note, there was some suggestion that the presence of additional CNS anomalies was associated with select aspects of academic, executive, behavior and social functioning, and complete AgCC was associated with aspects of academic and executive functioning. Future studies examining age, social risk and

neurological factors associated with neuropsychological functioning in larger samples will be important.

The findings of this study should be considered in the context of its limitations. Due to our inclusion criterion for children to have the ability to engage in testing, we acknowledge that our cohort likely represents higher functioning AgCC children (see Figure 2 for participant flow). However, it is also possible our cohort is biased toward individuals with sufficient clinical need for referral for brain scan (only 35.7% were diagnosed prenatally). Given the rapid advances in neuroimaging, including ultrasound, and its growing use in obstetric populations, increased detection of patients with AgCC during fetal life through routine ultrasound screening, including those who are asymptomatic, may result in research documenting alternative profiles of neuropsychological functioning to those that exists in the historical literature (Pisani et al., 2006). Moreover, we used a subjective method for reviewing MRI scans to describe neurological characteristics, in particular properties of the anterior and posterior commissures that could be involved in compensation mechanisms in individuals with AgCC (Barr & Corballis, 2002; Hannay et al., 2009; Lassonde et al., 1991). The use of quantitative measures could provide new insights into compensation mechanisms in this population, such as volumetric or quality of the fibers crossing these commissures, to explore associations with neuropsychological outcomes. The use of test norms rather than a local representative comparison group of children, and the small sample of children across a relatively wide age range with a range of varying etiologies and brain abnormalities on MRI are limitations that should be considered. This study provides a broad understanding of neuropsychological functioning in children with AgCC presenting for clinical services, and future studies examining in further detail neuropsychological domains will contribute to a greater understanding of neuropsychological outcomes.

Conclusion

To our knowledge, this is the first cohort study to comprehensively report on general intellectual, academic, executive, behavioral and social consequences of AgCC in school-age children who present for clinical services to a hospital. We showed that while children with AgCC perform below their peers across a range of neuropsychological domains, they demonstrate some relative strengths within domains. Specifically, we identified relative

strengths in non-verbal skills, word reading, spelling, and everyday behavioral regulation. Our results do not support a clear and unique neuropsychological phenotype for AgCC in childhood, further highlighting the heterogeneity of this condition. The variability in neuropsychological functioning we observed appears to be differentially associated with individual factors, in particular social risk. These findings have important clinical implications, suggesting that providing children and their families with a supportive social environment could promote positive neuropsychological outcomes across a range of domains, for example through school support and aid, parenting advice, access to tailored interventions according to the child's individual difficulties such as psychological, speech or occupational interventions. Further research in a larger cohort of patients with AgCC is needed to better understand the neuropsychological outcomes in this heterogeneous population.

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Additional materials

For general intellectual function, as reported in the present article, mean scores of the AgCC cohort were in the borderline range for Full-Scale IQ and Verbal IQ, and in the low average range for Performance IQ. Scores ranged from extremely low to high average for Verbal IQ, to superior for Full-Scale IQ, and to very superior for Performance IQ. The overall distribution for each IQ indices was skewed toward the lower end, Figure 19.
Specific characteristics of the AgCC cohort are provided in the Appendix 4.

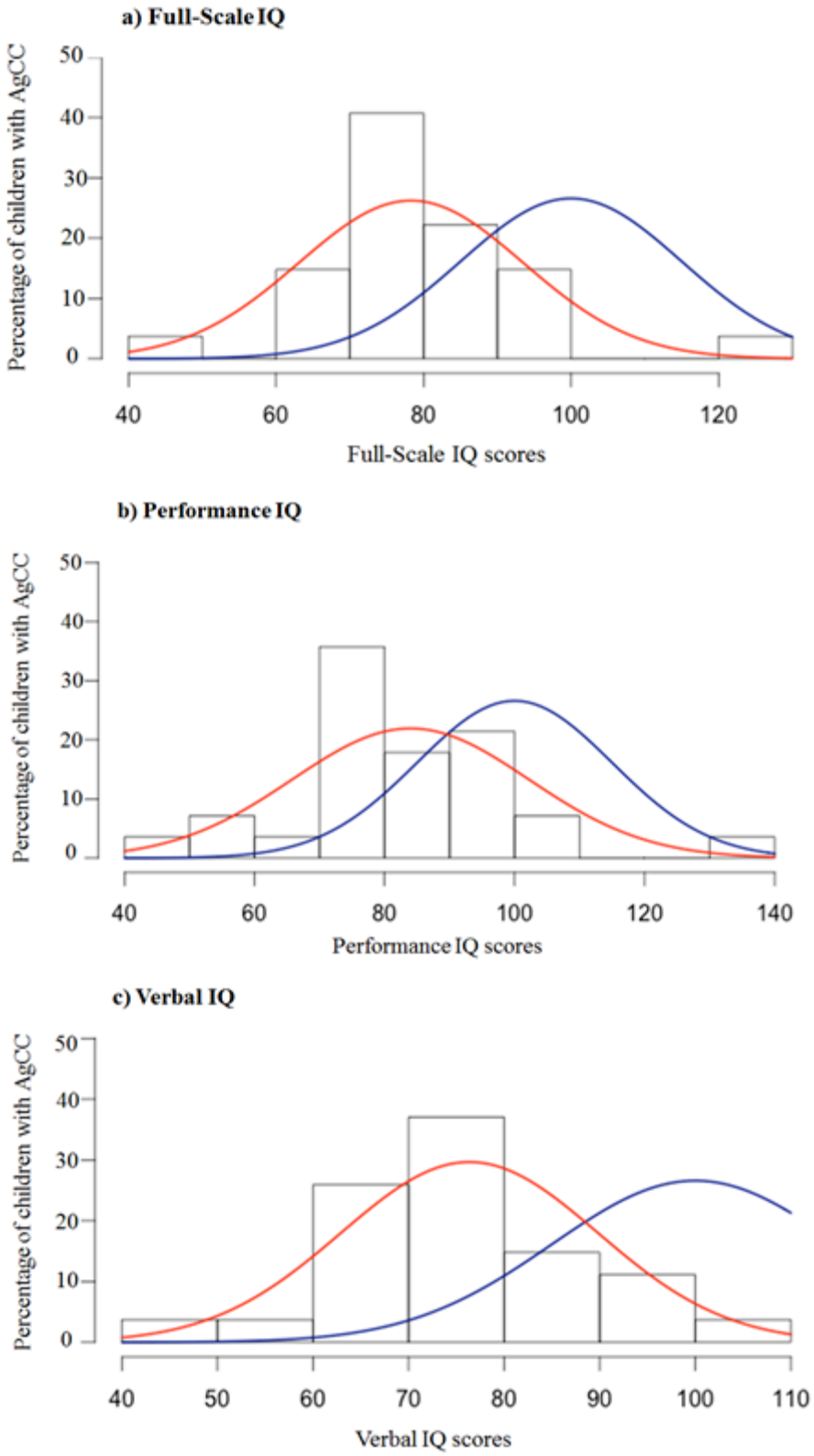

Figure 19. Rates of (a) Full-Scale, (b) Performance and (c) Verbal IQ scores of the AgCC cohort. The red curve represents distribution of the AgCC cohort and the blue curve represents distribution of normative data.

Supplementary table. Clinical characteristics and MRI findings of children and adolescents with AgCC included in the study.

ID	*Age*	*Sex*	*H*	*Education*	*Help*	*FSIQ*	*P/C*	*CC status*	*AC*	*PC*	*PB*	*CO*	*Additional MRI findings*	*Seizures*	*Genetic*
001	15.67	F	L	Mainstream	+	81	C	CC absent	++	++	+	+	Bilateral periventricular nodular heterotopia	+	+ FLNA gene
002	14.33	F	R	Special		40	P	Presence of a thin middle posterior body and posterior body	tiny	tiny	+	-	(a) irregular crowded sulci posteriorly in the occipital region and medial parasaggital region (b) shunt: enter R post-parietal region going into R lateral ventricle (c) bilateral periventricular nodules heterotopia = frontal predominant, lining frontal horns and mid bodies of lateral ventricles	-	-
003	11.75	M	L	Mainstream	+	96	P	Presence of part of the genu	+	+	+	+	None	-	-
007	14.75	F	L	Special		69	P	Presence of thin rostrum, genu, and anterior body	+	+	-	-	Agenesis of the septum pellucidum, semilobar holoprosencephaly	+	-
008	8.33	M	L	Mainstream & Special	+	73	C	CC absent	+	+	+	+	Cortical dysplasia	-	-
010	9.67	M	L	Mainstream	+	62	P	Presence of the rostrum	tiny	+	-	+	None	-	-
011	11.67	M	L	Mainstream	+	75	C	CC absent	+	+	+	+	None	-	-
012	15.33	F	R	Mainstream	-	100	P	Presence of the rostrum	++	+	+	+	Bilateral periventricular heterotopic grey matter	+	-
013	9.50	M	L	Mainstream	-	81	P	Presence of the rostrum and of the genu	+	+	-	-	Cerebellar hemispheric hypoplasia, Dandy Walker variant, Heterotopic grey matter, small interhemispheric cyst	-	-
015	10.25	F	L	Mainstream	-	73	P	Presence of the middle-posterior body, posterior body, and the splenium	+	+	-	-	Abormal grey matter around the frontal horns of the lateral ventricles, abnormal sulci medio in frontal lobe	+	-

016	13.42	F	R	Mainstream	-	93	P	Presence of the anterior body	tiny	++	+	-	None	-	-
017	8.83	F	R	Special	-	71	C	CC absent	tiny	+	+	+	Bilateral periventicular heterotopic grey matter	-	-
018	12	M	R	Mainstream Special (high school)	+	72	C	CC absent	+	+	+	+	None	-	+ dup 3p26.3
019	8.58	M	R	Mainstream	+	73	C	CC absent	+	tiny	+	+	None	-	+ dup 3p26.3
020	12.67	M	L	Mainstream	+	76	C	CC absent	tiny	tiny	+	-	Abnormal deep sulcation (right parietal) lined by polymicrogyria	-	-
021	10.67	M	R	Special	-	84	C	CC absent	++	++	+	+	Unilateral periventricular heterotopic grey matter (right frontal horn)	-	-
024	10.83	M	R	Mainstream	+	82	C	CC absent	++	+	+	+	None	-	-
025	12.58	M	R	Mainstream Special (high school)	+	74	P	Presence of the middle-posterior body, posterior body, and the splenium	+	+	-	+	Right schizencephaly, polymicrogyria	-	-
026	14.83	F	R	Mainstream	-	70	P	Presence of the rostrum, genu, anterior body, and a thin middle anterior body	+	tiny	-	-	Bilateral polymicrogyria	-	-
107	11.58	M	L	Mainstream	+	66	C	CC absent	++	++	+	+	Left interhemispheric cyst, hypoplasia of the left cerebral hemisphere.	-	-
108	10.17	M	L	Montesori School	+	83	C	CC absent	+	+	+	-	Left interhemispheric cyst, grey matter heterotopia, left anterior hemispheric cortical dysplasia	-	-
109	9.67	F	R	Mainstream	-	126	P	Presence of a thin rostrum, genu and anterior body	+	+	+	+	None (history of haemorrhagic cerebral AVM (due to genetic condition))	-	+ Hereditary haemorrhagic telangectasia
110	9	M	L	Mainstream	-	95	C	CC absent	+	+	+	+	Interhemispheric cyst with saptation in the left hemisphere, causing pressure in the right.	-	-

110	9	M	L	Mainstream	-	95	C	CC absent	+	+	+	+	Interhemispheric cyst with saptation in the left hemisphere, causing pressure in the right. Cortex around the cyst is malformed	-	-
112	17.08	M	R	Mainstream	+	82	P	Presence of the rostrum	-	+	+	+	Frontonasl dysplasia, sphenoidal encephalocele, non visualization of the pituitary gland	-	-
113	10	F	R	Mainstream	+	73	C	CC absent	+	+	+	+	None	-	-
022	8.67	F	M	Mainstream & Special	+	71	C	CC absent	+	++	+	-	Unusual deep sulci (right central sulcus, parasagittal region posteriorly)	-	+ Oro facial digital syndrome Type 1
009	12.25	F	M	Special		PIQ=59	P	Presence of the genu, anterior and middle	+	+	+	-	None	-	-

Abbreviations: Age (in years); Sex: F female, M male; H Handedness: L left, R right, A ambidextrous; Help: Intervention and remedial support at school; P/C: P partial AgCC, C complete AgCC; CC details: corpus callosum structural properties details; AC: anterior commissure, - absent, + present and normal size, ++ enlargement; PC: Posterior commissure, - absent, + present and normal size, ++ enlargement; PB: probst bundles + present, - absent; CO: colpocephaly + present, - absent; MRI finding: other MRI findings; Seizure + present, - absent; Genetic: Genetic condition or syndrome + present, - absent

5.2. Results from Study 2 – Working Memory Outcomes in School-Age Children with Agenesis of the Corpus Callosum

Comparisons with normative expectations

Children with AgCC achieved poorer scores than the normative test mean on all WM measures, Table 6. Short term memory and WM mean scores derived from the WISC were both in the borderline range. WM abilities were particularly at risk with 45% of children showing mild to severe impairment.

Factors associated with working memory outcomes

Here we will only report models that reached the Bonneferoni-corrected level of significance ($p<0.006$), Table 7. There was only one factor that reached the Bonneferoni-corrected level of significance. The presence of associated CNS anomalies ($\beta=-.57$, $p=.001$) was associated with a poorer Digit Span Backward score.

Potential impact of working memory capacity on academic functioning

Only models that reached the Bonneferoni-corrected level of significance ($p<0.005$) are reported, Table 8. Reading and Math Computation were both associated with Digit Span Backward Score ($p=.001$) and the contribution of other factors were either non-significant or did not reached the Bonneferoni-corrected level of significance. Spelling was uniquely associated with Performance IQ. In this model, Performance IQ accounted for 45.9% of the variance ($R^2=0.459$, $F(1,25)=20.376$, $p=<0.001$).

Table 6. WM abilities in the AgCC cohort: comparison with normative test means and impairment rates.

	AgCC cohort		Test M (SD)	Mean difference	One sample t or Wilcoxon signed-rank tests		Impairment rates		
	n	M (SD) or Mdn			t (dl) or Z	p value	Average or above	Mild	Moderate to severe
Working Memory (WISC-IV)									
Digit Span Forward	27	7.93 (3.22)	10 (3)	-2.07	t(26)=-3.35	.003	66.7%	25.9%	7.41%
Digit Span Backward	27	7.59 (3.5)	10 (3)	-2.41	t(26)=-3.57	.001	55.6%	33.3%	11.1%
Executive functioning in daily life, Parent ratings (BRIEF)									
Working Memory subscale	28	68.18 (11.91)	50 (10)	+18.18	t(27)=8.07	<.001	14.3%	50%	35.7%
Executive functioning in daily life, Teacher ratings (BRIEF)									
Working Memory subscale	17	74.71 (17.92)	50 (10)	+24.71	t(16)=5.68	<.001	23.5%	5.9%	58.8%

Table 7. Linear models of association between WM abilities with age, social risk and neurological factors.

	n	Predictors	B	Standard Error B	r^2	β	p
Working Memory (WISC-IV)							
Digit Span Forward	27	Constant	3.39	2.134			.125
		Anterior commissure intactness	1.59	.72	.163	.4	.037
Digit Span Backward	27	Constant	11.67	2.64			.000
		AgCC comorbidities*	-4.03	-.566		-.57	.001*
		Social risk	-.6	.235		-.38	.018
		AC intactness	1.46	.340	.506	.34	.03
Executive functioning in daily life, Parent ratings (BRIEF)							
Working Memory subscale	28	Constant	62.04	3.42			.000
		Social risk index	2.23	.98	.166	.407	.032
Executive functioning in daily life, Teacher ratings (BRIEF)							
Working Memory subscale	17	No significant predictor					

Note: 1. Gender had no significant impact on results for WM measures. Therefore, gender was not used as covariate in regression analyses; 2. Factors that reached the Bonneferoni-corrected level of significance (p<.006) are indicated with *.

Table 8. Linear models of association between academic performance with age, social risk, neurological factors as well as WM abilities.

	n	Predictors	B	Standard Error B	r^2	β	p
Academic abilities (WRAT-IV)							
Word Reading	25	Constant	101.54	12.87			.000
		Social Risk Index	-2.84	1.43		-.297	.06
		Anterior commissure intactness	-11.22	4.12		-.421	.013
		Digit Span Backward*	3.63	.899	-.57	.651	.001*
Spelling	26	Constant	24.88	13.25			.073
		Performance IQ*	.686	.152	.459	.678	.000*
Math Computation	27	Constant	65.56	6			.000
		Social Risk Index	-2.21	.915		-.35	.024
		Digit Span Backward*	2.19	.577	.543	.55	.001*

Note: Factors that reached the Bonneferoni-corrected level of significance (p<.005) are indicated with *.

CHAPTER 6: Study 3 - Results and validation of a modified Brown-Peterson task to examine working memory processes in typically developing children and adolescents

Examining distinct working memory processes in children and adolescents using fMRI: results and validation of a modified Brown-Peterson paradigm

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Megan Spencer-Smith	Megan Spencer-Smith	20/10/17
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6.1. Abstract

Verbal working memory (WM) comprises different processes (encoding, maintenance, retrieval) that are often compromised in brain diseases, but their neural correlates have not yet been examined in childhood and adolescence. To probe WM processes and associated neural correlates in developmental samples, and obtain comparable effects across different ages and populations, we designed an adapted Brown-Peterson task (verbal encoding and retrieval combined with verbal and visual concurrent tasks during maintenance) to implement during functional magnetic resonance imaging (fMRI). In a sample of typically developing children and adolescents (n=16), aged 8 to 16 years, our paradigm successfully identified distinct patterns of activation for encoding, maintenance, and retrieval. While encoding activated perceptual systems in posterior and ventral visual regions, retrieval activated fronto-parietal regions associated with executive control and attention. We found a different impact of verbal versus visual concurrent processing during WM maintenance: at retrieval, the former condition evoked greater activations in visual cortex, as opposed to selective involvement of language-related areas in left temporal cortex in the latter condition. These results are in accord with WM models, suggesting greater competition for processing resources when retrieval follows within-domain compared with cross-domain interference. This pattern was found regardless of age. Our study provides a novel paradigm to investigate distinct WM brain systems with reliable results across a wide age range in developmental populations, and suitable for participants with different WM capacities.

6.2. Introduction

The ability to maintain relevant information in mind in the presence of interference or distracting information is critical for higher cognitive functions required in daily life. Working memory (WM) is the theoretical construct used to refer to this capacity to simultaneously maintain and process information over brief periods of time according to current task goals (Baddeley, 1986; Baddeley et al., 2011; Just & Carpenter, 1992). Studies in children and adolescents show that WM capacity plays a crucial role in the development of many cognitive activities (e.g., learning, reasoning, problem solving, language comprehension), and also predicts academic performance and achievement (Barrouillet et al., 2008; Gathercole & Pickering, 2000; Gathercole, Pickering, Knight, et al., 2004). Moreover, WM is impaired in various developmental disorders, e.g. attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) or specific language impairment (SLI), providing a crucial neuropsychological measure in several neuropsychiatric conditions and useful risk marker for cognitive development (Gathercole et al., 2006; Savage, Cornish, Manly, & Hollis, 2006; Swanson & Beebe-Frankenberger, 2004).

From a developmental point of view, WM capacity develops rapidly over childhood (Barrouillet, Gavens, Vergauwe, Gaillard, & Camos, 2009; Gathercole, 1999; Klingberg, 2006; Klingberg et al., 2002). This is usually measured by the increase in the amount of information that can be retained and transformed using complex memory span tasks that require maintaining information for further recall while performing a concurrent activity (Gathercole et al., 2006). An important component of WM maintenance, involving active verbal rehearsal and attentional refreshing, emerges around 7 years of age (Camos & Barrouillet, 2011). Evidence suggests that multiple mechanisms contribute to childhood development of WM, affecting all the processes involved in encoding, maintenance, and retrieval (e.g., increase in attentional capacity, process automatisation, increase in knowledge, mnemonic strategies, and so forth; see Cowan & Alloway, 2009).

In terms of neural substrates, development of WM ability parallels structural changes in frontal-parietal cortices affecting grey matter (Sowell et al., 2004) and white matter (Darki & Klingberg, 2014). Similar to neuroimaging findings in adult populations, this core network of fronto-parietal brain areas is consistently found to activate in children and adolescents, and is apparent as early as 5 years of age during different verbal and visuospatial tasks thought to

evaluate WM functions (Ciesielski et al., 2006; Crone et al., 2006; Jolles, Kleibeuker, Rombouts, & Crone, 2011). One recent imaging study compared encoding and retrieval processes in a Sternberg item recognition paradigm with digits in children and adolescents from 9 to 19 years (van den Bosch et al., 2014). Encoding of digits activated the right prefrontal and parietal cortex, left motor areas, occipital cortex, and cerebellum; retrieval activated the left prefrontal and parietal cortex, right motor areas, as well as anterior and posterior cingulate cortex, and cerebellum. Other functional neuroimaging studies investigating WM in school-age children have used an n-back task in which a sequence of stimuli is presented to the participant who must indicate when the current stimulus matches the one from *n* steps earlier in the sequence (e.g.,). Despite its popularity in fMRI studies, empirical evidence shows that the n-back task correlates weakly with WM span tasks, suggesting that it is unlikely that these two types of tasks reflect a single construct, and questionning the empirical validity of using n-back tasks (continuous-recognition or updating measures) as a WM task (Kane et al., 2007; Wilhelm et al., 2013). Other tasks, such as the Steinberg item recognition paradigm (e.g., Klingberg et al., 2002; Spencer-Smith et al., 2013), have also been used to study WM in developmental populations. However, these tasks require the maintenance of information in short-term memory, but not the simulatenous maintenance and manipulation of information as the theorethical construct of WM specifies (Baddeley et al., 2011; Barrouillet & Camos, 2015). Thus, very few developmental studies have explored the neural correlates of WM using tasks requiring not just maintenance, but also active manipulation of information (Crone et al., 2006; Jolles et al., 2011). To our knowledge, brain activity associated with WM processes of maintenance during the simultaneous processing of a concurrent task and retrieval have not yet been studied in developmental fMRI studies.

Previous literature has identified the major challenges inherent in studying both typical and atypical development, including designing tasks that can be administered to individuals across a wide age range in both typical and atypically developing groups (Price & Friston, 1999). In this study, our aims were to design a novel WM paradigm that: i) is demanding of WM capacity but simple enough to be administered to both children and adolescents and both healthy and clinical paediatric populations (e.g., populations with mild intellectual difficulties), and for which brain activity could not be explained by difference in age or WM performance; ii) would enable investigation of neural substrates for encoding, maintenance

and retrieval WM processes during fMRI; and could identify the effect of different concurrent processing tasks on maintenance and retrieval.

Among the paradigms appropriate for measuring the impact of concurrent processing on maintenance, the Brown-Peterson task is best suited to examine encoding, maintenance, and retrieval processes in WM. The original Brown-Peterson task requires participants to encode and retrieve a string of letters with a concurrent task (i.e., counting backward by three) interposed between encoding and subsequent retrieval (J. Brown, 1958; Peterson & Peterson, 1959). In opposition to the immediate serial recall paradigm, the concurrent task in Brown-Peterson paradigm impairs maintenance and thus retrieval of the encoded information. Here, we designed a novel task inspired from the Brown-Peterson paradigm in which children and adolescents had to maintain verbal information (letters) while performing a concurrent task involving either verbal (lexical decision) or visual (face decision) task appropriate for children and adolescents. This design allowed us to compare not only encoding and retrieval components of verbal WM during fMRI, but also to probe for neural substrates differentially modulated by the concurrent task, both within-domain (i.e. verbal distractors) and cross-domain (i.e. visual distractors). According to the influential model of Baddeley (1986), verbal and visuo-spatial maintenance and processing involve separate and domain-specific systems, a phonological loop for verbal information and a visuospatial sketchpad for visuospatial information. Thus, processing irrelevant verbal information should produce selective interference with verbal maintenance because verbal processing would mobilize the phonological loop, thus impeding the articulatory rehearsal process in charge of verbal maintenance. By contrast, processing visuospatial information should involve the domain-specific visuospatial sketchpad and should not have any effect on verbal maintenance.

To validate this novel paradigm, we applied it in children and adolescents aged 8 to 16 years. We expected that all would successfully complete our adapted Brown-Peterson fMRI paradigm, which tailors task difficulty to each participant according to their WM capacity. We predicted that distinct activation patterns would be elicited by the two concurrent tasks (i.e. within and cross-domain), not only during the maintenance interval, but also during the subsequent retrieval period. Based on Baddeley's WM model (1986), the nature of the concurrent task was expected to differentially impact verbal WM and thus modulate brain areas recruited during retrieval, despite the fact that identical verbal stimuli were encoded. Specifically, exposure to words vs faces during the maintenance interval should hamper vs

favour the engagement of language-related regions in the left hemisphere during the subsequent retrieval phase.

6.3. Material and Methods

Participants

Participants were 16 healthy children and adolescents aged 8 to 16 years (8 to 10 year-old, n = 5; 11 to 13 year-old, n = 8; 14 to 16 year old, n = 3; mean age = 12.19; SD = 2.25), 9 females and 7 males, recruited though advertisements in local schools and staff at the Royal Children's Hospital. The wide age range of this sample allowed us to examine whether the adapted Brown-Peterson task was suitable for both children and adolescents. No participant had a documented history of a brain lesion, neurological disability or neurodevelopmental disorder such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD). All participants were right-handed as measured by a score between +40 and +100 at the Edinburgh Handedness Inventory (Groen et al., 2012; Oldfield, 1971), English speaking, had a Full Scale Intellectual Quotient (FSIQ) based on the Wechsler Abbreviated Scale of Intelligence (WASI; [34]) higher than 85 (M = 116.2, SD = 10.4) and normal or corrected-to-normal vision and hearing. The study was approved by the Human Research Ethics Committee at the Royal Children's Hospital. Written informed consent was obtained from the caregivers of the children and adolescents prior to participation.

Material and design

Participants completed an adapted version of the Brown-Peterson paradigm (J. Brown, 1958; Peterson & Peterson, 1959) implement during functional magnetic resonance imaging (fMRI). A mixed block and event-related design allowed separate examination of specific WM processes: encoding, maintenance and retrieval. The task required a combination of verbal storage and maintenance during either verbal (within-domain) or visual (cross-domain) concurrent tasks. Each active trial consisted of three active phases (Figure 20):

1) Encoding period.

Participants were presented with a series of single upper-case letters for further recall displayed sequentially in the middle of the screen at a rate of one letter per second. All consonants of the English alphabet were used as memory items except W, which is three-syllabic. Series of two and three letters were created for within-domain and cross-domain

blocks in such a way that each letter appeared with the same frequency in both blocks. Participants were asked to maintain the letters in order of appearance.

2) Maintenance delay filled with a concurrent task.

During the maintenance delay of 6 seconds, a concurrent task required to process either verbal or non-verbal stimuli involving within- or cross-domain interference respectively.

The within-domain concurrent task was a lexical decision task. Two successive letter-strings were presented for 3 seconds each and required simple motor responses (i.e. press as quickly and as accurately as possible the left-most/green button if the letter-string was a word; or the right-most/red one if it was a non-word). Words were selected from the "Oxford Wordlist", which is an Australian database of high frequency words in young children's writing and reading development (Bayetto et al., 2007). Among the 307 most frequently used words, only nouns were selected based on the following search terms: any gender, any location (urban or rural), any socioeconomical status, any text type (e.g., description, discussion, narrative) and appearing during the first three years of school (40% were within 1 to 100 most frequently used words; 35% were within 101 to 200 most frequently used words; 25% were within 201-307 most frequently used words). Non-words with orthographically existing onsets and bodies were selected from the "ACR Nonword database" (Rastle et al., 2002). Three to eight letter-strings (words and non-words) were displayed centrally on the screen. Words and non-words were equally often presented.

The cross-domain concurrent task was a face decision task. Two successive pictures were presented for 3 seconds each, requiring similar motor responses (i.e. press as quickly and as accurately as possible the left-most/green button if a real face was presented; or the right-most/red one if it was a scrambled face). Ten males and 10 females faces with a neutral expression were selected from the NimStim database (Tottenham et al., 2009), and converted into greyscale using Matlab R2013a (The MathWorks, 2012). Scrambled faces were created from the original faces using Matlab (size of square = 300, iterations = 2). Faces and scrambled faces were equally often presented.

3) Retrieval period.

At retrieval, one single upper-case letter was presented along with either one or two place-holders (for paradigm with 2 or 3 letters to remember, respectively) made of dashes with a question mark. Participants had to decide if the single letter matched the letter that was presented in that serial position during the encoding period by giving a simple motor response, i.e. press as quickly and as accurately as possible the left-most/green button or the

right-most/red one for positive and negative responses respectively. This was done to make sure that participants memorised both item and serial order information.

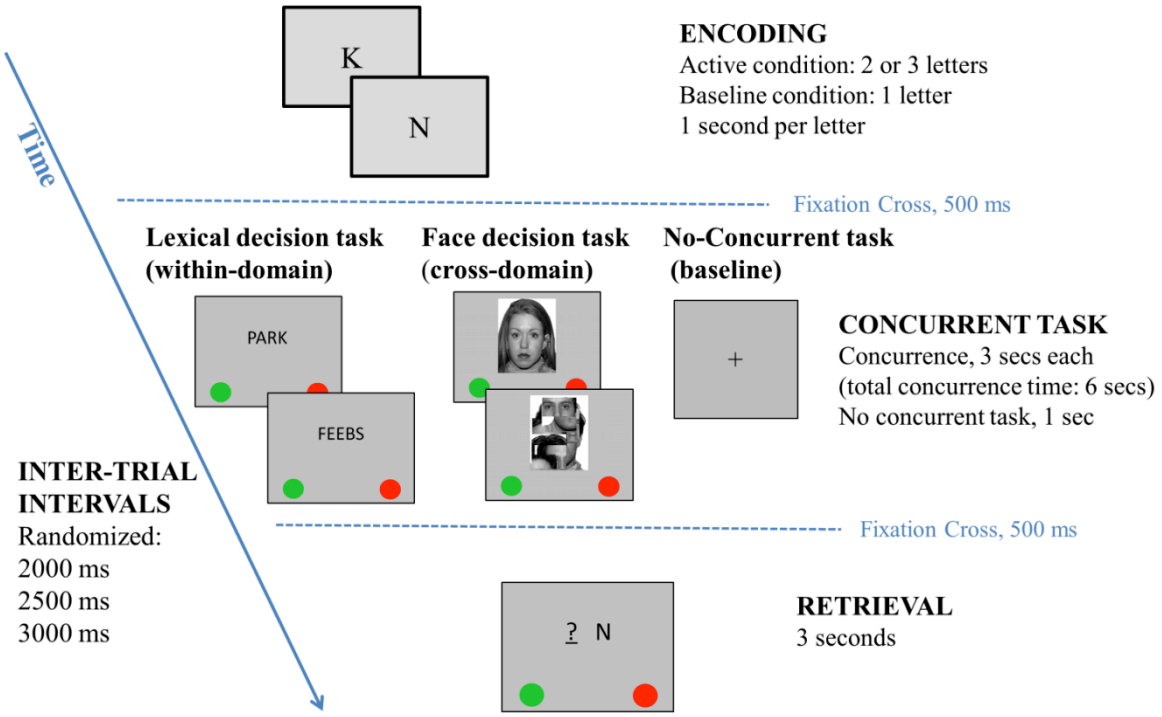

Figure 20. Adapted Brown-Peterson fMRI paradigm using within- and cross-domain concurrent tasks.

In addition to the active condition, there was a baseline condition (no-concurrent task) in which participants were required to encode a single letter and recognise it after a short empty delay of 1 second. They were instructed to press as quickly and as accurately as possible the left-most/green button if the single letter was the same during encoding and retrieval; or the right-most/red one if it was a different letter.

For both the active and baseline conditions, a randomized inter-trial interval of 2000, 2500, or 3000 milliseconds was presented before the next trial. Three types of blocks of 10 trials each were created: two active blocks, one including the within-domain concurrent task and the

other including the cross-domain concurrent task, and a third baseline block. The order of presentation of these three blocks was counterbalanced across participants and repeated twice for a total of six blocks of 10 trials. Within each block, half of the probes were positive (i.e., 5 trials required a "yes" response) and the position of positive and negative probes were randomized within each blocks.

Two important challenges of brain imaging studies examining cognitive development are that differences in both participant age and task performance may influence activation patterns. One concern is whether changes in neural activity reflect changes in functional maturation of the central nervous system, independently of behavioural efficiency, or whether they reflect changes in task performance consequent upon increasing age (Kwon et al., 2002; Schweinsburg et al., 2005). For these reasons, in our paradigm, task difficulty was adapted to each participant by adapting the number of verbal items to remember. Based on pilot testing conducted outside the scanner, participants with a backward digit span of 5 or more were presented with the version of the paradigm with 3 letters to be remembered, and those with a backward digit span lower than 5 were presented with the version of the paradigm with 2 letters to be remember. In our sample, seven participants completed the 3-letters paradigm (age range = 10 to 15 years; M = 12.53; SD = 1.44) and nine participants completed the 2-letters paradigm (age range = 8 to 16 years; M = 11.93; SD = 2.78). All participants had a retrieval accuracy of 80% or more, which suggested that task difficulty was appropriate for each participant.

Procedure

Participants completed the adapted Brown-Peterson fMRI paradigm. This fMRI paradigm was presented visually during fMRI using E-prime2 (Psychology Software Tools, PST, Pittsburgh). Initially, participants successfully completed a mock MRI scanner training protocol before the MRI. Participants were prepared for the adapted Brown-Peterson paradigm through training initially outside (5 trials for each of the three conditions described above) and then inside the scanner before starting fMRI acquisition (again 5 new trials for each of the three conditions). All participants demonstrated understanding of the paradigm before being placed in the scanner. The paradigm was projected onto a screen at the foot of the MRI bed, and participants viewed the images from a mirror attached to the head coil. To minimize head motion during scanning, a soft cloth was placed on the child's forehead, then

taped to the head tray, and foam pads were inserted around the head. Responses were provided using an MRI compatible response box with four response buttons. The response box was placed centrally on the child's stomach and responses were provided by pressing the left-most/green button with the left thumb or the right-most/red button with the right thumb, respectively.

Statistical analysis of behavioural data on concurrent task and retrieval

Separate repeated measures analyses of variance (ANOVA) were conducted on accuracy measures (percent correct) for the concurrent tasks (within domain/lexical decision task and cross-domain/face decision task) and the retrieval period with the type of the previous concurrent task (within- or cross-domain) as within-subject factor. Independent-sample t tests were used to explore sex differences in accuracy. Pearson's correlation was used to study the relationship between age and accuracy. Statistical analyses were performed using SPSS Statistics V22.0 (IBM, Released 2013).

Image acquisition

MRI was performed on a Siemens 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany) at the Royal Children's Hospital. The scanner was equipped with the Syngo MR B17 software release, and a 12-channel receive-only head coil was used. T1-weighted MP-RAGE sequence (Magnetization Prepared Rapid Gradient Echo) were obtained using the following parameters: repetition time (TR)=1900 ms, echo time (TE)=2.71 ms, inversion time (TI)=900 ms, flip angle (FA)=9°, field of view (FoV)=256mm, voxel size=0.7 x 0.7 x 0.7 mm. Functional images were acquired using a T2-weighted with a gradient-echo-planar imaging (EPI) sequence with 32 interleaved slices with 5% gap, voxel size=2.6 x 2.6 x 3 mm, TR=2400ms, TE=35ms, FA=90°, FoV=240mm.

Image analysis

fMRI data were preprocessed and analysed using SPM8 (Wellcome Department of Imaging Neuroscience, University College London, UK) implemented in Matlab R2014a. The images of each subject were corrected for slice acquisition timing, and spatially realigned to eliminate movement artefacts. Head motions were small in any direction (Maximum translation, X=0.39mm, Y=0.76mm, Z=1.69mm; Maximum rotation (converted from degrees to

millimetres, 40): X=0.04mm, Y=0.2mm, Z=0.01mm; Mean translation: X=0.08mm, Y=0.11mm, Z=0.25mm ; Mean rotation : X=0.004mm, Y=0.003mm, Z=0.002mm) and therefore no participant was excluded from further processing [40]. To allow for inter-subject comparison, data were normalized using the MNI brain template (Montreal Neurologic Institute) and resampled to 1.9 x 1.9 x 3 mm. These functional images were finally smoothed using a Gaussian filter of full width at half maximum=8mm to increase signal-to-noise ratio.

Statistical analyses were performed using a two-step process, taking into account the intra-individual and inter-individual variance (Friston et al., 1995). First level single subject statistics were assessed by a voxel-based statistics according to the General Linear Model implemented in SPM8. Given the high rate of correct responses across participants (above 90%, see Results section for further detail) and to guarantee an equal number of trials for each condition, brain activity was analysed pooling the correct and incorrect trials together. The onsets of each event of interest were convolved with the canonical hemodynamic response function (HRF) and used as regressors in the individual design matrix. For the encoding period, these onsets included encoding of the active condition and encoding of the baseline condition, using a boxcar function of 2 or 3 seconds for active encoding (depending of the difficulty level) and 1 second for the baseline encoding. The maintenance delay filled with a concurrent task was modelled using a boxcar function of 6 seconds for the within-domain (lexical decision) and the cross-domain (face decision) concurrent tasks. Finally, the retrieval period was modelled using a boxcar function of 3 seconds for the tree retrieval types, i.e., retrieval after within-domain concurrent task, retrieval after cross-domain concurrent task and retrieval of the baseline condition.

All six movement parameters (translation: x, y and z; rotation: pitch, roll and yaw) were included as covariates of no interest in the model. The individual statistical images from each condition were then entered in a group analysis at the second level using a flexible factorial design, which provides the flexibility to specify the different period of our mixed block and event-related paradigm. In this random-effects model, independence and unequal variance between subjects and conditions were assumed, allowing for violation of sphericity, as implemented in SPM8. Considering a possible impact of gender on brain-activation, we also added this binary variable as a covariate in the flexible factorial design (Nagel et al., 2005; Schweinsburg et al., 2005; Spencer-Smith, Ritter, Murner-Lavanchy, et al., 2013; Spencer-Smith, Ritter, El-Koussy, et al., 2013). In line with guidelines used in neuroimaging studies of complex cognitive functions (Lieberman & Cunningham, 2009), whole-brain analysis was

conducted with a significance threshold of p<.001 at the voxel level, uncorrected for multiple comparisons, and a minimum extent threshold of 20 voxels (Murner-Lavanchy et al., 2014; Spencer-Smith, Ritter, Murner-Lavanchy, et al., 2013). Anatomical location of activations was verified using SPM Anatomy toolbox (Eickhoff et al., 2005).

We performed exploratory analyses to examine age- and retrieval accuracy-related changes in brain activation during the Brown-Peterson fMRI paradigm. The largest and most relevant clusters of activation identified at the group level were used to define functional regions of interest (ROIs) for each of the different conditions using the marsBaR toolbox (Brett et al., 2002). Beta values were extracted from each ROI, by contrasting activation during the encoding or retrieval WM conditions relative to the respective baseline conditions. Beta values from each ROI and each participant were then used to compute Pearson's correlation coefficients in order to evaluate any age- and accuracy-related effects on ROI activity using SPSS (IBM, Released 2013). Beta values from the encoding or retrieval periods were contrasted to the baseline values (rather than to each other) to test for condition-specific effects without mixing any positive vs negative correlation with one vs the other active condition.

We also performed a whole-brain analysis where different active phases were compared (encoding vs retrieval, within-domain concurrent task vs cross-domain concurrent task, retrieval following within-domain concurrent task vs retrieval following cross-domain concurrent task), but now including age and retrieval accuracy as covariates of interest in a multiple parametric regression design using SPM8. For these regressions, a significant threshold of p<.001 uncorrected for multiple comparisons with a minimum extent threshold of 20 voxels was used.

6.4. Results

Behavioural data

As far as the concurrent tasks were concerned, the percentage of correct responses was 97% (SD=4.3) for the within-domain (lexical decision task) and 98% (SD=3.5) for the cross-domain (face decision task). For the effect of the type of the concurrent task, assumption of normality was violated, as assessed by inspection of histograms and results of the Shapiro-

Wilk test (p=.001). Therefore, related-sample Wilcoxon-signed rank test was used and showed no significant effect of the type of concurrent task (W_s =33, z=.58, p=.565). Concerning retrieval of the active condition, repeated-measures ANOVA showed no effect of type of concurrent task on response accuracy, F (1,15) = 1.278, p = .276 (90.9%, SD = 8.8, and 93.4%, SD = 5.3, for the within-domain/lexical and cross-domain/face decision tasks, respectively). Hence, differences in brain activity patterns at retrieval could not be explained by differences in WM performance.

There was no significant relationship between age and response accuracy on the retrieval of the active condition whatever the type of the previous concurrent task (r = .318, p = .23, and r = .299, p = .261 for the within- and between-domain concurrent task respectively), and no significant relationship between age and response accuracy on the concurrent tasks (r = .493, p = .052, and r = .185, p = .492 for the lexical decision and face decision concurrent tasks, respectively). There was no significant gender difference for any of the measures, ts < 1, ps > .50.

Taken together, these behavioural data show good performance overall on the adapted Brown-Peterson paradigm. Moreover, this pattern was stable across the age range of our sample and gender. Therefore, from a behavioural point of view, our task appears to be suitable for a wide age range of children and adolescents.

Functional magnetic resonance imaging

Active Encoding and Retrieval vs. Baseline

To delineate brain regions generally recruited during WM, we first contrasted the active encoding period relative to the baseline encoding period, regardless of the domain of concurrent task during the maintenance interval. This showed activation in a widespread network, including bilateral visual areas in the occipital lobes, parahippocampal gyri, as well as left prefrontal regions, the caudate nucleus, and the cerebellum (Table 9). Likewise, we contrasted the active retrieval relative to the baseline retrieval period, regardless of concurrent conditions, which revealed a distributed pattern of activation encompassing mainly bilateral prefrontal cortices, but also temporal and parietal areas (Table 9). These data confirm that our working memory paradigm successfully engaged brain networks associated with visual stimulus processing and executive functions.

Table 9. List of activations for active encoding and retrieval compared to baseline condition.

Region		Hemisphere	Number of voxels	t value	x, y, z
ENCODING (compared to encoding baseline)					
Frontal	Inferior (BA 47)	L	108*	4.46	-38, 30, -14
	Superior and middle (BA 9)	L	160*	4.42	-27, 40, 43
	Superior and superior medial (BA10)	L	193*	4.22	-15, 57, 13
Occipital	Lingual, inferior, calcarine (BA18)	L	515*+	6.33	-25, -95, -11
				4.66	-11, -99, -8
		R	631*+	6.08	25, -91, -11
				5.89	21, -91, -2
Temporal	Parahippocampal gyrus	L	130*+	5.07	-40, -28, -11
		R	71*	4.77	13, -13, -17
Subcortical	Caudate nucleus (BA 48)	L	563*+	5.87	-17, 19, 10
	Pulvinar	R	24	3.64	13, -32, 13
	Cerebellum	L	222*	4.77	-10, -30, -14
RETRIEVAL (compared to retrieval baseline)					
Frontal	Prefrontal, putamen, middle and inferior (BA 49, 10, 44)	L	7684*+	6.10	-15, -6, 13
				6.07	-27, 8, -2
				5.83	-29, 42 19
				5.05	-61, 11, 22
	Middle and superior (BA 10, 6)	R	572*+	4.91	27, 46, 7
				4.43	28, 51, 10
			23	4.01	36, -2, 64
	Superior orbital (BA 11)	L	74*	4.77	-21, 53, -14
	Precentral gyrus (BA 6, 4)	L	268*	5.13	-34, -4, 61
		L	56	4.18	-49, 0, 40
		L	32	3.49	-36, -17, 40
	Middle cingulate (BA 24)	L	42	3.82	-17, -25, 46
Parietal	Angular (BA 39)	R	169	4.21	40, -65, 46
	Inferior and superior lobule (BA 7)	L	1813*+	5.02	-36, -55, 55
				4.92	-32, -61, 55
	Inferior lobule and postcentral gyrus (BA 40, 1)	L	404*+	4.85	-51, -25, 46
				4.19	-57, -23, 28
Temporal	Middle extending calcarine gyrus (BA23)	R	189*+	5.74	32, -65, 16
				3.49	28, -57, 10
	Superior and middle (BA 39)	L	82	4.25	-61, -47, 19
	Middle (BA 21)	R	58	3.83	51, -34, -14
Occipital	Lingual (BA 18)	L	214	3.98	-6, -76, -2
Subcortical	Vermis	L	229	4.68	-2, -53, -5
	Cerebellum	L	156	4.32	-25, -61, -17

Note: Coordinates are in MNI space. x, y, z coordinates refer to voxels with highest statistical significance within a cluster (location of the peak coordinate). Clusters used to define ROIs for specific subsequent analyses are marked with a sign *. Clusters reaching a significance threshold of $p<.05$ at the voxel level, corrected for multiple comparison, are marked with a sign +. BA = Brodmann Area

Active Letter Encoding vs.Letter Retrieval

We next sought to identify regions selectively recruited by distinct WM processes. Encoding, as compared to retrieval (during the active task), was associated with widespread activations bilaterally in the occipital and ventral temporal lobes (inferior occipital and fusiform gyri), as well as in medial frontal areas (supplementary motor area (SMA), middle cingulate gyrus) and precentral gyrus. Smaller activation foci were found in the insula (Figure 21 and Table

10). Conversely, the retrieval phase, compared to encoding, activated bilateral dorsolateral prefrontal areas (mainly inferior and middle, but also superior frontal gyri), as well as the anterior cingulate cortex (ACC), inferior parietal lobule (angular, supramarginal, and postcentral gyri), and lateral temporal areas (superior and middle temporal gyri).

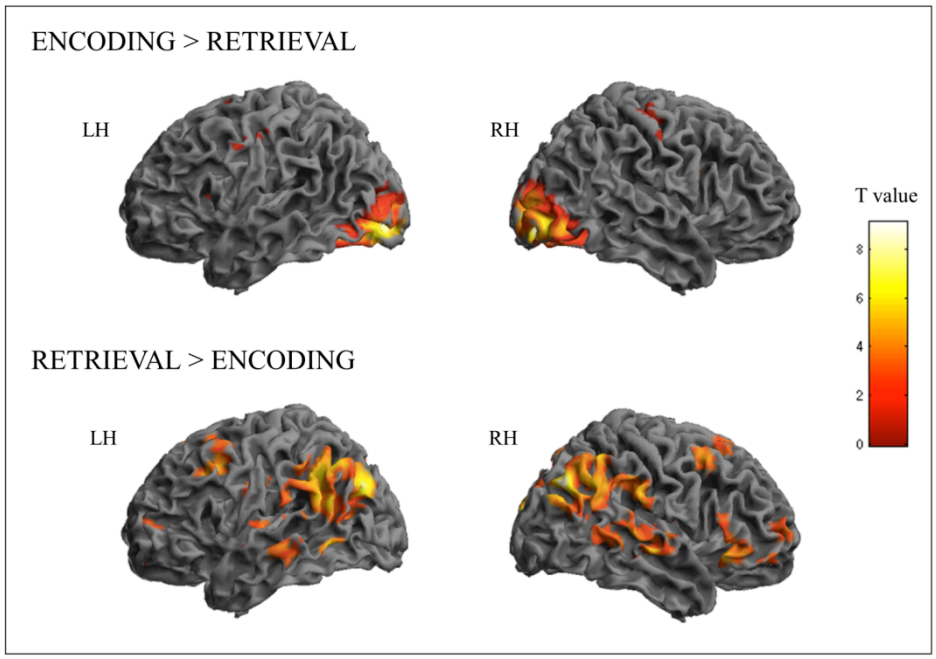

Figure 21. Activation maps related to the contrasts encoding vs retrieval.

Table 10. List of activations for contrasts of interest.

Region		Hemisphere	Number of voxels	t value	x, y, z
ENCODING > RETRIEVAL					
Frontal	SMA, middle cingulate (BA 6)	L&R	640*+	6.84	-6, 8, 49
				5.45	8,10,49
	Pre and post central gyrus (BA 4)	L	175	4.07	38, -21, 55
	Precentral gyrus (BA 6)	R	104+	5.32	46, 6, 28
	Medial (BA 11)	L	23	3.68	-0, 38, -17
Parietal	Postcentral gyrus (BA 6, 1)	L	70+	5.09	-53, -6, 49
		R	25	4.05	61, -13, 46
Occipital	Inferior (cuneus, precuneus, lingual), fusiform (BA 18, 19, 37)	L	2468*+	13.24	-23, -89, -11
				11.65	-36, -80, -11
				8.94	-36, -51, -17
		R	2692*+	13.11	27, -87, -11
				8.28	34, -49, -17
				8.25	32, -89, 10
Other	Insula (BA 13)	L	31	3.63	-30, 13, 10
RETRIEVAL > ENCODING					
Frontal	Precentral, middle (BA 8, 6)	L	500*	4.87	-36, 11, 40
				4.78	-38, 13, 37
	Middle (BA 8, 10)	R	227*	4.6	40, 10, 49

		L	59	3.64	-44, 51, 10
	Inferior, middle (BA 47, 10)	R	487*	4.68	47, 23, -8
				4.27	44, 53, -11
	Superior and middle (BA 10)	R	212	4.2	30, 63, 4
	Superior, SMA (BA 8, 6)	R	242*	4.1	25, 23, 55
				4.08	9, 25, 58
	Anterior cingulate (BA 32)	R	227*	4.09	2, 36, 19
	Precentral gyrus (BA 4)	L	34	4.04	-19, -27, 55
	Middle orbital (BA 10)	L	34	3.93	-29, 57, -11
	Superior medial (BA 8)	R	24	3.57	2, 34, 40
Parieto-temporal	Angular, superior temporal, supramarginal, inferior parietal lobule (BA 39, 22)	R	3563*	7.3	46, -74, 34
				5.17	59, -19, -5
				4.94	46, -53, 49
	Angular, middle temporal, inferior parietal lobule	L	5998*	6.41	-42, -55, 40
				6.02	-55, -51, 22
				5.35	-49, -51, 37
	Postcentral gyrus (BA 4)	L	188*	4.91	-42, -13, 31
Temporal	Superior extending to putamen (BA 49)	L	301	4.7	-30, -13, 4
	Middle (BA 21)	L	190	4.18	-65, -25, -8
Occipital	Lingual (BA 18)	R	25	3.8	11, -74, -8
Subcortical	Putamen (BA 49)	R	199	4.44	30, -13, 7
WITHIN-DOMAIN > CROSS-DOMAIN CONCURRENT TASK					
Frontal	Frontal pole (BA 10)	R	266*+	5.3	27, 55, 4
Occipital	Medial fusiform (BA 19)	R	36*	4.43	30, -53, -8
CROSS-DOMAIN > WITHIN-DOMAIN CONCURRENT TASK					
Occipital	Inferior (lingual, precuneus, fusiform), cuneus, including fusiform face area (FFA; BA 19, 18, 37)	R	2873*+	9.1	42, -84, -11
				8.97	34, -91, -5
				5.92	49, -53, -14
	Middle, lingual, inferior, lateral fusiform, including FFA (BA 19, 18, 37)	L	878*+	5.64	-34, -91, -5
				4.76	-44, -72, -14
				4.6	-48, -51, -17
	Precuneus gyrus (BA 7)	R	30	3.79	8, -59, 64
	Lingual (BA 18)	L	39	3.79	-0, -61, 7
Frontal	Inferior (BA 47)	L	238*+	5.11	-38, 36, -14
	Precentral (BA 4)	R	156+	4.9	38, -13, 43
	Medial frontal (BA 11)	L	92	4.79	-2, 46, -17
	Middle cingulate (BA 24)	R	92	4.22	13, -17, 49
	SMA (BA 6)	L	59	3.82	-6, -13, 55
Temporal	Inferior (BA 20)	R	39*+	5.29	47, -27, -20
	Middle (BA 21)	L	60	4.12	-61, -9, -20
	Parahippocampal gyrus	L	806*+	5.63	-29, -11, -14
Parietal	Inferior lobule (BA 40)	R	119+	5.06	57, -27, 55
	Postcentral gyrus (BA 4)	L	92	4.32	-42, -27, 64
	Angular (BA 39)	L	169	4.1	-36, -59, 22
	Superior lobule (BA 7)	R	59	4.06	25, -70, 52
Subcortical	Pulvinar	R	207*+	5.28	25, -30, 7
RETRIEVAL AFTER WITHIN-DOMAIN > RETRIEVAL AFTER CROSS-DOMAIN CONCURRENT TASK					
Occipital	Cuneus, fusiform, middle and inferior occipital (BA 18, 19)	R	3181*+	8.71	15, -101, 7
				8.44	27, -78, -8
				7.58	30, -89, 10
				7.17	42, -72, -8
	Inferior and middle occipital, fusiform, calcarine (BA 18, 37)	L	1620*+	7.15	-25, -80, -8
				6.71	-32, -61, -14
				6.62	-15, -101, 4
				5.47	-6, -91, -11
RETRIEVAL AFTER CROSS-DOMAIN INTERFERENCE > RETRIEVAL AFTER WITHIN-DOMAIN CONCURRENT TASK					
Temporal	Middle and superior (BA 21)	L	27*	3.74	-40, -47, 4
		L	23*	3.39	-59, -34, 4

Occipital	Calcarine (BA 17)	R	279*	4.79	2, -91, 10
	Inferior (BA 37)	L	22*	3.83	-53, -63, -14

Note: Coordinates are in MNI space. x, y, z coordinates refer to voxels with highest statistical significance within a cluster (location of the peak coordinate). Clusters used to define ROIs for specific subsequent analyses are marked with a sign *. Clusters reaching a significance threshold of $p<.05$ at the voxel level, corrected for multiple comparison, are marked with a sign +. BA = Brodmann Area.

Maintenance Delay Filled with a Concurrent Task (Within-Domain vs. Cross-Domain)

Comparing activations during the within-domain concurrent task (lexical decision task), relative to the cross-domain concurrent task (face decision task), revealed differential increases in the right middle frontal gyrus (Brodmann area 10) and medial fusiform cortex only (Table 10 and Figure 22). Conversely, the cross-domain concurrent task (face decision task) compared to within-domain concurrent task (lexical decision task) produced a more extensive pattern of activation, particularly in bilateral visual areas, including occipital and fusiform cortex overlapping with the fusiform face areas (FFA). Activations were also found in several frontal areas (left inferior and medial frontal gyri, SMA, right middle cingulate cortex, precentral gyrus), the temporo-parietal junction, left parahippocampal gyrus, and right pulvinar. Thus, the cross-domain concurrent task appeared to recruit a more widespread network than the within-domain concurrent task, even though behavioural data show that this could not be explained by task difficulty since accuracy did not significantly differ in the two concurrent tasks.

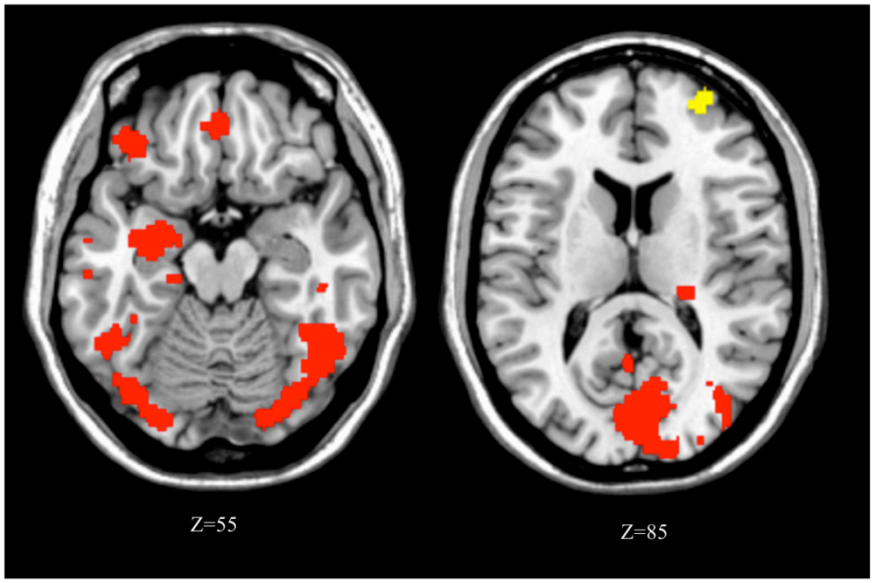

Figure 22. Activation map for the contrast within-domain vs cross-domain concurrent tasks (MRIcron reference slices). Activations in yellow: within-domain concurrent task > cross-domain. Activations in red: cross-domain concurrent task > within-domain.

Letter Retrieval Following Within-Domain vs. Cross-Domain Concurrent Tasks

The most critical question concerning the WM system in our paradigm is whether the nature of the concurrent task during the maintenance interval may produce different degrees of competition and thus result in different neural substrates during retrieval. We therefore tested for brain regions that would be differentially activated during the retrieval period when following within-domain concurrent task (lexical decision) or when following cross-domain concurrent task (face decision). Greater increases following the within-domain concurrent task were found in visual areas, with large bilateral clusters in occipital cortices (bilateral middle and inferior occipital gyri, fusiform gyri, right cuneus and left calcarine). Conversely, greater increases were found after the cross-domain concurrent task in the left middle and superior temporal cortex, overlapping with usual location of phonological processing (Bitan et al., 2007; Burton, Locasto, Krebs-Noble, & Gullapalli, 2005), plus left calcarine gyrus and bilateral medial occipital cortex (Table 10 and Figure 23).

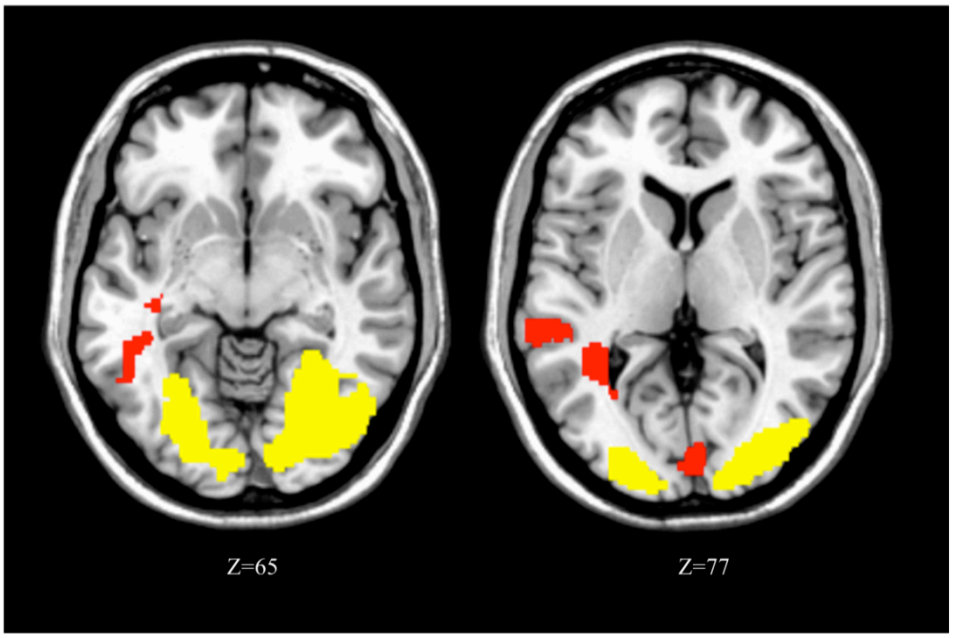

Figure 23. Activation map for retrieval following within-domain vs cross-domain (MRIcron reference slices). Activations in yellow: retrieval following within-domain concurrent task > cross-domain. Activations in red: retrieval following cross-domain concurrent task > within-domain. For illustration purpose, activations observed in retrieval following within-domain concurrent > cross-domain are represented with a threshold of p<.005 uncorrected for multiple comparisons.

Age and retrieval accuracy-related activations

Several functional ROIs were defined for each of the contrast of interest described above (marked with a star in Tables 9 and 10) and used for additional analyses to examine any modulation by individual characteristics of the participants. Parameter estimates (beta values) extracted and averaged across voxels from these ROIs were then submitted to Pearson's correlation with age and WM retrieval accuracy. No significant correlation was found between encoding- or retrieval-related activation (relative to baseline activation) with neither age nor WM retrieval accuracy on the adapted Brown-Peterson paradigm for any of these ROIs. Table 11 summarizes these correlation coefficients.

We also performed an exploratory whole-brain regression analysis in SPM using (a) age; and (b) WM retrieval accuracy for the main contrasts of interest as described above (encoding vs retrieval, within vs cross domain concurrent tasks). None of these analyses revealed any significant overlap with activations identified by the main contrasts of interest reported in Table 10 indicating that all effects reported above are largely independent of age (within the range of our sample) and WM retrieval accuracy.

Table 11. Pearson's correlations between activity of functional ROIs and (a) age or (b) retrieval accuracy.

Functional ROIs					**Age**		**Accuracy**	
Region	**Side**	**Number of voxels**	**Peak coordinates**	**r**	**P value**	**r**	**P value**
ENCODING (compared to encoding baseline condition)							
Frontal Inferior	L	108	-38, 30, -14	-.351	.183	-.275	.304
Superior and middle	L	160	-27, 40, 43	-.041	.881	-.269	.314
Superior and superior medial	L	193	-15, 57, 13	-.101	.711	-.360	.171
Occipital Lingual, inferior, Fusiform	L	515	-25, -95, -11	.322	.224	.235	.382
	R	631	25, -91, -11	.308	.245	.182	.501
Temporal Parahippocampal Gyrus	L	130	-40, -28, -11	.455	.077	.214	.426
	R	71	13, -13, -17	.225	.401	.389	.137
Subcortex Caudate Nucleus	L	563	-17, 19, 10	-.225	.402	-.111	.683
Other Cerebellum	L	222	-10, -30, -14	.241	.369	.361	.169
RETRIEVAL (compared to retrieval baseline condition)							
Frontal Inferior extending to putamen and insula	L	7684	-15, -6, 13	-.174	.519	-.100	.171
Middle and superior	R	572	27, 46, 7	-.010	.969	.055	.839
Precentral	L	268	-34, -4, 61	.242	.367	.282	.289
Superior orbital	L	74	-21, 53, -14	.030	.911	.076	.780
Temporal Middle extending to precuneus	R	189	32, -65, 16	.187	.489	.405	.120
Parietal Inferior and superior lobule	L	1813	-36, -55, 55	.395	.130	.248	.354
Inferior lobule, postcentral	L	404	-51, -25, 46	.338	.201	.381	.145

Note: Activity was measured during either encoding or retrieval periods depending on the phases recruiting each ROI. Coordinates in MNI space and number of voxels are given for each functional ROI, as well as Pearson's correlation coefficients, r, and corresponding p values.

6.5. Discussion

We report and validate an adapted Brown-Peterson fMRI paradigm that probes for the neural correlates of different WM processes, including encoding, maintenance and retrieval, as well as the effect of within- and cross-domain concurrent tasks during maintenance. Results indicate that this paradigm can be performed equally well by children and adolescents of different ages, with reliable results across different levels of performance. To our knowledge, this is the first study to propose a paradigm to delineate distinct patterns of brain activity for the different WM processes in children and adolescents. We provide the first exploratory results on brain activity related to encoding, maintenance, and retrieval WM processes in children and adolescents, and compare verbal WM in the presence of both verbal (within-domain) and visual (cross-domain) concurrent tasks.

As expected, our adapted Brown-Peterson paradigm was successfully completed with high accuracy in the MRI scanner by typically developing children as young as 8 years of age, indicating that it is suitable to examine WM processes in children and adolescents from 8 to 16 years of age. It is important to note that task difficulty was adapted to each participant's WM capacity using a simple procedure (based on backward digit span performance, the participant completed the paradigm with two or three letters to remember), and we found no significant association between age or task performance and brain activation patterns. These findings indicate that our paradigm is well suited to examine brain systems associated with different WM capacities in different age groups. This may be an important advantage when comparing groups with different developmental trajectories, because previous studies show that WM-related activations may increase with age in parallel with changes in performance and improvements in WM capacity (Crone et al., 2006; Klingberg et al., 2002).

Secondly, our imaging results demonstrate that, while distributed networks in frontal and visual areas activated in the context of the verbal WM paradigm used here (i.e. during the active conditions compared to the baseline), distinct neural substrates were selectively recruited during the encoding and retrieval periods. The verbal encoding period induced stronger activations in posterior and ventral brain regions, with large bilateral increases in occipital, as well as parahippocampal cortices. In contrast, the verbal retrieval period induced stronger activations in more anterior and dorsal regions, in particular in prefrontal and parietal areas, and to a lesser extent in lateral temporal areas.

The predominance of activity in visual cortex together with medial temporal lobe (parahippocampal gyrus) during encoding is consistent with the need to extract discriminative visual information from the to-be-remembered stimuli and store this information into short-term memory. On one hand, ventral occipito-temporal areas differentially engaged during encoding are crucial for perceptual shape analysis, especially for letters with a letter-sensitive activation in these regions (Flowers et al., 2004; Garrett et al., 2000). We did not find selective activations corresponding to the "visual word form area" but this region is typically responsive to letter-strings or words rather than isolated letters (L. Cohen et al., 2000; Dehaene & Cohen, 2011; Dehaene et al., 2010). Moreover, we did not find language-related activation during verbal encoding, in particular Broca's area which has been implicated in the subvocal rehearsal system (Paulesu et al., 1993). However, language-related activation has been mainly found during encoding of words (Reber et al., 2002) and not during encoding of letters (Manoach, Greve, Lindgren, & Dale, 2003).On the other hand, the parahippocampal cortex is a key brain region at the interface between perception and memory, therefore likely to make an important contribution to efficient storage of visual information into WM (Strange, Otten, Josephs, Rugg, & Dolan, 2002).

As expected, predominant activity in frontal and parietal areas during retrieval is consistent with executive control and attentional focusing. The executive control system serves as an attention controller that allocates and coordinates attentional resources for cognitive tasks, such as retrieval of information encoded in working memory (Baddeley, 1996a; Engle, Tuholski, et al., 1999). Our findings accord with previous studies showing the involvement of frontal areas, especially prefrontal and anterior cingulate cortices, in the executive control required during WM demands (M. Osaka et al., 2003; N. Osaka et al., 2004). Focusing attention is crucial for efficient executive control (Cowan, 2001) and recruits parietal regions (M. Osaka, Komori, Morishita, & Osaka, 2007), which were strongly implicated during the retrieval period in our study. In addition, WM retrieval of serial order is dissociable from the type of information contained in the item sequence (Delogu, Nijboer, & Postma, 2012) and also relies on activation in frontal and parietal activations (Marshuetz, Smith, Jonides, DeGutis, & Chenevert, 2000).

Overall, our findings converge with those of van den Brosh and colleagues (2014), who reported a similar posterior and perceptual network during the encoding phase compared to a

more anterior and executive network during the recall phase of a Sternberg item recognition paradigm (which did not include a distracting phase) in children and adolescents aged 9 to 19 years. However, these authors did not find any temporal or parahippocampal activations, possibly reflecting differences in the paradigm and material used (digits in their study vs. letters in ours). More generally, our findings of extensive fronto-parietal and visual activity during WM also dovetail with previous neuroimaging studies investigating brain systems associated with verbal WM in children and adolescents, across different kinds of verbal WM paradigms, such as the Steinberg item recognition task using letters (Finn et al., 2010; O'Hare et al., 2008; van den Bosch et al., 2014) or n-back tasks using letters (Brahmbhatt, White, & Barch, 2010; Thomason et al., 2009).

Study hypotheses were supported by results revealing that brain activation patterns differ as a function of the nature of the concurrent task performed during the maintenance interval. Our design allowed us to compare the impact of within-domain (lexical decision task) versus cross-domain (face decision task) concurrent task processing during the maintenance period intervening between encoding and retrieval, while information stored in WM itself did not differ. A lexical decision task was expected to produce within-domain interference, as it involved verbal material resembling the to-be-remembered material (i.e. letters), while a face decision task was considered to induce cross-domain interference as it relied on non-verbal visual processes.

As predicted, the within-domain and cross-domain concurrent tasks evoked distinct brain activations when compared to each other. Localised and right-sided activations in the right frontal pole (Brodmann area 10) and medial fusiform gyrus were observed during the within-domain/lexical concurrent task, whereas the cross-domain/face concurrent task elicited much more distributed activations in occipital temporal extrastriate areas, but also left parahippocampal gyrus and fronto-parietal regions. These differences could not be attributed to task difficulty (since there were no significant difference in accuracy between the within-domain/lexical and the cross-domain/face decision task) but most likely reflect the different task demands and perhaps different strategies and processes applied during the maintenance interval. Since verbal information had to be held in WM, it might have produced stronger interference and greater conflict in resource allocation during the within-domain/lexical decision task than the cross-domain/face decision task, eventually affording less efficient engagement of task-specific networks in the former condition and hence lower accuracy. The

involvement of the right frontal pole (Brodmann area 10), thought to organize an optimal use of cognitive resources and overcome potential impasses (Burgess, Dumontheil, & Gilbert, 2007), may reflect this conflict in resource allocation and an increase in cognitive load during a verbal concurrent task. Such recruitment of attentional control mechanisms during interference appears consistent with the time-based resource-sharing model (TBRS; Barrouillet & Camos, 2001; Barrouillet & Gaillard, 2010; Vergauwe et al., 2014). This model postulates the existence of attention-based mechanisms involved to maintain relevant verbal information when the capacity of the verbal-specific system (comparable to the phonological loop in Baddeley and Hitch's model) is exceeded (Vergauwe et al., 2014). Alternatively, greater activation of visual and fronto-parietal areas as well as temporal regions, including parahippocampal gyrus, during the cross-domain/face decision task might reflect the dual process of face decision task and active maintenance of verbal information.

Critically, and in keeping with our hypotheses, the two concurrent tasks (within- and cross-domain) elicited distinct patterns of brain activity during the subsequent retrieval phase, despite the fact that identical stimuli were encoded, maintained and retrieved from WM. This indicates that partly different processes mediated retrieval after within- and cross-domain interference, and thus WM retrieval differed according to the nature of the preceding concurrent task. Large bilateral occipital activations were engaged during retrieval after the within-domain/lexical concurrent task, whereas only limited activity was observed in medial occipital cortex in addition to left superior and middle temporal cortex during retrieval after the cross-domain/face concurrent task. Interestingly, the latter cluster in temporal cortex overlapped with regions often reported in phonological tasks and associated with language networks (Bitan et al., 2007; Burton et al., 2005). A plausible explanation for such difference would be that the maintenance of letters relied on a preferentially visual format when a concurrent verbal task had to be performed (i.e., within-domain concurrent task), hindering the use of the phonological loop for maintenance. On the other hand, the visual concurrent task may not prevent maintenance in the phonological loop, explaining a lesser involvement of visual cortex but conversely greater recruitment of language-related areas (left superior and middle temporal) during retrieval. These interpretations would accord with Baddeley and Hitch's model previously mentioned, and the proposed effect of articulatory suppression on verbal WM (Baddeley, 1996a; Camos et al., 2009; Oberauer, Farrell, Jarrold, Pasiecznik, & Greaves, 2012).

The current study is not without limitations. The study sample size could be considered relatively small. We note, however, that it is comparable with previous studies exploring neural correlates of WM (Finn et al., 2010; Klingberg et al., 2002; Vuontela et al., 2009). Even if our data showed no hint of any systematic modulation of brain activity patterns by age or retrieval accuracy, correlation and regression analysis performed here can be sensitive to small size. Nevertheless, by design, our procedure of tailoring task difficulty to each participant according to their WM capacity precisely aimed at avoiding age related effects and minimizing confounding effects due to individual differences in performance. We acknowledge that the lack of variability and the high retrieval accuracy resulting from this procedure may have limited the sensitivity of our study to activations modulated by age or other individual factors. Another limitation is that our paradigm did not test the reverse situation of verbal versus visual concurrent tasks on visual information held in WM. Examining both verbal and visuospatial WM in the presence of verbal and visuospatial interference could map more precisely how the different processes subserving verbal and visuospatial WM are influenced by different kinds of concurrent tasks.

6.6. Conclusions

Our study provides new insights into WM-related brain activity. We show a greater role of perceptual brain systems for encoding processes, and a fronto-parietal attentional network for retrieval processes. More critically, we show that a concurrent task during maintenance in WM produced distinct activations not only during the concurrent task itself, but also during subsequent retrieval. We conclude that the specific demands of the concurrent task affect the way memory items are maintained in WM, selective verbal interference resulting in greater reliance on visual cortex for retrieval, whereas visual interference leaves verbal systems of maintenance unaffected, hence resulting in the involvement of language-related areas in left temporal cortex for retrieval. These data accord with WM models postulating differentiated cognitive processes, with distinct neural substrates, according to the concurrent material interfering in verbal WM (Baddeley, 1996a; Camos et al., 2009; Oberauer et al., 2012). In addition we show that these activation patterns are robust across different ages and different WM capacities. More generally, our work validates a new WM paradigm derived from the Brown-Peterson task allowing us to probe for the neural correlates of different WM processes. Because the difficulty of the task was adapted to each participant and results were stable across age, this fMRI paradigm may be usefully applied in developmental populations with a

wide age range and also feasible in clinical paediatric population (e.g., populations with mild intellectual difficulties).

6.7. Acknowledgements

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CHAPTER 7: Study 4 - Neural correlates of working memory in children with agenesis of the corpus callosum

Neural correlates of working memory in children and adolescents with agenesis of the corpus callosum: an fMRI study

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Authors	Siffredi, V., Spencer-Smith, M., Barrouillet, P., Vaessen, M., Leventer, R., Anderson, V., Vuilleumier, P.	
Student's contribution (%)	80 %	
Journal or book name	Neuropsychologia	
Volume/page numbers	106, 71-82	
Status	☐ Accepted and In press ☒ Published	Date accepted/ published Sept 2017

B. STUDENT'S DECLARATION

I declare that the publication above meets the requirements to be included in the thesis

Student's name	Student's signature	Date *(dd/mm/yy)*
Vanessa Siffredi		25.10.2017

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Megan Spencer-Smith	Megan Spencer-Smith	20/10/17
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7.1. Abstract

The ability to temporarily maintain relevant information in mind in the presence of interference or distracting information, also called working memory (WM), is critical for higher cognitive functions and cognitive development. In typically developing (TD) children, WM is underpinned by a fronto-parietal network of interacting left and right brain regions. Developmental absence (agenesis) of the corpus callosum (AgCC) is a congenital brain malformation resulting from disruption of corpus callosum formation. This study aims to investigate functional organisation of WM in children and adolescents with AgCC using functional magnetic resonance imaging (fMRI). Nine children with AgCC and a comparison group of sixteen TD children aged 8 to 17 years completed an fMRI WM paradigm designed to enable investigation of different WM processes, i.e., encoding, maintenance and retrieval. We found that AgCC children recruited globally similar brain regions as the TD comparison group during the WM task, despite significant disparity in brain development, i.e., bilateral occipito-frontal activations during verbal encoding, and bilateral fronto-parietal executive control network during retrieval. However, compared to their TD peers, children with AgCC seemed less able to engage lateralised brain systems specialised for particular memory material (i.e. less supramarginal activations for verbal material and less fusiform activations for face processing) and particular memory process (i.e. absence of right-predominant activations during retrieval). Group differences in the pattern of activation might also reflect different cognitive strategies to cope with competition in processing resources with different susceptibility to concurrent tasks (verbal vs visual), such as differential recruitment of associative visual areas and executive prefrontal regions in the AgCC compared with the TD group depending on the concurrent task completed during maintenance. This study provides a first step towards a better understanding of functional brain networks underlying higher cognitive functions in children with AgCC.

7.2. Highlights

- First study of brain related-activation during working memory in callosal agenesis
- Globally similar network in AgCC as the comparison group
- Group differences in activation may reflect different cognitive strategies
- Group differences linked to different hemispheric lateralisation
- Alternative neural pathways might compensate for callosal agenesis

7.3. Introduction

The corpus callosum (CC) is the largest cerebral commissure in the brain and a major white matter pathway that connects homologous structures between both halves of the central nervous system (Paul et al., 2007; Raybaud, 2010). In typical development, this bundle of fibres is a major conduit that transfers information between the two hemispheres, and also contributes to the integration of information across hemispheres for various cognitive and sensorimotor tasks (Bloom & Hynd, 2005; Chiarello, 1980).

Developmental absence, or agenesis, of the CC (AgCC) is a congenital brain malformation that results in the complete or partial failure of callosal fibres to form connections between cortical areas of the two hemispheres (dos Santos et al., 2002). Diagnosis of AgCC can be made prenatally or postnatally based on characteristic neuroimaging changes using ultrasound, computerised tomography (postnatally) or magnetic resonance imaging (MRI), including fetal MRI (Tang et al., 2009). Improvements in neuroimaging techniques, such as higher field strength for MRI, its growing use in paediatric populations as well as the growing use of routine prenatal ultrasound have resulted in increased rates in the detection of patients with AgCC (Moutard et al., 2003; Pisani et al., 2006). In the general population, its estimated prevalence is ~1-7 in 4000 live births (Glass et al., 2008; L. W. Wang et al., 2004). AgCC can be complete, with interruption of callosal development occurring at early stage in embryological development before 6 gestational weeks (Edwards et al., 2014), or partial, with disruption occurring slightly later in gestation (Huang et al., 2009; Paul, 2011; Richards et al., 2004). It may present as an isolated condition with other common secondary effects including colpocephaly, Probst bundles and cingulate gyrus absence (Booth et al., 2011). It may also be associated with other brain malformations including hydrocephalus, grey matter heterotopia, holoprosencephaly, interhemispheric cysts, gyral abnormalities (Bedeschi et al., 2006) , and neurological sequelea such as epilepsy, macro or microcephaly, hearing and vision impairments (Moes et al., 2009) . The causes are heterogeneous, however, genetic conditions including single-gene and chromosomal abnormalities are reported (Edwards et al., 2014). Consistent with the variability in presentation and aetiology of this brain malformation, previous studies have reported cognitive abilities ranging from “normal”, with children attending mainstream school and adults having a conventional career (Caillé et al., 1999), to severe cognitive difficulties, with individuals attending special developmental school and requiring assistance in daily living activities (Graham et al., 2008; Graham et al., 2003). In a

systematic review of neuropsychological functioning in AgCC (n=110 patients), mean intellectual functioning was described to be in the low average range for adults (IQ: Mean=88.2, SD=15.18, n=41) and in the borderline range for children (IQ: Mean=76.4, SD=30.12, n=48; Siffredi et al., 2013) . Therefore, studying this brain malformation has been a challenge as the heterogeneity is inherent to this clinical population. In contrast to split-brain patients (acquired destruction of the CC), individuals with AgCC show very little, if any, evidence of interhemispheric disconnection, and do not present with the typical disconnection deficits (Jea et al., 2008; Lassonde & Jeeves, 1994; Siffredi et al., 2013; Vuilleumier, 2001). This suggests that brain organisation and functions are capable of major plasticity, and determine long-term neurodevelopmental outcomes (V. Anderson et al., 2011).

In children and adolescents, working memory (WM) is a fundamental cognitive system that involves actively storing and manipulating information over brief periods of time (Baddeley, 1986) and relies on distributed brain networks across the two hemispheres. WM is considered a building block for the development of other higher cognitive functions, such as reasoning, language, social cognition and academic performance (e.g., Alloway et al., 2004; Barrouillet et al., 2008; Gathercole et al., 2004) . WM capacity, as measured by the amount of information that can be retained and transformed in complex memory span tasks, develops dramatically across childhood and adolescence (Klingberg et al., 2002). In typically developing (TD) children and adolescents, a core bilateral fronto-parietal network is known to underpin verbal and visuo-spatial WM (e.g., Kwon et al., 2002; O'Hare et al., 2008; Spencer-Smith et al., 2013; van den Bosch et al., 2014) . Intrahemispheric as well as interhemispheric connectivity, mostly supported by the CC, is likely to play a crucial role in WM processes by promoting efficient functional integration between brain areas (Hillary et al., 2011; Koshino et al., 2005; Schlösser et al., 2006). Indeed, in typically developing children, a significant correlation between visual WM performance and development of white matter in the anterior corpus callosum has been described (Nagy et al., 2004). In brain-injured children, microstructural integrity of the CC has been associated with variance in verbal and visuospatial WM capacity (Treble et al., 2013). As a consequence, in AgCC a disruption of normal functional connectivity between the two hemispheres would be expected to impact on WM processes (Quigley et al., 2001). However, WM and concomitant interhemispheric interactions have not previously been studied in AgCC individuals. To our knowledge, two case studies have been published examining WM abilities in AgCC, both adults. However, results are contradictory, with impaired performance on a 2-back task in one case (Simon et

al., 2008), and average performance on auditory-verbal and visual WM tasks in the second case (Reddy et al., 2010). In addition, Sauerwein and Lassonde (1994) reported working memory performance below the average range but not significantly different from the control group in 9 individuals with AgCC from 10 to 29 year-old.

Our study aimed to investigate the functional organisation of WM in children and adolescents with AgCC compared with TD children using fMRI. We designed an fMRI WM paradigm developmentally appropriate for participants across a wide age range and with different WM capacities (Siffredi, Barrouillet, et al., 2017). Specifically, our paradigm was adapted from the Brown-Peterson task (J. Brown, 1958; Peterson & Peterson, 1959), which allows us to: 1) explore brain systems recruited by different verbal WM processes: encoding, maintenance and retrieval; and 2) investigate the effect of different concurrent tasks (verbal and visual) during maintenance and retrieval. As hemispheric lateralisation of verbal versus visual processing and communication between hemispheres might differ in the context of AgCC, we expect that brain networks in AgCC children will show different patterns of activation compared with TD children during the fMRI WM paradigm.

7.4. Methods

Participants

Nine participants with AgCC diagnosed on MRI were recruited from clinics and radiology records at The Royal Children's Hospital in Melbourne, Australia, as part of the "Agenesis of the corpus callosum project" at the Murdoch Children's Research Institute. Individuals with a diagnosis of AgCC confirmed on MRI were aged 9 to 17 years at assessment. In addition to a diagnosis of AgCC on MRI. Further inclusion criteria were: English speaking, and ability to engage in the assessment. A comparison group of 16 typically developing (TD) children and adolescents was recruited through advertisement in local schools and through staff at The Royal Children's Hospital. TD participants were aged 8 to 16 years at assessment, English speaking, with no documented history of a brain lesion, neurological disability or neurodevelopmental disorders. Participants from the AgCC and TD groups had normal or corrected-to normal vision and hearing.

Descriptive measures

Verbal working memory capacity was estimated using the standard scores of the Digit Span Backward subtest from the Wechsler Intelligence Scale for Children 4th edition (WISC-IV; Wechsler, 2003) and from the Wechsler Adult Intelligence Scale 4th edition for the 17 year-old participant (WAIS-IV; Wechsler, 2010; M=10, SD=3). Participants listened to a sequence of digits, which they were required to repeat in the reverse order. Full-Scale Intelligence Quotient (IQ) was estimated using the 4-subtests version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Handedness was estimated using the Edinburgh Handedness Inventory (EHI), a ten-item self-report questionnaire assessing preferred hand for daily life activities (Oldfield, 1971).

Neuroimaging

Image Acquisition

MRI was performed on a Siemens 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany) at the RCH. The scanner was equipped with the Syngo MR B17 software release, and a 32-channel receive-only head coil was used. T1-weighted MP-RAGE sequence (Magnetisation Prepared Rapid Gradient Echo) were obtained, TR=1900 ms, TE=2.71 ms, TI=900 ms, FA=9°, FoV=256mm, voxel size=0.7 x 0.7 x 0.7 mm. Functional images were acquired using a T2*-weighted gradient-echo-planar imaging (EPI) sequence with 32 interleaved slices with 5% gap, voxel size=2.6 x 2.6 x 3 mm, TR=2400ms, TE=35ms, FA=90°, FoV=240mm.

Scan Coding

Using a revised coding system for brain malformations (Leventer et al., 1999), sagittal T1- and coronal T2-weighted structural MR images were qualitatively reviewed by a paediatric neurologist (RJL). Absence of the CC was classified as complete if no callosal tissue was present or partial only a part of the callosum was absent. Any associated brain anomalies were noted.

fMRI Paradigm

Participants completed an adapted version of the Brown-Peterson paradigm (Brown, 1958; Peterson and Peterson, 1959) previously described in Siffredi and colleagues (2017), presented visually during fMRI using E-prime2 (Psychology Software Tools, PST,

Pittsburgh). A mixed block and event-related design allowed us to separately examine different processes of WM. The task required a combination of verbal encoding and maintenance during either verbal (within-domain) or visual (cross-domain) concurrent tasks. Each trial consisted of three parts, Figure 24: 1) an encoding period during which participants were presented with a series of single upper-case letters for further recall displayed sequentially in the middle of the screen at a rate of one letter per second; 2) a maintenance delay of 6 seconds filled with a concurrent task requiring to process either verbal or visual stimuli involving within- or cross-domain interference respectively (see below); and 3) a letter retrieval period of 3 seconds during which participants were presented with one single upper-case letter among one (paradigm with 2 letters to remember) or two (paradigm with 3 letters to be remembered) dashes with a question mark in the middle of the screen. Participants have to indicate as quickly and as accurately as possible whether this letter matched the letter previously seen in that serial position, by pressing the green key [left side] for yes (same letters and same order) or the red key [right side] if not. This was done to make sure that participants memorised both the item and order of information. The within-domain concurrent task was a lexical decision task. Two successive letter-strings were presented for 3 seconds each and required a simple motor response (i.e. press as quickly and as accurately as possible the green key if the letter-string was a word or the red one if it was a non-word). The cross-domain concurrent task was a face decision task of two successive pictures presented for 3 seconds each, requiring a motor responses (i.e. press as quickly and as accurately as possible the green key if a real face was presented or the red key if it was a scrambled face).
A randomised inter-trial interval of 2000, 2500, or 3000 milliseconds was used before the next trial. Two types of blocks of 10 trials each were created: one including the within-domain concurrent task and the other including the cross-domain concurrent task. The order of presentation of these two blocks was counterbalanced across participants and repeated twice for a total of four blocks of 10 trials. Within each block, half of the probes were positive (i.e., 5 trials required a “yes or green” response) and the position of positive and negative probes were randomized within each blocks.

Because a challenge of brain imaging studies examining cognitive development is that differences in both age and task performance may influence activation patterns, the memory load in our fMRI WM paradigm was tailored to each participant. At issue is whether changes in neural activity reflect changes in functional maturation of the central nervous system, independently of behavioural efficiency, or whether they reflect changes in task performance

naturally associated with increasing age (Kwon et al., 2002; Schweinsburg et al., 2005). Therefore, in our paradigm, task difficulty was adapted to each participant by adapting the number of verbal items to remember, while keeping the protocol similar to avoid other issues related to differences in the timing and sampling of brain activity measures. Consistent with our previous study (Siffredi, Barrouillet, et al., 2017), children with a backward digit span of 5 or more were presented with 3 letters to be remembered, whereas children with a backward digit span lower than 5 had only two letters to remember. In the AgCC group, seven participants completed the 2-letters paradigm (age range=9-17.08, M=12.21, SD=2.78), and two completed the 3-letters paradigm (age range=9.67-15.58, M=12.63, SD=4.18). In the TD comparison group, 10 participants completed the 2-letters paradigm (age range=8.33-16.42, M=11.97, SD=2.63), and six completed the 3-letters paradigm (age range=10.92-15.08, M=12.57, SD=1.58). There was no significant group difference between the numbers of participants who completed the 2-letters or 3-letters versions of the paradigm (p= .661, Fisher's exact test).

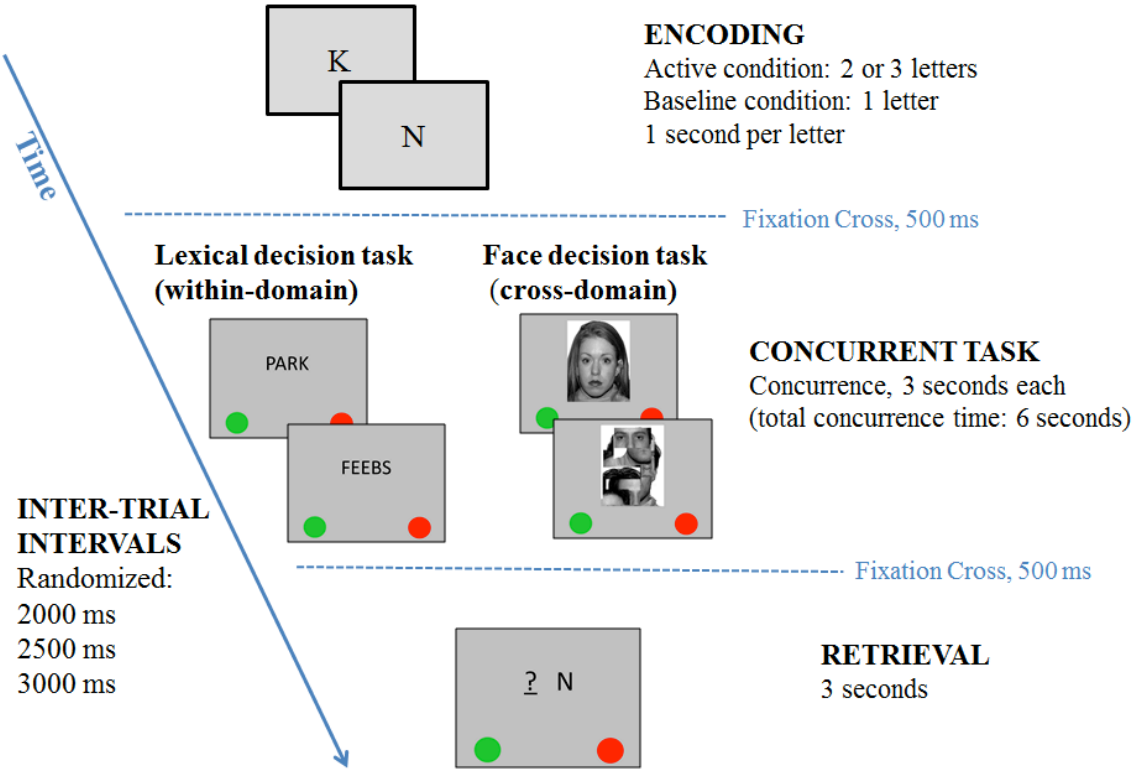

Figure 24. Adapted Brown-Peterson fMRI WM paradigm.

Procedure

This study was approved by The Royal Children's Hospital Human Ethics in Research Committee. Written informed consent was obtained from the caregivers prior to participation in the study. Children completed a mock MRI scanner training protocol. They were prepared extensively for the fMRI task through training outside and inside the scanner. The fMRI WM paradigm was projected onto a screen at the foot of the MRI bed, and participants viewed the images from a mirror attached to the head coil. Responses were provided using an MRI compatible response box with four response buttons, which was placed centrally on the child's stomach.

Statistical analyses

fMRI WM Paradigm Behavioural Data

To examine differences in performance accuracy between the within- and cross-domain concurrent tasks and following retrieval, Wilcoxon signed-rank tests were performed (given that the assumption of normality was violated for the accuracy measure in all conditions in both groups as assessed by inspection of histograms and results of the Shapiro-Wilk test, ranging from $p<0.001$ to $p=0.003$). Group differences in performance accuracy were explored using Kruskal-Wallis tests. To examine the effect of the concurrent tasks on retrieval in the two groups, linear regressions were performed. Regression plots presenting various residual values were inspected to establish the validity of regression assumptions. Statistical analyses were performed in SPSS (IBM, Released 2013).

Image Analyses

fMRI data were preprocessed and analysed in SPM8 (Wellcome Department of Imaging Neuroscience, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in Matlab R2014a. Images of each subject were spatially realigned to eliminate movement artefacts, and corrected for slice acquisition timing. As noted by Tyszka and colleagues (2011), morphological differences between AgCC and TD individuals are minimal on the lateral cortical surfaces, but are pronounced around the midline and ventricles due to the absence of the CC, and the presence of Probst bundles, mesial cortical reorganisation and colpocephaly. Therefore, we created a customised template using the DARTEL algorithm following the procedure outlined by Salami and colleagues (2014) , which is close to the procedure used by Tyszka and colleagues

(2011). First, individuals' T1-weighted images were segmented into grey and white matter using the toolbox "New Segment". Secondly, a group-specific template (n=25) was created using Exponentiated Lie Algebra (DARTEL). Grey and white matter tissue class images were imported using the normalisation parameter yielded during the segmentation step followed by resampling to isotropic voxels (1.5 x 1.5 x 1.5 mm). Then, the imported images went through and interactive procedure that began by producing an initial template as a mean of grey and white matter across all participants. Deformation from the initial template to each individual's grey and white matter images was computed and the inverse of the deformation was applied to each individual's images. A second template was created as the mean of the deformed individuals' grey and white matter images across all participants, and this procedure was repeated until a sixth template was created, Figure 25. Finally, the realigned and resliced fMRI images and the flow field grey matter image were nonlinearly normalised to the sample-specific template for each individual independently (voxel size of 1.9 x 1.9 x 3 mm); and affine-aligned into MNI space. These functional images were finally smoothed using a Gaussian filter of full width at half maximum=8 mm to increase signal-to-noise ratio.

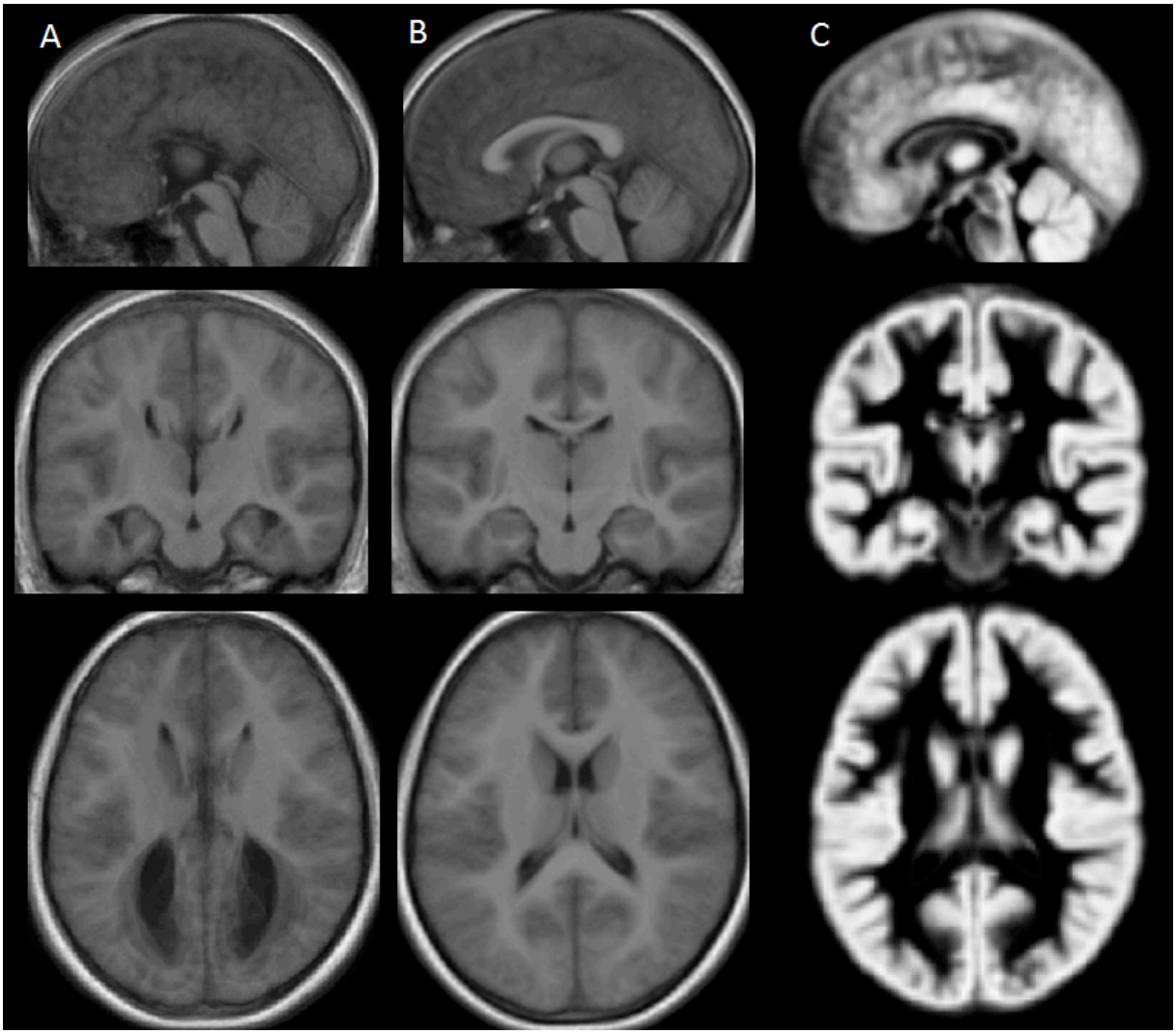

Figure 25. Creation of a customised template using DARTEL: (a) Mean T1-weighted image of the AgCC group; (b) Mean T1-weighted image of the TD comparison group; (c) Customised template created using DARTEL based on structural images from the total sample of AgCC and TD children (6 iterations).

Statistical analyses were performed using a two-step process, taking into account the intra-individual and inter-individual variance (Friston et al., 1995). First level single subject statistics were assessed by a voxel-based statistics according to the General Linear Model implemented in SPM8. Activity was analysed pooling across the correct and incorrect trials together. The onsets of each event of interest, i.e., verbal encoding, lexical decision task (within-domain concurrent task), face decision task (cross-domain concurrent task), retrieval following within-domain concurrent task, retrieval following cross-domain concurrent task, were convolved with the canonical hemodynamic response function (HRF) and used as regressors in the individual design matrix. The letter encoding period was modelled using a

boxcar function of 2 or 3 seconds (depending of the difficulty of the task); the maintenance delay filled with one of the concurrent task was modelled using a boxcar function of 6 seconds; and finally, the letter retrieval period was modelled using a boxcar function of 3 seconds.

All six movement parameters (translation: x, y and z; rotation: pitch, roll and yaw) were included as covariates of no interest in the model. The individual statistical images from each condition were then entered group-averaged at the second level using a flexible factorial design, with a main-effect of subject and an interaction of conditions and groups. In this random-effects model, we modelled independent levels for subject and group, but dependent levels for conditions. For the three factors, we modelled unequal variances, which allows for violation of sphericity, as implemented in SPM8. In line with guidelines used in neuroimaging studies of complex cognitive functions (Lieberman & Cunningham, 2009), whole-brain analysis was conducted with a significance threshold of $p<0.001$ at the voxel level, uncorrected for multiple comparisons, and a minimum extent threshold of 20 voxels. Conjunction analysis was performed to define regions commonly activated in both groups (Friston, 1999). Between group contrasts were conducted to define regions differentially activated in the two groups. The condition x group interaction was masked by the main effect of this same condition in one group to identify condition-specific effects for the given group. We used inclusive masks of within group contrast with an uncorrected mask p-value of 0.05 and a significance threshold of $p<0.001$ at the voxel level, uncorrected for multiple comparisons, and a minimum extent threshold of 20 voxels. Anatomical location of activations was verified using SPM Anatomy toolbox (Eickhoff et al., 2005) and xjView (Cui, 2007). In addition, results in AgCC were reviewed individually to make sure that the locations of group activations corroborate activations at the individual level.

A series of multiple regressions with retrieval accuracy as the covariate and the factor group as the regressor was conducted for the whole brain in the AgCC and the TD groups separately during encoding, retrieval following within-domain concurrent tasks and following cross-domain concurrent tasks. Similarly, multiple regressions were used to explore any association between brain activations with WM capacity measured by Digit Span Backward or IQ scores. In the AgCC group, multiple regressions were used to investigate association between brain activity and handedness or extent of agenesis (complete or partial). For these regressions, a significant threshold of $p<0.001$, and a minimum extent threshold of 20 voxels was used. To explore the impact of potential covariates on the activation pattern, analyses were initially

conducted without any covariates and then repeated with the following covariates: IQ scores, Digit Span Backward scores, handedness and sex.

7.5. Results

Sample characteristics

The AgCC group was similar to the TD comparison group in age (t(23)=.111, p=0.312), sex (X^2(1, n=25)=2.71, p=0.1) and Digit Span Backward standard scores (t(23)=-1.43, p=0.17), Table 12. Six children had complete AgCC, and three had partial AgCC, Table 13. Six of the nine children with AgCC and all TD children were right-handed. Full-Scale IQ was significantly lower in the AgCC than the TD group (t(10.17)=-4.05, p=0.002).

Table 12. Characteristics of the agenesis of the corpus callosum (AgCC) and typically developing (TD) groups.

	AgCC	**TD**
n	9	16
Mean age in years	12.31 (SD=2.83)	12.19 (SD=2.25)
Sex	7 males, 78%	7 males, 44%
Handedness	6 right-handed, 67%	16 right-handed, 100%
Mean Full-Scale IQ	85.44 (SD=21.42)	116.19 (SD=10.4)
Mean Digit Span Backward standard score	9 (SD=3.61)	11.1 (SD=3.38)

Table 13. Demographic and neuroimaging details of children with agenesis of the corpus callosum (AgCC).

ID	**Age**	**Sex**	**H**	**FSIQ**	**C/P**	**CC details**	**AC**	**PC**	**PB**	**CO**	**Associated MRI findings**
102	12.67	M	R	70	C	absent	++	+	+	+	None
103	11	M	R	76	C	absent	+	tiny	+	+	None
104	15.58	M	L	113	P	part of genu present	+	+	+	+	None
105	14.42	M	R	67	C	absent	+	+	+	+	None
106	11.33	M	L	67	C	absent	+	+	+	+	Cortical dysplasia in L frontal lobe
109	9.67	F	R	126	P	genu and anterior body present, thin rostrum	+	+	+	+	History of haemorrhagic cerebral AVM due to hereditary haemorrhagic telangiectasia
110	9	M	L	95	C	absent	+	+	+	+	L interhemispheric cyst with septation, malformed cortex around cyst
112	17.08	M	R	82	P	rostrum present	-	+	+	+	Frontonasal

											dysplasia, sphenoidal encephalocele
113	10	F	R	73	C	absent	+	+	+	+	None

Note: ID study identification number; Age in years; Sex: F female, M male; H Handedness: L left, R right; P/C: P partial AgCC, C complete AgCC; CC details: corpus callosum structural properties details; AC: anterior commissure, and PC: posterior commissure: - absent, + present and normal size, ++ enlargement; PB: Probst bundles, and CO: colpocephaly: + present, - absent; Associated MRI findings: L left, R right.

fMRI WM paradigm – Behavioural findings

Percentages of correct trials (i.e., accuracy) were calculated for the different conditions, Figure 26. For the concurrent tasks, accuracy was similar on the cross-domain and within-domain tasks for the total sample (Ws=121.5, z=1.59, p=0.113), the AgCC group (Ws =29.5, z=1.62, p=0.106) and the TD group (Ws =33, z=0.58, p=0.565). On the within-domain concurrent task, the AgCC group performed less accurately than the TD group (H(1)=5.86, p=0.015) but similar to the TD group on the cross-domain concurrent task (H(1)=0.13, p=0.716). For the retrieval period, retrieval accuracy was similar after the cross-domain concurrent task and within-domain concurrent task in the total sample (Ws =103, z=0.78, p=0.439), the AgCC group (Ws =18.5, z=0.071, p=0.943) and the TD group (Ws =36.5, z=0.93, p=0.352). The AgCC group performed similar to the TD group differences in retrieval accuracy after the cross-domain (H(1)=2.33, p=0.127) or within-domain (H(1)=1.45, p=0.229) concurrent task. Performance on the concurrent task did not predict performance on the retrieval period in the total sample (F(1;1198)=2.35, p=0.126), in the AgCC group (F(1;518)=.491, p=0.484) or the TD group (F(1;678)=2.74, p=0.98). There was no significant association between age and performance accuracy for the different tasks in the AgCC group or the TD group (r ranging from -0.126 to 0.493).

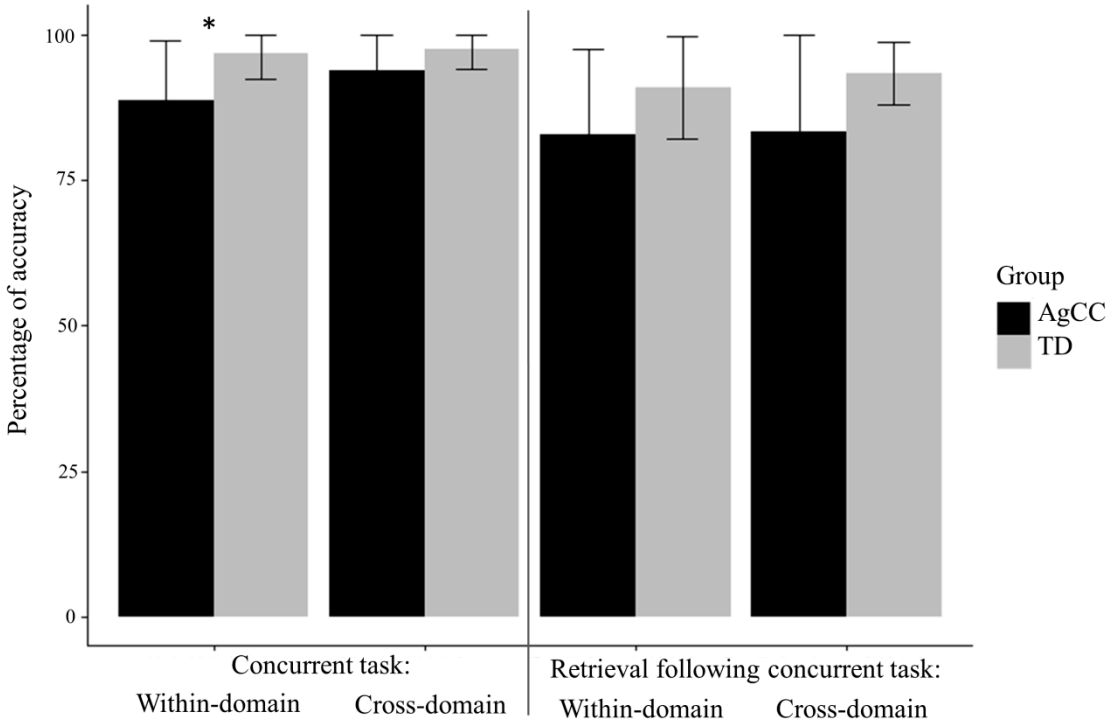

*Figure 26. Percent of accurate performances on the fMRI WM paradigm conditions for the AgCC and TD groups. * Significant group differences, p<.05.*

fMRI WM paradigm – Neuroimaging findings

Movement

Head motions were small in any direction and therefore no participant was excluded from further processing: Maximum translation: AgCC group X=0.68mm, Y=1.08mm, Z=1.44mm and TD group X=0.39mm, Y=0.76mm, Z=1.69mm; Maximum rotation (converted from degrees to millimetres): AgCC group X=0.03mm, Y=0.04mm, Z=0.008mm and TD group X=0.04mm, Y=0.2mm, Z=0.01mm; Mean translation (considering absolute values): AgCC group X=0.35mm, Y=0.56mm, Z=1.77mm and TD group X=0.08mm, Y=0.11mm, Z=0.25mm; Mean rotation: AgCC group X=0.03mm, Y=0.02mm, Z=0.004mm and TD group X=0.004mm, Y=0.003mm, Z=0.002mm. Overall, the mean largest translational motion across the X, Y, and Z head directions (taken from realignment parameters) was 1.77mm (SD=0.52) for the AgCC group and 0.84mm (SD=0.17) for the TD group; and the mean largest rotation motion across X, Y, Z was 0.02mm (SD=0.008) for the AgCC group and 0.01mm

(SD=0.004) for the TD group. Finally, movement for the AgCC group was similar to the TD group (translation X: t(23)=0.506, p=0.126; Y: H(1)=.051, p=0.821; Z: H(1)=2, p=0.157; Rotation X: t(23)=-0.485, p=0.632; Y: t(23)=1.466, p=0.156; Z: t(23)=1.566, p=0.131).

Activations during encoding vs. retrieval

We first compared activations shared for the AgCC group with the TD comparison group during encoding compared to the retrieval period using a conjunction analysis, which revealed large occipital and frontal activations bilaterally. Group comparisons identified some differences in the pattern of activations in these regions. Specifically, the AgCC group showed increased right-lateralised activations in occipital regions, prefrontal ventrolateral regions (BA 44 and 47) and superior temporal regions (limits of BA 40), while the TD group showed amplified activation in bilateral lingual and inferior occipital regions, Table 14 and 15, Figure 27A and Figure 28.

For the retrieval compared to the encoding period, conjunction analyses showed shared activations across the AgCC and TD groups in bilateral frontal areas (middle and inferior) and anterior cingulate, as well as temporo-parietal cortex (angular and middle temporal) and occipito-parietal cortex (angular, middle occipital, cuneus and precuneus). Group comparisons again identified some differences in the pattern of activations in these regions. Specifically, the AgCC showed a small significant left-lateralised activation in the posterior cingulate gyrus and the TD group showed right-lateralised activation in ventrolateral prefrontal, middle and superior temporal, and calcarine regions, as well as a left-lateralised activity in supramarginal regions, Figure 27B.

Activations during concurrent tasks (within-domain vs. cross-domain)

Conjunction analyses for activations during the lexical decision concurrent task (within-domain) compared to the face decision concurrent task (cross-domain) revealed no significant similarities between the AgCC and TD groups. Group comparisons indicated increased activity in the AgCC group in the right fusiform cortex, as well as bilateral orbital (BA10) and ventrolateral (BA45) prefrontal areas, plus a small cluster in the left middle temporal gyrus. In TD children, differential activations were found in left anterior cingulate regions, Table 14 and 15, Figure 27C.

For the face decision concurrent task (cross-domain) compared to the lexical decision concurrent task (within-domain), conjunction analyses showed shared activations across the AgCC and TD groups in bilateral occipital and inferior temporal areas. Group comparisons

revealed differential increases in anterior cingulate regions in the AgCC group, while the TD group showed significantly stronger activity in a large right-lateralised fusiform cluster, overlapping with reported location for the right occipital face area (Minnebusch, Suchan, Koster, & Daum, 2009), as well as smaller increases in prefrontal (BA10), temporal, and subcortical areas, Figure 27D.

Activations during retrieval following within-domain vs. cross-domain concurrent tasks

Finally, we tested whether the nature of the concurrent task during the maintenance interval produced different activations during the retrieval period, and whether these effects differed between groups. For retrieval following within-domain (lexical decision) compared to retrieval following cross-domain concurrent task (face decision), conjunction analyses showed shared activations across the AgCC and TD groups in large occipital areas. Group comparisons identified some differences in the pattern of activations in these regions. The AgCC group showed increases in the right calcarine and left precuneus, while the TD group showed a large increase in right occipito-temporal regions (middle occipital, fusiform, and inferior temporal). Notably, the TD group also showed differential increases in the right dorsolateral prefrontal cortex, Table 14 and 15, Figure 27E.

Conversely, for retrieval after the cross-domain concurrent task (face decision), conjunction analyses revealed shared activations across the AgCC and TD groups in small bilateral medial frontal regions. Group comparisons revealed more anterior activations in prefrontal areas (right dorsolateral and cingulate) for the AgCC group, and significant increase in bilateral posterior areas (occipital cortex and precuneus) for the TD group, Figure 27F.

Association between fMRI activations and fMRI task performance, IQ and verbal WM scores, extent of agenesis and handedness

To test for any systematic modulation of brain activation patterns by individual factors, we performed additional exploratory whole-brain analysis using a parametric regression design in SPM with covariates of interest reflecting several potentially relevant differences in participants with AgCC compared with the TD group (with a significance threshold of $p<0.001$ and a minimum extent threshold of 20 voxels). For both the AgCC and TD groups, we observed no significant associations between brain activations during either encoding or retrieval with WM retrieval accuracy during fMRI, nor with IQ or verbal WM scores from neuropsychological tests. Furthermore, in the AgCC group, no significant association was observed with the extent of callosal agenesis (complete versus partial) or handedness.

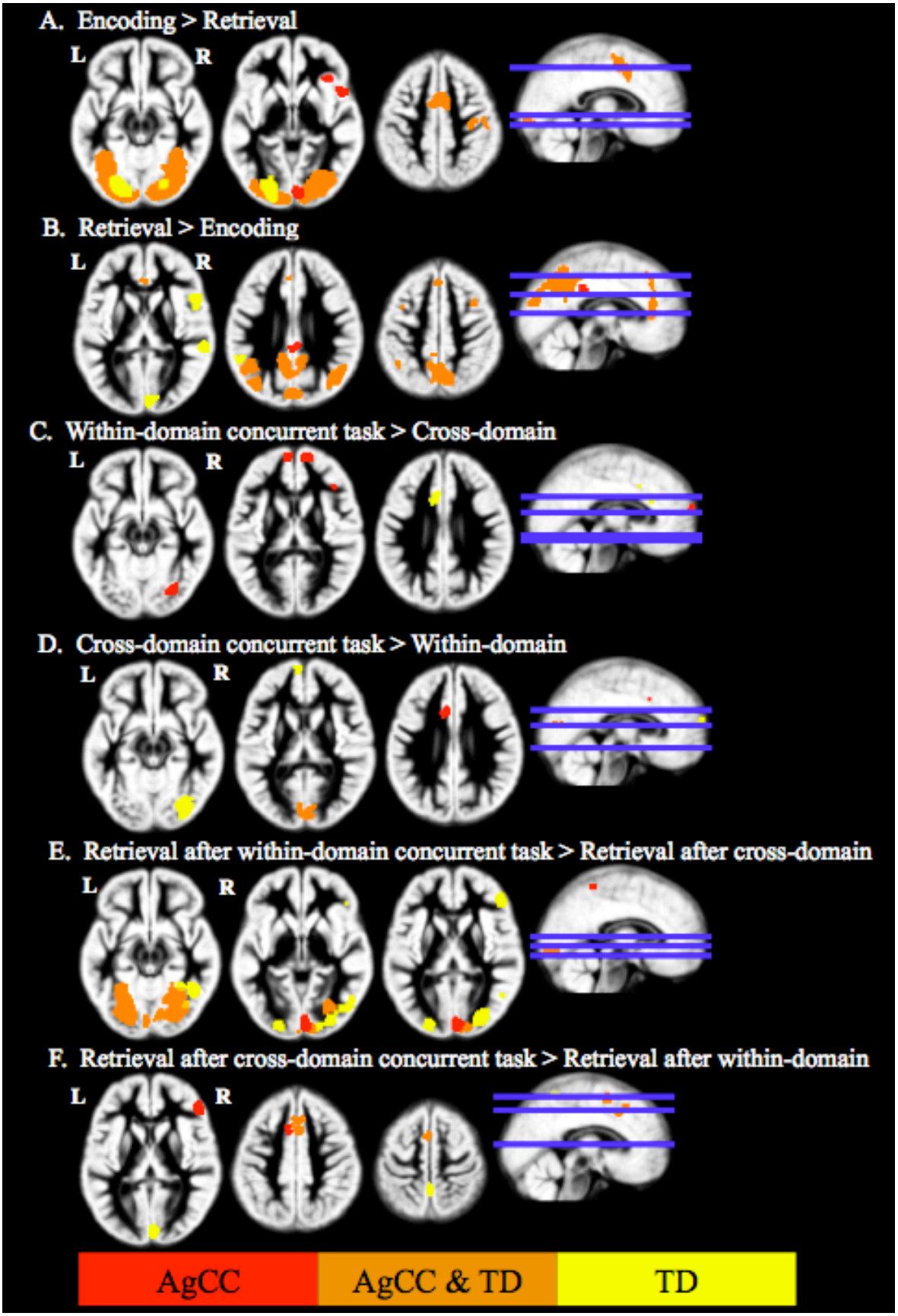

Figure 27. Activation maps for the comparisons of interest.

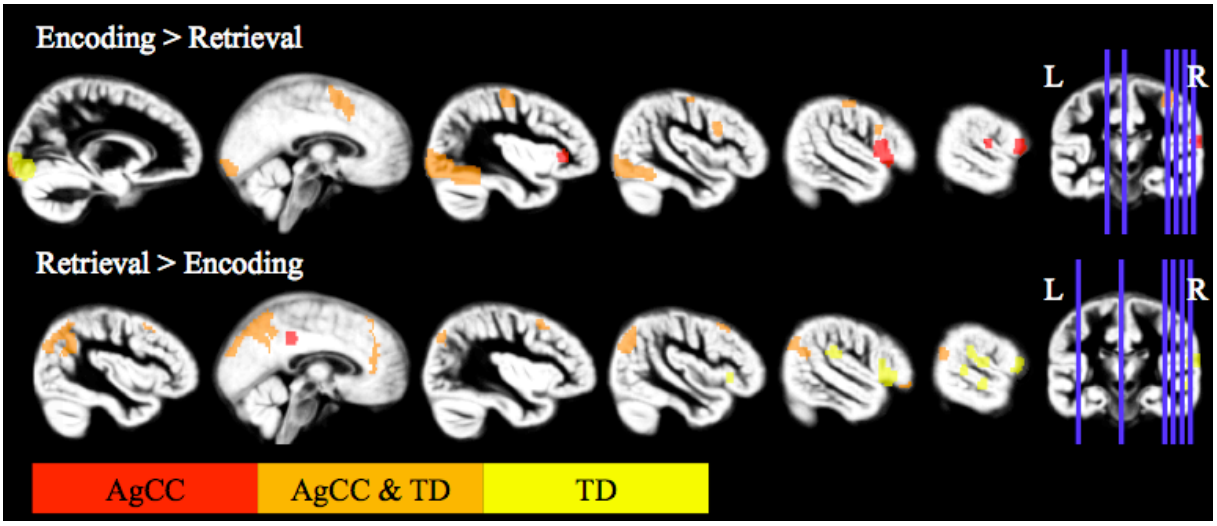

Figure 28. Activation maps for the comparisons of the encoding vs retrieval periods showing more precisely frontal activations.

Table 14. Conjunction analyses between the AgCC and TD comparison groups for the comparisons of interest.

Region		Hemisphere	Number of voxels	t value	x,y,z
Encoding > Retrieval					
Occipital	Inferior	R	1701 *	9.22	32 -82 -9
	Lingual			9.14	21 -89 -9
	Fusiform			5.55	38 -51 -15
	Inferior	L	1355 *	7.79	-34 -84 -12
	Fusiform			7.28	-38 -55 -15
	Calcarine			5.54	-8 -97 -6
Frontal	Anterior cingulate	R	348 *	5.17	6 4 48
		L		4.53	-8 11 39
	Inferior	R	45 *	4.27	44 9 27
	Precentral Gyrus	R	84	4.07	42 -15 54
Retrieval > Encoding					
Frontal	Middle	R	88 *	4.24	38 11 45
	Anterior cingulate	L	176 *	3.41	0 36 15
	Superior medial			3.91	0 32 48
	Middle	L	33	4.05	-40 9 45
	Inferior	R	32	3.87	49 36 -9
Parieto-temporal	Angular	R	478 *	6.06	40 -72 36
	Middle temporal			4.66	55 -51 18
	Angular	L	632 *	5.31	-44 -57 33
Occipito-parietal	Middle occipital			4.86	-40 -72 30
	Precuneus	R	1529 *	5.42	4 -68 48
	Precuneus	L		5.08	-9 -51 36
	Cuneus	R		4.78	4 -78 39
	Cuneus	L		4.61	-4 -91 21
Temporal	Middle	L	47	3.97	-65 -32 -9
Within-domain Concurrent Task > Cross-domain					
No suprathreshold cluster					
Cross-domain Concurrent Task > Within-domain					
Occipital	Calcarine	R	92	3.9	4 -89 12
Temporal	Inferior	L	22 *	4.05	-51 -48 -6
Retrieval after within-domain > Retrieval after cross-domain concurrent task					

Occipital	Fusiform	R	831 *	6.43	30 -76 -9
	Cuneus			5.44	13 -97 6
	Lingual			4.77	13 -80 -9
	Fusiform	L	701 *	6.03	-23 -80 -12
	Inferior			3.64	-40 -80 -9
	Calcarine	L	67 *	5.34	-2 -91 -9
	Middle	L	28 *	4.14	-40 -82 15
Retrieval after cross-domain > Retrieval after within-domain concurrent task					
Frontal	Medial	R	150	4.03	8 15 48
	Posterior-medial	L		3.41	0 9 57

Coordinates are given in MNI space. x, y, z coordinates refer to voxels with highest statistical significance within a cluster (location of peak coordinate). Analyses conducted with and without covariates (i.e., IQ scores, Digit Span Backwards scores, sex and handedness) showed very similar pattern of activations but at a much smaller threshold in general when the covariates were added to the model. Therefore, clusters reaching the significant threshold of $p<0.001$, and a minimum extent threshold of 20 voxels when the covariates were added to the model, are marked with a sign *.

Table 15. Between group comparisons for encoding, concurrent tasks and retrieval using an inclusive contrast mask for each group.

Region		**Hemisphere**	**Number of voxels**	**t value**	**x,y,z**
Encoding > Retrieval					
TD group					
Occipital	Lingual	L	504*	6.51	-19 -87 -12
	Inferior			6.25	-21 -89 -3
	Lingual	R	29	4.13	23 -84 -12
	Middle	R	21	3.76	30 -67 30
AgCC group					
Occipital	Calcarine	R	143 *	5.28	8 -91 6
Frontal	Inferior	R	149*	4.4	53 13 6
	Inferior	R		4.31	51 19 0
	Inferior	R	27	3.51	34 28 3
Temporal	Superior	R	31 *	3.93	61 -21 15
Retrieval > Encoding					
TD group					
Frontal	Inferior	R	159 *	4.4	53 13 6
	Inferior	R		4.31	51 19 0
Temporal	Rolandic Operculum	R	109	3.97	53 -27 21
	Superior	R		3.93	61 -21 15
	Middle	R	69	3.96	61 -36 6
	Middle	R	24 *	3.69	57 -19 -6
Parietal	Supramarginal	L	48 *	3.7	-57 -49 24
Occipital	Calcarine	R	105 *	5.28	8 -91 6
AgCC group					
Parietal	Posterior cingulate	L	66	3.84	0 -38 33
Within-domain concurrent task > Cross-domain					
TD group					
Frontal	Anterior cingulate	L	56	3.94	-8 21 27
AgCC group					
Occipital	Fusiform	R	78	5.05	32 -78 -12
Frontal	Superior medial	L	53	4.57	-8 63 12
		R	36	3.98	10 61 12
	Inferior	R	23	3.62	46 32 15
Temporal	Middle	L	26	4.4	-61 -25 -18
Cross-domain concurrent task > Within-domain					

TD group					
Occipital	Fusiform	R	306 *	5.05	32 -78 -12
	Inferior Occipital	R		4.56	38 -86 -15
Frontal	Superior Medial	L	39	4.57	-8 63 12
Temporal	Middle	L	32	4.4	-61 -25 -18
Limbic	Putamen	L	27	4	-28 -10 3
AgCC group					
Frontal	Anterior cingulate	L	45	3.94	-8 21 27
Retrieval following within-domain > Retrieval following cross-domain concurrent task					
TD group					
Occipito-temporal	Middle occipital	R	698 *	7.06	30 -86 9
	Inferior temporal			4.98	48 -53 -12
	Fusiform			4.3	30 -49 -15
	Middle occipital	L	86	4.43	-23 -93 3
Frontal	Inferior	R	64 *	4.12	49 40 6
AgCC group					
Occipital	Calcarine	R	168 *	5.95	6 -91 3
Parietal	Precuneus	L	22	3.8	0 -49 60
Retrieval following cross-domain > Retrieval following within-domain concurrent task					
TD group					
Occipital	Calcarine	R	97 *	5.95	6 -91 3
Parietal	Precuneus	L	38 *	3.8	0 -49 60
AgCC group					
Frontal	Inferior	R	82 *	4.12	49 40 6
	Anterior cingulate	L	30	3.67	-15 17 33
		R	37	3.48	2 25 30

Coordinates are given in MNI space. x, y, z coordinates refer to the voxels with highest statistical significance within a cluster (location of the peak coordinate). Analyses conducted with and without covariates (i.e., IQ scores, Digit Span Backwards scores, sex and handedness) showed very similar pattern of activations but at a much smaller threshold in general when the covariates were added to the model. Therefore, clusters reaching the significant threshold of $p<0.001$, and a minimum extent threshold of 20 voxels when the covariates were added to the model, are marked with a sign *.

7.6. Discussion

This study aimed to investigate the functional organisation of WM in children with AgCC using fMRI. The few previous functional imaging studies in individuals with AgCC have largely focused on activations in response to simple motor (Lum et al., 2011) or sensory stimuli (e.g., Duquette et al., 2008; Paiement et al., 2010), language lateralisation (e.g., Pelletier et al., 2011) or emotionally laden information (Lungu and Stip, 2012). To our knowledge, this is the first study to explore brain activity related to WM in this population. Understanding WM functioning in children with AgCC is crucial as WM might be an important contributor to difficulties in everyday activities, including academic achievement (e.g., Alloway et al., 2009; Gathercole et al., 2004).

Although children with AgCC have a major abnormality of early brain development, they recruited globally similar regions as our comparison group of TD children during both the encoding and retrieval phases of our verbal WM paradigm. Nevertheless, group differences in

activation patterns were observed. These findings did not depend on the fMRI task performance, IQ or WM scores in either of the AgCC or TD groups, or handedness and extent of agenesis (complete or partial) in children with AgCC.

Verbal encoding and retrieval

During verbal encoding compared to retrieval, both AgCC and TD children recruited widespread visual areas bilaterally, consistent with their role in perceptual shape analysis, including those involved in letter processing (Flowers et al., 2004; Garrett et al., 2000). There were, however, group differences in the pattern of occipital regions, with larger right-lateralised increased activations in children with AgCC but greater left-lateralised activations in the TD group. These differences presumably reflect less visual word form than letter specific processing in AgCC compared to TD children, conversely to the typical lateralisation of the "visual word form area" (L. Cohen et al., 2000). This might point to differential hemispheric dominance patterns in visual cortical areas in AgCC, subsequent to atypical interhemispheric interactions. In addition to occipital activations, both groups recruited large bilateral frontal areas during encoding (anterior cingulate, ventrolateral, and precentral). These findings corroborate previous results showing involvement of these regions during encoding and maintenance of different kinds of information in WM and long-term memory (Axmacher, Haupt, Cohen, Elger, & Fell, 2009; Chein & Fiez, 2001; Rastle et al., 2002).

During retrieval compared to encoding, activations were observed in AgCC as well as the TD children in extensive bilateral fronto- and parieto-temporal regions. These findings are consistent with previous studies showing involvement of frontal-parietal regions (dorsolateral prefrontal, anterior cingulate, and parietal angular regions) in attention and executive control systems during WM, especially during retrieval of information (Crone et al., 2006; Marshuetz et al., 2000; M. Osaka et al., 2007). Group differences were observed, however, in the extent of these activations, with reduced right-lateralised activations in lateral prefrontal and temporal areas for children with AgCC compared to TD children. In heathy individuals, recruitment of ventrolateral prefrontal regions is commonly associated with the active retrieval of information (Petrides, Alivisatos, & Frey, 2002; Wager, Spicer, Insler, & Smith, 2014). Right-predominant activation observed in our comparison group of TD children during retrieval is also consistent with the Hemispheric Asymmetry Encoding-Retrieval (HERA) model (Habib, Nyberg, & Tulving, 2003; Nyberg, Cabeza, & Tulving, 1996). Such

hemispheric specialisation might be less present in AgCC children. The AgCC group also differentially activated the left posterior cingulate cortex during retrieval, a region recognised to play a central role in episodic memory retrieval and monitoring task outcome (Heilbronner & Platt, 2013; Leech & Sharp, 2014). In contrast, the TD group differentially recruited the left-lateralised supramarginal region, implicated in language processing (Hartwigsen et al., 2010; Stoeckel, Gough, Watkins, & Devlin, 2009), indicating that they could more efficiently recruit regions specialised in the retrieval of verbal information. This could possibly reflect the use of different retrieval strategies in the two groups.

Together, our findings highlight important similarities in brain activation for children with AgCC and their TD peers, with bilateral occipito-frontal activity during verbal encoding, and involvement of bilateral fronto-parietal executive control network during retrieval. Nevertheless, group differences in activation patterns were observed that presumably reflect different hemispheric lateralisation as well as different cognitive strategies to encode and retrieve verbal information. Overall, children with AgCC seemed less able to engage lateralised brain systems specialised for particular memory material (e.g. verbal) and particular memory process (encoding and retrieval) compared to their TD peers.

Consequences of the nature of the concurrent tasks on maintenance and retrieval

We investigated the impact of the nature of the concurrent tasks (verbal versus visual) on maintenance and retrieval of verbal information. According to the influential model of Baddeley (Baddeley, 1986; Baddeley et al., 2011; Baddeley & Hitch, 1974), maintenance of information involves separate and domain-specific systems: a phonological loop for verbal information and a visuospatial sketchpad for visuospatial information. Thus, processing irrelevant verbal information should produce greater interference on verbal maintenance because verbal processing would mobilise the phonological loop, thus impeding the rehearsal process in charge of verbal maintenance. In contrast, processing visuospatial information should involve the visuospatial sketchpad and thus have a reduced effect on verbal maintenance and retrieval. For retrieval performance, our behavioural results did not identify any difference between the within- and cross-domain conditions or between the AgCC and TD groups. Nevertheless, weaker within-domain concurrent task performance (lexical decision) was observed in children with AgCC, suggesting that they were less able to deal

with verbal material or resist competition between the verbal encoded items and verbal concurrent items.

During the maintenance interval for the within-domain concurrent task, there was no evidence of similarities in regions activation for the AgCC and TD groups, suggesting different processing of verbal material during maintenance. For the cross-domain concurrent task, only small bilateral occipital clusters were commonly activated in the two groups, in line with the visual shape processing demands of this condition (face decision task). Moreover, differences in processing concurrent stimuli during maintenance were reflected by distinct activation patterns in right extrastriate visual areas and anterior cingulate cortex.

A region in the right fusiform area showed greater activation during the word lexical decision task in children with AgCC, while in the TD children greater activation was observed in this region during the face decision task, as typically reported in healthy populations (Minnebusch et al., 2009). This again suggests atypical hemispheric lateralisation of word and face processing in AgCC individuals (as also observed during the encoding period). Anterior cingulate responses further pointed to a different impact of verbal and visual interference during maintenance in the AgCC compared with TD children. Children with AgCC demonstrated increased activations in this region during the cross-domain concurrent task. Conversely, in TD children, we observed greater recruitment of this region during within-domain concurrence, in accordance with higher conflict for processing resources in this condition and its well-known role in the management of conflict and competition for cognitive resources (Badre & Wagner, 2004; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001). It is possible that children with AgCC present differential susceptibility to interference.

In keeping with these differences in brain activity during the maintenance interval, activity during retrieval was also influenced by the nature of the preceding concurrent task. Retrieval following within-domain concurrent task (verbal) elicited large bilateral occipital activations in AgCC as well as TD children. These results suggest greater reliance on visual information when retrieval of letters takes place after distraction by verbal material (i.e., within-domain concurrent task). In contrast, retrieval after cross-domain interference (visual) elicited medial frontal activations in AgCC as well as TD children, consistent with a role of this region in decision and response selection processes (Harrington, Zimbelman, Hinton, & Rao, 2010). Furthermore, retrieval periods after within- and cross-domain interference showed group

difference in activations in the right dorsolateral prefrontal cortex. This region, implicated in executive control and WM (Ciesielski et al., 2006), was more strongly recruited in children with AgCC during retrieval after the cross-domain task; whereas TD children recruited this region more during retrieval after the within-domain concurrent task (i.e., condition with higher competition for resources), presumably reflecting different degrees of conflict produced by verbal and visual material during maintenance in AgCC and TD groups. Right prefrontal activation in the TD group corroborates expectation of the model of Baddeley (Baddeley, 1996a), i.e., increased executive control in the context of high competition for resources when a verbal concurrent task interferes with to-be remembered verbal items. This was not the case in children with AgCC, which might reflect the use of different cognitive strategies in this group, and possibly less segregated processing of verbal and visual material during the concurrent task, leading to distinct patterns of activation in executive regions during retrieval. This interpretation also accords with our finding of larger and right-predominant occipital activations in TD children after the cross-domain concurrent task, presumably reflecting more efficient retrieval of encoded information due to weaker processing competition with the concurrent tasks in the maintenance interval.

In summary, children with AgCC demonstrated similar activation to TD children in primary occipital areas during the cross-domain concurrent task and retrieval after within-domain concurrent task. However significant group differences in activation patterns were observed in associative visual areas and executive prefrontal regions, which might reflect different susceptibility to interference by the concurrent tasks and different cognitive strategies engaged to cope with competition in processing resources for AgCC compared with TD children. These differences could reflect different degrees of hemispheric lateralisation with AgCC children who seemed less able to recruit specialised brain systems during maintenance and thus differentially resist to verbal and visual interference during WM.

Potential study limitations

A limitation of our fMRI study is the relatively small sample of children with AgCC. Nevertheless, functional neuroimaging studies in this population are sparse, and their sample size is usually smaller than in the present study and include a much wider age range of participants (e.g., Lum et al., 2011; Quigley et al., 2003; Riecker et al., 2007) . Increasing the sample size would allow a more systematic and representative comparison of AgCC with TD

children, which would require a multi-centre approach. Another challenge in studying this brain malformation is the high heterogeneity of both clinical and anatomical presentations. A larger sample size would thus also allow for more thorough examination of the role of specific factors within the AgCC population, such as complete versus partial agenesis, as well as more thorough investigation of the potential impact of additional neuroanatomical and genetics factors. As extra-callosal anomalies are frequent, if not systematic, in AgCC (e.g. large ventricles or cingulate gyrus alteration), these might contribute to group differences not only in brain activation patterns but also in cognitive outcomes. Again, a larger sample size might help to disentangle these factors more clearly. Another possible limitation concerns the interpretation of localisation of functional activations in the AgCC group. First, a customised anatomical brain template was created using DARTEL, but, again, a bigger sample size might allow for a more representative and reliable template. Second, even though activation sites seen on each individual's anatomy showed high consistency with the anatomical localisation of functional activations observed at the group level, group differences in anatomo-functional organisation cannot be completely excluded, especially for areas around the midline such as the anterior cingulate cortex. From a clinical perspective, the inherent heterogeneity in our sample of AgCC children is an important advantage of our study because it gives a representative picture of the AgCC population, including higher and lower functioning individuals rather than focusing on isolated AgCC as most previous studies have.

Conclusion and implications

Our study reveals globally similar regions of activation for AgCC and TD children demonstrating that the functional brain architecture may develop in a relatively typical way despite the absence or partial absence of the corpus callosum. To some extent, many areas in visual and fronto-parietal networks were found to exhibit normal functional specificity during our WM task, independent of callosal agenesis. Alternative neural pathways for intra-hemispheric and/or inter-hemispheric transfer might compensate for the developmental absence of the corpus callosum. Interestingly, however, differences in activations were observed that suggest the use of different cognitive strategies during WM tasks in AgCC and TD children, with different degrees of hemispheric lateralisation during the processing of concurrent material and distinctive patterns of brain activity during subsequent retrieval. These differences in brain activation patterns for AgCC and TD children were found despite similar retrieval performance overall. Our results will need to be confirmed and extended with

further behavioural and neuroimaging testing, but give novel insight into possible ways to promote and improve WM capacity in children with AgCC. Considering the crucial role of WM in cognitive development, more effective implementation of targeted WM interventions could enhance the everyday functioning of individuals with AgCC. In addition, beyond WM, other cognitive functions might be differentially susceptible to functional integration of information and processing competition in widespread networks across the two hemispheres, and therefore more sensitive to absence of the corpus callosum, such as social or mathematics abilities.

In conclusion, individuals with AgCC and other early brain malformations present an exceptional opportunity to study the capacity and limits of brain plasticity and compensation mechanisms during development. This study provides a first step towards better understanding functional brain systems underlying higher cognitive functions in children with AgCC (apart from language functions). We report a WM paradigm that children with AgCC could successfully complete in the scanner, with overall performance controlled to be comparable to TD individuals across a wide age range. We showed that AgCC children recruit globally similar brain regions as their TD peers during encoding and retrieval periods of a WM task, despite marked differences in brain development. Our findings also highlight notable differences in brain activation patterns for AgCC compared TD children that might reflect different cognitive and executive strategies during the WM task, which are likely to be associated with different hemispheric lateralisation of memory material and processes. These activation patterns were stable across children with complete and partial agenesis, left and right handed children with AgCC, as well as stable across differences in behavioural WM performance and IQ in both groups, Further studies are needed to better understand how functional and structural connectivity may contribute to determine to brain plasticity in this atypically developing brain condition, and how these factors contribute to cognitive abilities and daily functioning during childhood and adolescence.

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CHAPTER 8: Discussion

The general purpose of this work was to investigate the impact of the brain malformation named agenesis of the corpus callosum (AgCC) on neurobehavioural outcomes and functional brain organisation during childhood and adolescence. Chapters 1 and 2 highlighted important limitations in our understanding of the neurobehavioural consequences of this common brain malformation. These limitations are not only due to the high heterogeneity of this condition, but also due to methodological weaknesses, including the small size of clinical samples, the lack of important medical information or recruitment procedure reported in the current literature. Additionally, neuroimaging studies in AgCC are very rare. In this thesis, we tried to address these limitations in order to provide a better understanding of neurobehavioural outcomes, as well as an insight onto functional brain organisation in school-age children with AgCC.

The first aim of this thesis was to describe the impact of AgCC on neurobehavioural functioning, especially WM functions, in school-age children. The role of age, social and neurological factors that might contribute to understand neurobehavioural outcomes in children with AgCC was also investigated. The second aim was to explore the functional organisation of WM in school-age children with AgCC using fMRI.

8.1. Summary of Results

Neurobehavioural outcomes in children and adolescents with agenesis of the corpus callosum

To my knowledge, this is the first study to provide a comprehensive description of neurobehavioural outcomes in a large cohort of school-age children with AgCC (n=28) and to give new insight on the association of neurobehavioural outcomes with age, social risk (providing an estimate of family and socio-economical risks) and neurological factors (Chapter 5, Studies 1 and 2).

Overall, neurobehavioural functioning in our cohort of school-age children with AgCC was below normative test expectations. Specifically, general intellectual functioning was in the borderline range and more than one standard deviation below the normative test mean for the general population. As often reported in the literature (Siffredi et al., 2013), there was an important variability within our paediatric cohort, with Full-Scale IQs ranging from extremely low to superior. The distribution for both Verbal and Performance IQs were skewed toward the lower end. In our cohort, Performance IQ was in the low average range, with 40% of children with AgCC performing in the average range or above, while Verbal IQ was in the borderline range, with only 30% performing in the average range, and significantly poorer than Performance IQ. This difference between Performance and Verbal IQ in AgCC has not been previously reported and might reflect the heterogeneity of the population (e.g., Caillé et al., 1999; Hines et al., 2002; D'Antonio et al., 2016) . We observed little evidence for the role of age, social risk and neurological factors in understanding the variability in general intellectual abilities. In line with the low general intellectual functioning in our cohort and previous child and adolescent AgCC studies (Siffredi et al., 2013), we observed high rates of parent reporting developmental delays, with 32% experiencing speech delay and 46% motor delay.

For academic functions, reading and spelling in our cohort was in the low average range, with about half of the children performing in the average range or above. In contrast, mathematics, which was in the borderline range, was identified as an academic domain of particular concern in our AgCC cohort. This finding is in line with previous case studies of children and adults with AgCC (W. S. Brown et al., 1999; Lamonica et al., 2009; Panos et al., 2001; Stickles et al., 2002). Without considering the role of WM, additional CNS anomalies as well as higher social risk, providing an estimate of environment and socio-economical risk, were associated with lower mathematics performance. In typically developing children, an "income gap" in mathematics achievement has been well documented, with children from low-income families performing significantly poorer than children from higher-income families (Jordan & Levine, 2009). In regards to schooling in our cohort, we observed more children attending mainstream school in earlier school levels, and an increased number of children (almost half of them) attending special developmental school in later school levels. It means that a significant number of children with AgCC are dropping off from mainstream school as the difficutly increases. It is important to note, however, that approximately half of the cohort was

reported by parents as performing at an average level at least in mainstream school (with or without the support of additional tutoring or aid).

Executive functioning in daily life in our AgCC cohort was between one and two standard deviations below the average normative test score for the general population. Parent ratings suggested children with AgCC had better metacognitive skills than behavioural regulation skills. Furthermore, higher social risk and complete AgCC were associated with lower parent ratings of executive functioning. The association between high social risk and low executive functioning has been documented in typically developing children (e.g., Farah et al., 2006; Sarsour et al., 2011). However, it is important to interpret these findings with caution as they have not been replicated using teacher ratings.

Behavioural and social functioning in children with AgCC were below normative expectations based on parent and teacher ratings. Consistent with findings in typically developing children (Cabaj, McDonald, & Tough, 2014), higher social risk in children with AgCC was associated with increased behavioural and emotional difficulties based on parent ratings. Additionally, parents and teachers rated more than half of our cohort as having mild to severe autistic symptoms, consistent with the overlap between AgCC and ASD discussed in the literature (Booth et al., 2011; Paul et al., 2014).

In our AgCC cohort, WM ability was in the borderline range, with half of the children performing in the average range or above. However, evaluation of WM in daily life by parent and teacher ratings were both in the clinical range and more than one standard deviation below the normative test mean. Parents and teachers reported a high number of children showing mild to severe WM difficulties in daily life (from 65 to 86%). Poorer WM scores were associated with the presence of additional CNS anomalies in children with AgCC. We also found that WM seems to play a role in academic outcomes, in particular for reading and mathematical abilities, and this persisted after accounting for age, social risk and neurological factors. This is in line with the large literature in typically developing children, as well as in developmental disorders reporting a predictive effect of WM abilities on academic performance (e.g., Gathercole & Pickering, 2000; Gathercole, Pickering, Ambridge, & Wearing, 2004; Lepine, Barrouillet, & Camos, 2005; Passolunghi & Siegel, 2001; Swanson & Beebe-Frankenberger, 2004; Gathercole & Alloway, 2006).

To summarise, in our cohort of school-age children with AgCC, general intellectual, academic, executive, behavioural and social functioning, as well as WM ability, were below normative test expectations. We observed important variability in functioning, with around 20% of children performing in the average range or above across all neurobehavioural domains investigated, except for WM with up to 55% performing in the average range based on face-to-face testing. WM played a role in understanding children's academic performance, in particular mathematics and reading skills. Additionally, social risk, providing an estimate of family and socio-economical risks, played an important role in understanding executive, behavioural and mathematical functioning. We identified neurological factors associated with WM, academic and executive outcomes, specifically additional CNS anomalies associated with WM and mathematical abilities as well as the degree of AgCC associated with executive functioning in daily life. Taken together, our results highlighted that there is no unique and clear neuropsychological profile of AgCC in childhood, but instead different neuropsychological profiles associated with individual cognitive, social and neurological factors that impact on functional outcomes.

Functional brain organisation of working memory in children and adolescents with agenesis of the corpus callosum

A challenge in using functional MRI in developmental samples and even more with clinical populations is that activation patterns can be influenced by both participant age and task performance. At concern is whether changes in neural activity reflect changes in functional maturation of the CNS, independently of task efficiency, or whether they reflect changes in task performance (Kwon et al., 2002; Schweinsburg et al., 2005). Our goal was therefore to design a paradigm that is demanding on WM capacity but also simple enough to be administered across different developmental stages, as well as potentially suitable for both healthy and clinical paediatric populations (e.g., populations with mild intellectual difficulties). To this aim, we designed a WM fMRI paradigm inspired from the classical Brown-Petterson paradigm (Chapter 6, Study 3; Peterson & Peterson, 1959) . Our findings showed activations in occipital and ventral temporal lobes during encoding (inferior occipital and fusiform gyri) as well as fronto-parietal activation during retrieval (dorsolateral prefrontal areas, anterior cingulate cortex, inferior parietal lobule). These results converge with those of previous fMRI studies using different WM paradigm including the Steinberg item recognition

task that uses letters (Finn et al., 2010; O'Hare et al., 2008; van den Bosch et al., 2014) and the n-back tasks using letters (Brahmbhatt et al., 2010; Thomason et al., 2009). We also found a differential impact of verbal versus visual concurrent processing during WM maintenance: at retrieval, the former condition evoked greater activations in the visual cortex, as opposed to selective involvement of language-related areas in the temporal cortex in the latter condition. These results are in line with Baddeley and Hitch's model, including the effect of the articulatory suppression (Baddeley, 1996a; Camos et al., 2009; Oberauer et al., 2012). Additionally, since verbal information had to be held in WM, it might have produced stronger interference and greater conflict in resource allocation during the lexical decision task (within-domain concurrent task) than the face decision task (cross-domain concurrent task). The right frontal pole is thought to coordinate an optimal use of cognitive resources and overcome potential impasses (Burgess et al., 2007).The involvement of this region during the verbal concurrent task (Broadman area 10) may reflect this conflict in resource allocation and an increase in cognitive load. These findings were also in line with the TBRS model with the existence of attention-based mechanisms involved in maintaining relevant verbal information when the capacity of the verbal-specific system (comparable to the phonological loop in Baddeley and Hitch's model) is exceeded (Barrouillet et al., 2004; Barrouillet & Camos, 2001; Barrouillet & Gaillard, 2010; Vergauwe et al., 2014). Therefore, our novel paradigm was validated in typically developing children and adolescents from 8 to 16 years of age by successfully identifying distinct brain networks associated with different WM processes, i.e., encoding, maintenance, and retrieval, with differential impact of verbal and visual concurrent processing.

Using the modified Brown-Petterson fMRI paradigm, we, then, compared WM-related activations in children and adolescents with AgCC to their typically developing peers (Chapter 7, Study 4). This study provided a first step towards a better understanding of functional brain organisation underlying higher cognitive functions, in particular WM, in children with AgCC. The findings showed important similarities in brain activations for the two groups. During verbal WM encoding, similar patterns of bilateral occipito-frontal activity were found in the two groups, reflecting the recruitment of occipital regions involved in letter processing on the one hand (Flowers et al., 2004; Garrett et al., 2000) and of frontal regions involved in encoding and maintenance of WM information on the other hand (Axmacher et al., 2009; Chein & Fiez, 2001; Rastle et al., 2002). During retrieval, the two groups similarly showed activations in bilateral fronto-parietal regions (dorsolateral prefrontal, anterior

cingulate and parietal angular regions). These findings corroborated previous studies showing involvement of these regions in attention and executive control systems during WM, especially during retrieval of information (Crone et al., 2006; Marshuetz et al., 2000; M. Osaka et al., 2007). Similar activations were finally observed when investigating the impact of the nature of the concurrent tasks (verbal versus visual) on the retrieval of verbal information. Retrieval following a within-domain concurrent task (verbal interference) resulted in occipital activity; whereas retrieval after a cross-domain concurrent task (visual interference) induced medial frontal activations. These results suggested greater reliance on visual information when verbal retrieval takes place after distraction by verbal material (i.e., within-domain concurrent task); and the involvement of decision making and response selection processes when verbal retrieval takes place after distraction by visual material (i.e., cross-domain concurrent task; Harrington et al., 2010) . These resemblances in activations suggest that some neural processes developed similarly in a brain with and (partially or completely) without a CC.

Nevertheless, we also observed notable differences in activations between the AgCC and the typically developing groups during the WM paradigm.

Firstly, differences in activations seemed to be linked to differences in hemispheric lateralisation. During encoding, compared to typically developing children, children with AgCC appeared to recruit less visual word form than letter-specific processing, with larger right-lateralised increases in the AgCC group and greater left-lateralised activations in the typically developing group. During retrieval, we observed reduced right-lateralised activations in lateral prefrontal and temporal areas for children with AgCC compared to typically developing children. In healthy individuals, recruitment of right ventrolateral prefrontal regions is typically associated with the active retrieval of information (Habib et al., 2003; Nyberg et al., 1996; Petrides et al., 2002; Wager et al., 2014). Additionally, the right fusiform area showed greater activation during the word lexical decision task in children with AgCC (i.e., within-domain concurrent task), while in typically developing children, greater activation was observed in this region during the face decision task (i.e., cross-domain concurrent task), as typically reported in healthy populations (Minnebusch et al., 2009). These findings suggest that there is some atypical lateralisation in children and adolescents with AgCC linked to the recruitment of a specialised brain system for specific memory material.

Secondly, it is possible that difference in activations between the AgCC and the typically developing groups reflect a different susceptibility to concurrent tasks and the use of different

cognitive strategies to cope with competition in processing resources. During the cross-domain concurrent task (face decision task), we previously mentioned the difference of lateralisation observed in associative visual regions with increased left fusiform activations in children with AgCC, while typically developing children showed increased activation in the right fusiform area, as we would expect. These increases in right visual areas could also allow typically developing children to recruit more specialised brain systems during maintenance, and thus differentially resist to verbal and visual interference during WM compared to children with AgCC. Additionally, it seems that this reduction of segregation in processing of verbal and visual material in children with AgCC during the concurrent tasks, leads to distinct patterns of activation in frontal regions during the concurrent task itself and during retrieval. According to the model of Baddeley, we would predict increased activation in executive control regions in the context of high competition for resources when a verbal concurrent task interferes with to-be remembered verbal items (Baddeley, 1996a). As expected, typically developing children showed increased activation in regions implicated in executive control during conditions that imply higher level of conflict for processing resources, i.e., anterior cingulate activations during within-domain interference (Badre & Wagner, 2004; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001) ; and right dorsolateral prefrontal activations during retrieval following within-domain interference (Ciesielski et al., 2006) . However, children with AgCC showed the opposite pattern of activations. They recruited more frontal regions for conditions considered to have lower competition for resources, i.e., anterior cingulate activations during cross-domain interference and right dorsolateral prefrontal activations during retrieval following cross-domain interference.

In summary, globally similar brain regions were recruited in AgCC and typically developing children during a WM task, despite significant disparity in brain development. However, we also highlighted notable differences that might reflect different degrees of hemispheric lateralisation during the task associated with different susceptibility to concurrent tasks.

8.2. Clinical Implications

Our study provides important information for families and clinicians (neonatologists, neurologists, and neuropsychologists) on what to expect from a cognitive point of view in children and adolescents with AgCC. It also supplies novel information about risk factors. On

one hand, children who present with associated CNS anomalies are particularly at risk for WM, mathematical and executive difficulties. Children with complete AgCC are also particularly at risk of executive impairment. On the other hand, it seems that social risk, providing an estimate of environment and socio-economical risk, plays an important role in understanding executive, mathematical and behavioural functioning in children with AgCC. This suggests that it is crucial to provide sufficient social and environmental support to children with AgCC and their families, in order to promote optimal developmental outcomes in this population. This includes providing children and their families with a more supporting social environment through school support and aid, parenting advice and access to tailored interventions according to the child's difficulties, such as psychological, speech or/and occupational interventions. In accordance with findings in typically developing children, WM abilities also played an important role in understanding variability in academic outcomes, especially reading and mathematical skills. It is therefore important to keep in mind that improving WM could facilitate certain academic domains in this population.

Finally, our study confirmed an important overlap between AgCC and ASD, with 55% to 60% of our cohort showing autistic symptoms based on parent and teacher ratings. This is an important aspect to keep in mind for clinicians, as children with AgCC could benefit from socio-behavioural interventions that are primarily designed for children diagnosed with ASD.

8.3. Theoretical Implications

Our neurobehavioural and neuroimaging findings suggest that the brain is capable of major changes and adaptation. During our fMRI WM paradigm, many areas in visual and fronto-parietal networks were found to exhibit somewhat normal functional specificity, independent of callosal agenesis. Neurobehavioural investigation showed that at least 20% and up to 60% of children in our cohort were performing in the average range in at least one neurobehavioural domain. The similarities in brain and neurobehavioural functioning between school-age children diagnosed with AgCC and their typically developing peers demonstrates, first, that the functional brain architecture may develop in a largely typical way despite the complete or partial absence of the CC; and second, the remarkable capacity of the brain for structural and functional plasticity and compensation mechanisms during development. It is possible that subsequent to atypical interhemispheric interactions, alternative neural pathways

for intra-hemispheric and/or inter-hemispheric transfer compensate for the developmental absence of the CC, such as atypical lateralisation observed in our fMRI study.

8.4. Study Limitations

The findings of this thesis should be considered in the context of its limitations. The relatively small sample of children with AgCC could be considered a limitation (Studies 1 and 2, n=29; Study 4, n=9). Nevertheless, behavioural studies (e.g., Paul et al., 1998, n=6; Huber-Okrainec et al., 2005, n=8) and neuroimaging studies (e.g., Lum et al., 2011, n=3; Quigley et al., 2003, n=3; Riecker et al., 2007, n=1) in this population are sparse and sample sizes are typically smaller than in the present study. Moreover, they include a much wider age range of participants, and in some cases, they even include individuals with CC hypoplagia. A few recent studies, however, have made an effort to address some of these concerns and increased the sample size (e.g., Paul et al., 2014, n=26; Hinkley et al., 2016, n=25). Larger sample sizes with a restricted age range and standardised recruitment procedure are likely to require a multi-centric approach and would allow for a more representative comparison of AgCC with typically developing children. It would also enable the investigation of the high heterogeneity in the clinical and anatomical presentation of AgCC population, and of the factors that might contribute to understanding the variability in neurobehavioural outcomes.

Another possible limitation of this study is the representativeness of our paediatric AgCC cohort. Due to our inclusion criterion (i.e., ability to engage in neurobehavioural testing), we acknowledge that our cohort might represent higher functioning children. However, it is also possible that our cohort is biased toward individuals with sufficient clinical need for referral for a brain scan (prenatal diagnosis of AgCC was reported in only 35.7% of the samples in Studies 1 and 2; and 33.3% of the sample in Study 4). The rapid advances in neuroimaging, including ultrasound, and its growing use in obstetric populations, such as routine ultrasound screening, might increase the detection of patients with AgCC during foetal life, including those who are asymptomatic. This may result in research documenting much more detailed but also alternative profiles of neuropsychological functioning in AgCC (Booth et al., 2011; Moutard et al., 2003; Pisani et al., 2006).

A potential limitation of Studies 1 and 2 is the use of a subjective coding system (Leventer et al., 1999) to review MRI scans and to document neurological characteristics, in particular properties of the anterior and posterior commissures. As previously acknowledged (Chapter 1.2), it has been suggested that the anterior and posterior commissures could be involved in compensation mechanisms in individuals with AgCC (Barr and Corballis, 2002; Brown et al., 1999; Fischer et al., 1992; Hannay et al., 2009; Lassonde et al., 1991; Paul et al., 2007), justifying the use of quantitative measures such as volumetric analyses or quality analyses of the fibres crossing these commissures (e.g., white matter fibre microstructure) to explore associations with neurobehavioural outcomes.

Finally, the design of the fMRI WM paradigm used in Studies 3 and 4 could be improved to increase its sensibility to WM abilities. Firstly, the task might show a ceiling effect, suggested by the absence of an effect of the concurrent task (verbal versus visual) on retrieval and the high rates of correct trials. Additional testing could be performed to evaluate whether the threshold we used to administer the paradigm with 2 or 3 letters to remember could be increased in order to make the paradigm more challenging. An additional paradigm with 4 letters or more to remember could also be used. We acknowledge that our fMRI WM paradigm did not test the reverse situation of verbal versus visual concurrent tasks on visual information held in WM, which was due to time constraint. Examining both verbal and visual WM in the presence of verbal and visual interference could provide important information to map more precisely how the different processes subserving verbal and visual WM are influenced by different kinds of concurrent tasks.

8.5. Future Directions

The findings presented in this thesis shed new light on the impact of AgCC on neurobehavioural outcomes and functional brain architecture during childhood and adolescence. However, many important questions remain and future research is necessary. There is a need to precisely document the rates of AgCC and recruit a representative paediatric cohort of AgCC to examine neurobehavioural outcomes. We suggest that this could be achieved through systematic ultrasound screening. In combination with longitudinal follow-up, this approach could map developmental trajectories of neurobehavioural outcomes from birth and across childhood.

Processes underlying this brain malformation could be examined using and integrating techniques from different disciplines.
First, using functional MRI paradigms beyond WM, could help to understand whether different cognitive functions are differentially susceptible to functional integration of information across the two hemispheres. This might be informative if some cognitive functions are more sensitive to the absence of the corpus callosum, such as social or mathematical abilities. Using fMRI to investigate other cognitive functions could contribute to a deeper understanding of brain functional organisation linked to behaviour in this population.

Second, the use of other neuroimaging techniques, such as functional connectivity or quantitative structural measures (e.g., microstructure of white matter fibres), could also provide insight to the neural and structural processes linked to development in the AgCC brain as well as in the typically developing brain. Preliminary analyses are indeed showing a significant increase in the volume of the anterior commissure, but not of the posterior commissure, in children with AgCC compared to their typically developing peers (Siffredi et al., in preparation).

Third, exploring genetic features associated with AgCC in a systematic way could significantly increase our understanding, not only in terms of neural processes linked to this brain malformation but also in terms of association with clinical presentation. A multidisciplinary approach that links behavioural, neuroimaging and genetic methods would bring precious information that could altogether help in understanding the bigger picture in AgCC.

Finally, subtle structural changes and alterations in the CC are frequently noted in various neurodevelopmental and psychiatric disorders, such as ASD (Barnea-Goraly et al., 2004; Hardan et al., 2009) , ADHD (Hynd et al., 1991; Lyoo et al., 1996) , schizophrenia (Swayze et al., 1990), mental retardation (Schaefer & Bodensteiner, 1999), developmental dyslexia (Hynd et al., 1995) and developmental language disorders (Preis et al., 2000). The wide range of disorders in which callosal abnormalities are found also highlights the importance of understanding the nature and function of the CC. AgCC may provide a model for these

neurodevelopmental disorders in terms of both the white matter abnormalities and resulting neurobehavioural impairments.

In conclusion, putting together a multidisciplinary approach and collecting follow-up data in a large-scale cohort starting very early on in life (even prenatally), is without doubt the solution to make a significant step in our understanding of AgCC, as well as to better understand the complex processes that occur in this brain malformation. This would provide very precise and useful clinical information in terms of long term diagnosis and prognosis, risk and protective factors, support and intervention to promote positive outcomes and enhance the quality of life for individuals with AgCC and their families. This would also contribute precious information about the capacity and limits of brain plasticity during development and its underlying genetic and neural processes; as well as the role and involvement of the CC in higher cognitive functions in typically developing individuals and in other neurodevelopmental disorders, such as ASD.

8.6. Conclusions

To our knowledge, our work provides the first comprehensive report of cognitive, behavioural and social consequences of AgCC in school-age children. It also provided new insights on functional brain organisation of higher cognitive function in children and adolescents with AgCC, in particular WM. This is also the largest school-aged group of individual with AgCC that has been studied to date. The present research has several advantages over previous studies in terms of sample size and methodology, such as rigorous recruitment process, characterisation of medical and neuroimaging details, and exploration of functional brainactivity within this atypically developing brain. Finally, this study underlines the amazing capacity of the brain to adapt from a neural but also from a behavioural point of view. It also highlighted the importance of additional CNS abnormalities and environmental factors, specifically social risk factors, during development and for understanding the variability in functional outcomes in school-age children with AgCC. Continued efforts and multidisciplinary researches from large-scale studies are needed to better understand the functional consequences of AgCC, to explain the underlying mechanisms and to improve intervention for at-risk children.

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APPENDICES

***Appendix 1**. Measures used for neuropsychological assessment*

Cognitive Domain	Material
General cognitive functions	- Wechsler Abbreviated Intelligence Scale [WASI] and Wechsler Intelligence Scale for Children, 4th edition [WISC-IV]: assessment of general intellectual abilities. Scores derived are Verbal IQ, Performance IQ, and Full Scaled IQ (Wechsler, 1999, 2003) - Adaptive Behaviour Assessment System [ABAS-2], parent and teacher questionnaire: assessment of adaptive skills in daily life
Short term and working memory	- Digit Span Forward and Backwards from the Wechsler Intelligence Scale for Children [WISC-IV]: Digit Span Forward provides an assessment of verbal short term memory and Digit Span Backwards provides an assessment of verbal working memory (Wechsler, 2003) - Automated Working Memory Assessment, 2nd Edition [AWMA-2]: assessment of working memory skills (Alloway, 2012) Subtests included: Letter Recall (verbal short-term memory), Processing Letter Recall (verbal working memory), Dot Matrix (visuospatial short-term memory), Block Recall (visuospatial short-term memory), Mr. X (visuospatial working memory), Backwards Dot Matrix (visuospatial working memory) - Working Memory Scale from the Behavioural Rating Inventory of Executive Function [BRIEF], parent and teacher questionnaire: assessment of working memory functions in everyday activities at home and at school over the past 6 months (Gioia et al., 2000)
Academic performance	- Wide Range Achievement Test, 4th Edition [WRAT-4]: assessment of word reading, spelling, and mathematics skills (Wilkinson & Robertson, 2006) Subtests included: Reading, Spelling, Math Computation
Executive and attentional functions	Test of Everyday Attention for Children [TEA-Ch]: assessment of different aspects of attentional functioning (Manly, Robertson, Anderson, & Nimmo-Smith, 1999) Subtests included: Sky Search (visual selective attention), Score ! (auditory selective attention), Sky Search DT (divided attention), Score DT (sustained attention), Walk Don't Walk (sustained attention and inhibition) Delis-Kaplan Executive Function System [D-KEFS]: assessment of verbal and nonverbal executive functions (D. Delis et al., 2001) Subtests included: Trail Making Test (cognitive flexibility, shifting attention, processing speed), Verbal Fluency Test (inhibition, flexibility, processing speed), Colour-Word Interference Test (inhibition, cognitive flexibility, processing speed), Tower Test (goal-setting, planning, inhibition) Rey Complex Figure: assessment of different cognitive and executive functions, such as goal setting, visuospatial abilities, memory, attention, planning, working memory (P. Anderson, Anderson, & Garth, 2001; Rey, 1941) - Behavioural Rating Inventory of Executive Function [BRIEF], parent and teacher questionnaire: measure of executive functions in everyday activities at home and at school over the past 6 months (Gioia et al., 2000) Scores derived from questionnaires: Behavioural Regulation Index (BRI) based

	on inhibit, shift and emotional control subscales, Metacognition Index (MCI) based on initiate, working memory, plan/organise, organisation of materials and monitor subscales, Global Executive Composite (GEC) overall executive functioning in daily life
Learning and memory	- California Verbal Learning Test – Children's Version [CVLT-C]: assessment of verbal learning and memory in children and adolescents (D. C. Delis, Kramer, Kaplan, & Ober, 1994) - Children's Memory Scale [CMS]: assessment of visual and visuo-spatial memory and learning in children (M. J. Cohen, 1997) Subtests included: Word Pairs (verbal learning and long term memory), Dot Location (visuo-spatial learning and long term memory)
Social functions	- Social Skills Improvement System Rating Scales [SSIS], parents, teacher and self-report questionnaire: assessment of social functioning (Gresham & Elliott, 2008). It provides a Social Skills scale, based on communication, cooperation, assertion, responsibility, empathy, engagement, and self-control) and a Problem Behaviour scale, based on sub-domains externalising, bullying, hyperactivity/inattention, internalizing, autism spectrum
Behavioural and emotional functions	- Strengths and Difficulties Questionnaire [SDQ], parent and teacher questionnaire: rating of children's behaviour and emotional functioning over the past 6 months (Goodman, 1997). It provides a Total Difficulties Score based on four subscales: Emotional Symptoms, Conduct Symptoms, Hyperactivity- Inattention, Peer Problems - Screen for Child Related Anxiety Disorders [SCARED], parent and self-report questionnaire: used to screen for childhood anxiety disorders (Birmaher et al., 1997)

***Appendix 2**. Demographic measures completed by the primary caregiver*

Domain	Material
Social Risk	Social Risk Index [SRI]: parent questionnaire (Roberts et al., 2008)
Family Functioning	Family Assessment Device [FAD]: parent questionnaire (Epstein, Baldwin, & Bishop, 1983)
Caregiver Functioning	Hospital Anxiety and Depression Scale [HADS]: parent questionnaire (Zigmond & Snaith, 1983)
Schooling	Parent interview (e.g., attendance at a mainstream or special developmental school, repetition of grades, access to an intervention aide, extra tutoring)

Appendix 3. *Structural MRI qualitative coding protocols of: 1) different structures of interest in the brain; and 2) sections of the CC*

ID:	**Date of MRI scan:**
Initial:	
Date of coding:	
Corpus callosum:	
Probst Bundles:	
Posterior commissure:	
Anterior commissure:	
Sylvian fissures:	
Cingulate gyrus:	
Basal Ganglia:	
Hippocampi:	
Pituary Gland:	
Cerebral ventricles:	
White matter volume:	
State of myelination:	
Cerebellar vermis:	
Cerebellar hemisphere:	
Midbrain:	
Pons:	
Medulla:	
Other cortical malformation:	

Regional subdivision of the CC (Witelson, 1989)	**Presence or Absence**	**Comments**
Lamina Rostralis		
Rostrum		
Genu		
Anterior body		
Middle-Anterior body		
Middle-Posterior body		
Posterior body		
Splenium		

Appendix 5. *Reprints of journal articles included in the present thesis.*

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A Neuropsychological Profile for Agenesis of the Corpus Callosum? Cognitive, Academic, Executive, Social, and Behavioral Functioning in School-Age Children

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Abstract

Objectives: Agenesis of the corpus callosum (AgCC), characterized by developmental absence of the corpus callosum, is one of the most common congenital brain malformations. To date, there are limited data on the neuropsychological consequences of AgCC and factors that modulate different outcomes, especially in children. This study aimed to describe general intellectual, academic, executive, social and behavioral functioning in a cohort of school-aged children presenting for clinical services to a hospital and diagnosed with AgCC. The influences of age, social risk and neurological factors were examined. **Methods:** Twenty-eight school-aged children (8 to 17 years) diagnosed with AgCC completed tests of general intelligence (IQ) and academic functioning. Executive, social and behavioral functioning in daily life, and social risk, were estimated from parent and teacher rated questionnaires. MRI findings reviewed by a pediatric neurologist confirmed diagnosis and identified brain characteristics. Clinical details including the presence of epilepsy and diagnosed genetic condition were obtained from medical records. **Results:** In our cohort, ~50% of children experienced general intellectual, academic, executive, social and/or behavioral difficulties and ~20% were functioning at a level comparable to typically developing children. Social risk was important for understanding variability in neuropsychological outcomes. Brain anomalies and complete AgCC were associated with lower mathematics performance and poorer executive functioning. **Conclusions**: This is the first comprehensive report of general intellectual, academic, executive social and behavioral consequences of AgCC in school-aged children. The findings have important clinical implications, suggesting that support to families and targeted intervention could promote positive neuropsychological functioning in children with AgCC who come to clinical attention. (*JINS*, 2018, *24*, 445–455)

Keywords: agenesis of the corpus callosum, congenital brain malformation, neuropsychological outcomes, pediatrics, cognitive functions, socio-behavioral functions

INTRODUCTION

With over 190 million axons, the corpus callosum (CC) is the largest brain white matter pathway and connects homologous structures in the left and right cerebral hemispheres (Paul et al., 2007). Developmental absence of the CC, or agenesis of the corpus callosum (AgCC), is among the most common brain malformations observed in humans, with an estimated prevalence of 1 to 7 per 4000 live births (Glass, Shaw, Ma, & Sherr, 2008). Diagnosis is based on brain imaging including prenatal ultrasound and postnatal neuroimaging and can be complete or partial, see Figure 1. AgCC may occur as an isolated malformation or can be associated with other brain malformations or multiple congenital anomaly

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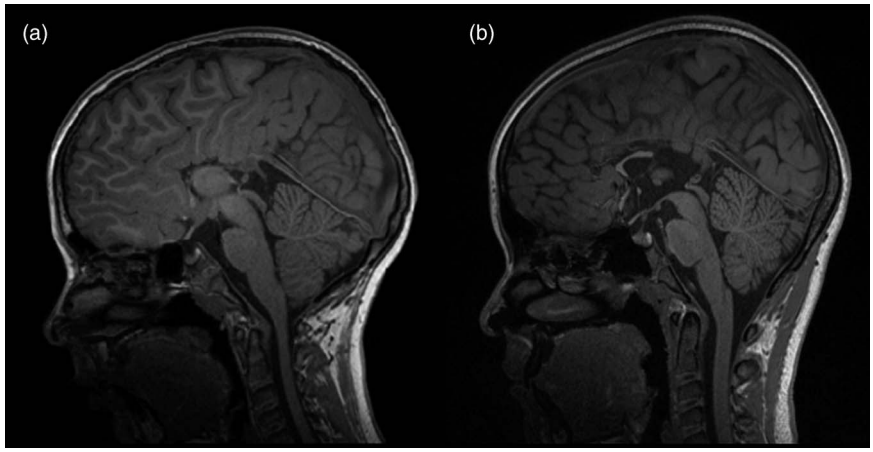

Fig. 1. Postnatal neuroimaging.

syndromes. It can result from environmental, metabolic, or genetic causes (Edwards, Sherr, Barkovich, & Richards, 2014).

Consistent with the variability in presentation and etiology of this brain malformation, previous studies have reported cognitive abilities ranging from "normal," with children attending mainstream school and adults having a conventional career (Caillé et al., 1999), to severe cognitive difficulties, with individuals attending special developmental school and requiring assistance in daily living activities (Graham et al., 2008, 2003). Initial studies of individuals with AgCC reported a pattern of reduced performance across multiple cognitive domains (Chiarello, 1980; Lassonde & Jeeves, 1994; Sauerwein & Lassonde, 1994). However, these study samples collapsed across children and adults, and had specific selection criteria (e.g., IQ > 70). Furthermore, participants were not routinely diagnosed based on MRI scan, which may have impacted diagnostic accuracy (e.g., diagnosis based on CT may lead to hypoplasia being incorrectly diagnosed as AgCC) (Sauerwein & Lassonde, 1994).

In a systematic review of neuropsychological functioning in AgCC, where diagnosis was based on MRI ($n = 110$ patients), intellectual functioning was described to be, on average, in the low average range for adults (IQ: mean = 88.2; $SD = 15.18$; $n = 41$) and significantly lower for children (IQ: mean = 76.4; $SD = 30.12$; $n = 48$; Siffredi, Anderson, Leventer, & Spencer-Smith, 2013). Qualitative examination highlighted that individuals (adults and children) with AgCC are at particular risk of impaired arithmetic skills, with 86% demonstrating impairments. In contrast, executive functions, reading, and spelling skills were relatively preserved. Studies examining social functioning in individuals with AgCC report a range of impairments, such as reduced understanding of jokes and humor (Brown, Paul, Symington, & Dietrich, 2005), proverb and non-literal items (Paul, Van Lancker-Sidtis, Schieffer, Dietrich, & Brown, 2003), complex social scenes (Brown & Paul, 2000; Paul, Schieffer, & Brown, 2004; Turk, Brown, Symington, & Paul, 2010), integration of social information from multiple sources (e.g., paralinguistic cues, nonliteral language; Symington, Paul, Symington, Ono, & Brown, 2010), story-generation skills (Paul et al., 2004), and difficulties experiencing and thinking about complex but not basic emotions in the context of social interactions (Anderson, Paul, & Brown, 2017).

Links between AgCC and autism spectrum disorder (ASD) symptoms have also been examined, but results have been mixed. In a convenience sample of 189 children and adults with AgCC, 8.5% met criteria for ASD diagnosis (*vs.* 1% of their siblings; Doherty, Tu, Schilmoeller, & Schilmoeller, 2006) while in a more recent convenience sample of 26 individuals with AgCC, 8 (30.8%) were reported as having autism symptoms but only 3 of 22 (13.6%) met criteria for an ASD diagnosis (Paul, Corsello, Kennedy, & Adolphs, 2014).

Numerous factors are likely to influence neuropsychological development in children with AgCC, as outlined by Maureen Dennis and colleagues (Dennis, 2000; Dennis, Yeates, Taylor, & Fletcher, 2006) in their developmental framework. Age is important for understanding level of cognitive functioning, and in AgCC better general intellectual function have been observed in adults compared with children (Siffredi et al., 2013). Social factors, including demographic characteristics and family function, can influence a child's neuropsychological development (Hackman & Farah, 2009; Sirin, 2005). Neurological factors should also be considered in understanding neuropsychological outcomes in this atypically developing brain.

In the context of AgCC, some of the neurological factors that might influence outcomes include clinical co-morbidities [e.g., additional central nervous system (CNS) anomalies] or the presence of seizures, and associated genetic conditions (Dennis et al., 2006). Some genetic conditions, such as Aicardi syndrome, are uniformly associated with AgCC, and single gene disorders (e.g., Edwards et al., 2014; Palmer & Mowat, 2014) and multiple chromosomal abnormalities associated with AgCC have also been described (D'Antonio et al., 2016). Recently, the first gene for isolated AgCC, DCC, was identified (Marsh et al., 2017). The genetic etiology may also be polygenic and/or reflect complex genetic interactions (Paul et al., 2007).

Several studies suggest that isolated AgCC appears to carry the best prognosis, with up to 85% of individuals exhibiting average cognitive functioning (Pilu et al., 1993; Vergani et al., 1994). Several potential candidates for compensation have been suggested, in particular enlargement of the anterior and posterior commissures, as well as the degree of AgCC (partial or complete). Enlargement (hyperplasia) of the anterior commissure, found in approximately 10% of individuals with AgCC (Hetts, Sherr, Chao, Gobuty, & Barkovich, 2006; Loeser & Alvord, 1968) and enlargement of posterior commissure might be indicators of CC fibers using these commissures as alternative interhemispheric conduits (Hannay, Dennis, Kramer, Blaser, & Fletcher, 2009). Similarly, the degree of AgCC (complete or partial) could differentially allow white matter fibers to cross the midline, and, therefore, increase the presence of interhemispheric functional connections (Huber-Okrainec, Blaser, & Dennis, 2005).

Currently our understanding of the consequences of AgCC for school-age children on neuropsychological functioning and factors that modulate the consequences of AgCC on these functions is restricted by the inherent problem of small sample studies and conflicting results (Bedeschi et al., 2006; D'Antonio et al., 2016; Moutard et al., 2003; Shevell, 2002). The challenge of studying the high heterogeneity of this population has previously been addressed by focusing on individuals with isolated AgCC only, which does not reflect the AgCC population.

A detailed MR-based study of 82 patients with AgCC showed that it was truly isolated in only 4% of patients, with most having additional brain abnormalities such as cortical malformations (Hetts et al., 2006). Clinicians, therefore, lack the necessary knowledge to provide the families of children with AgCC the information regarding prognosis or optimal intervention targets. This study aimed to describe general intellectual, academic, executive, social and behavioral functioning in a large cohort of school-aged children who presented for clinical services to a hospital and diagnosed with AgCC. The influence of age, social risk and neurological factors on neuropsychological functioning was examined. Patients included both those with isolated AgCC and AgCC associated with other brain malformations. This study represents a first step in providing an understanding of the neuropsychological profile of children with AgCC.

METHOD

Sample

Our AgCC cohort was recruited as part of the "Paediatric Agenesis of the Corpus Callosum Project" at the Murdoch Children's Research Institute in Melbourne, Australia. Twenty-eight participants (85% of those eligible; $n = 33$), aged 8 to 17 years ($M = 11.54$; $SD = 2.35$) were ascertained by review of the radiology database at The Royal Children's Hospital (RCH), see Figure 2 for participant flow. Inclusion criteria were: (1) aged 8.0 to 16.11 years at recruitment between September 2009 and February 2014; (2) evidence of

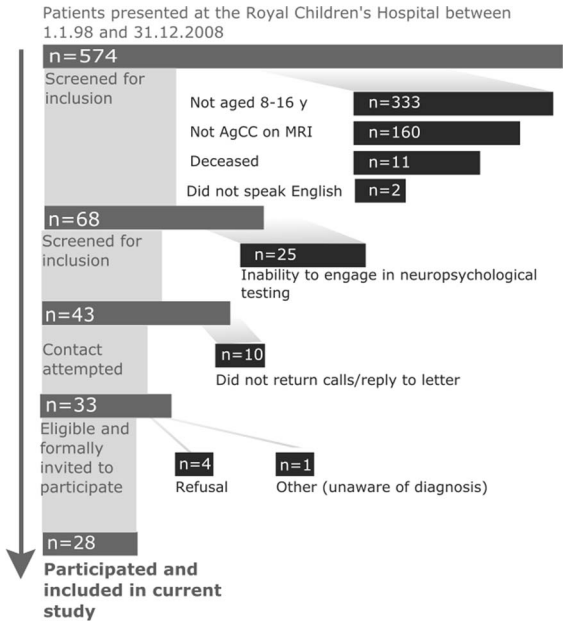

Fig. 2. Participant flow.

AgCC on MRI; (3) English speaking; and (4) ability to engage in neuropsychological testing. Thirty-seven percent of children who were screened for inclusion in the study were excluded due to severe impairment and inability to engage in neuropsychological testing but otherwise met inclusion criteria.

Procedure

The RCH Human Research Ethics Committee approved the study. Caregivers, and when appropriate participants (based on age), provided informed written consent before participation. Participants completed a neuropsychological assessment and MRI, or gave consent to use previous clinical MRI scans. Caregivers and teachers completed questionnaires.

Measures

Neuropsychological functioning

Child testing was conducted by training child psychologists (M.S.S., A.M., V.S. under supervision by V.A.) using standardized tests to estimate: (1) *General intelligence:* Full Scale, Verbal and Performance IQ ($M = 100$; $SD = 15$) were generated from the four subtest version of the Wechsler Abbreviated Intelligence Scale (WASI: Wechsler, 1999; $n = 21$; 75%) or the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV: Wechsler, 2003; $n = 7$; 25%) based on 10 subtests. (2) *Academic functioning:* The Wide Range Achievement Test 4 (WRAT-4: Wilkinson & Robertson, 2006) was administered to estimate: single Word Reading, Spelling and Math Computation ($M = 100$; $SD = 15$).

Parents and teachers completed age standardized questionnaires to estimate: (3) *Executive function in everyday life:* The Behavioral Rating Inventory of Executive Function: parent

form (BRIEF: Gioia, Isquith, Guy, & Kenworthy, 2000) estimates executive abilities in everyday life over the past 6 months. It generates two summary index scales: Behavioral Regulation Index (BRI: based on Inhibit, Shift and Emotional control subscales) and Metacognition Index (MCI: based on Initiate, Working memory, Plan/organize, Organization of materials and Monitor subscales); as well as a Global Executive Composite (GEC) based on both indices. Higher scores reflect increased difficulties in executive functioning (M = 50; *SD* = 10). (4) *Behavior:* Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) generates a Total Difficulties score estimating general behavioral and emotional functioning over the past 6 months (based on the subscales Emotional Symptoms, Conduct Symptoms, Hyperactivity-Inattention and Peer Problems). Australian test norms were used (Mellor, 2005). (5) *Social function:* Social Skills Improvement System (SSIS; Gresham & Elliott, 2008) estimated aspects of social functioning. It generates the Social Skills scale and the Problem Behavior scale, including the Autism Spectrum subscale that estimates ASD behaviors. A higher score on the Social Skills scale indicates better social functioning and a lower score on the Problem Behavior scale indicates better behavioral functioning (M = 100; *SD* = 15).

Risk factors

(1) *Age at testing*. (2) *Social risk*: estimated using the Social Risk Index, a composite score based on information collected from a caregiver questionnaire: family structure, education of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home, and maternal age at birth. Scores range from 0 to 12, with higher scores representing higher socio-economical risk (Roberts et al., 2008). (3) *Neurological factors*: Structural MR images acquired on 3 Tesla Siemens Magnetom Trio Scanner using a 32-channel head coil [repetition time (TR) = 1900 ms; echo time (TE) = 2.71 ms; Inversion time (TI) = 900 ms; flip angle (FA) = 9°, field of view (FoV) = 256 mm, and voxel size = 0.7 × 0.7 × 0.7 mm) were qualitatively reviewed by a pediatric neurologist with expertise in brain malformations (R.J.L.).

A specially modified protocol (Anderson et al., 2009; Leventer et al., 1999) was used to characterize AgCC and associated CNS anomalies: (a) AgCC type: AgCC was classified as partial = a section of the corpus callosum absent, or complete = the entire corpus callosum absent; (b) anterior and posterior commissures: were classified as absent, reduced, normal or enlarged; (c) CNS anomalies: additional to the AgCC were classified as absent or present (excluding common concomitant anatomical changes due to the absence (complete or partial) of the CC such as Probst bundles, cingulate gyrus alteration, and colpocephaly; Booth, Wallace, & Happe, 2011; Lee, Kim, Cho, & Lee, 2004; Paul, 2011; Paul et al., 2007). Based on medical records and parent interview, (d) diagnosed genetic condition: classified as present or absent and (d) seizure disorder: classified as present or absent.

Developmental delay

Caregivers completed a structured interview that elicited information on when the child reached developmental milestones and was used to estimate whether the child had a developmental delay. The child was classified as having a motor delay if they achieved the milestones of rolling after 6 months, crawling after 9 months, and walking after 15 months; and a speech delay if they achieved the milestone of speaking single words after 15 months and speaking sentences of 2 to 3 words after 24 months.

Statistical Analyses

To examine differences between the AgCC group mean scores and test norms, one-sample *t* test or Wilcoxon signed-rank test in the case of violation of normality was used. Mean differences in test scores within each functional domain were examined using paired-sample *t* test or Wilcoxon signed-rank test. Based on previous studies reporting on individuals with AgCC and the developmental framework of Dennis (Dennis, 2000; Dennis et al., 2006), backward hierarchical regressions were used as an exploratory model building method to examine associations between risk factors as predictors and neuropsychological functions as outcomes.

The order in which predictors were entered into the model was guided by Dennis' framework: (1) age at testing; (2) social risk index; and (3) neurological factors, including AgCC type (complete *vs.* partial), size of the anterior and of the posterior commissures (absent, reduced, normal, or enlarged), additional CNS anomalies (present or absent), diagnosed genetic condition, presence of a seizure disorder. The default stepping criteria of $p < .05$ was used for inclusion and for removal of variables in the models. To address type II error, Bonferroni correction for multiple comparisons (Field, 2013) was applied to the resulting regression models: α altered = α original 0.05 / 8 comparisons = 0.006.

RESULTS

Sample Characteristics

Table 1 presents the characteristics of our pediatric AgCC cohort ($n = 28$), which included more males than females. Half of the cohort was right-handed, almost just as many were left-handed, and a small number showed mixed handedness. There were similar proportions of children with complete AgCC ($n = 14$) and partial AgCC ($n = 14$). There were fewer children with isolated AgCC ($n = 11$) and more children with AgCC associated with other CNS anomalies ($n = 17$) in our cohort. Table 1 highlights the heterogeneity in clinical presentation of children with AgCC. The supplementary table provides details of individuals' clinical characteristics.

AgCC Neuropsychological Functioning Compared With Normative Expectations

Children with AgCC achieved poorer scores than the normative test mean on all neuropsychological measures, see

Table 1. Characteristics of the Pediatric Agenesis of the Corpus Callosum Cohort

Total ($n = 28$)		*n*	Percentage
Sex	Female	10	35.7
	Male	18	64.3
Handedness[a]	Right	14	50
	Left	12	42.9
	Mixed	2	7.1
Neurological characteristics			
AgCC type	Complete AgCC	14	50
	Partial AgCC	14	50
CNS anomalies	None	11	39.3
	AgCC associated with other CNS anomalies	17	60.7
Associated conditions	Seizure disorder	4	14.3
	Diagnosed genetic condition	6	21.4
Age at AgCC diagnosis	Prenatal (ultrasound)	10	35.7
	First month of life	4	14.3
	Infancy (before 3 years)	9	32.1
	Early childhood (4 to 6 years)	1	3.6
	Middle childhood (7 to 9 years)	1	3.6
	Late childhood (10 to 12 years)	3	10.7
Developmental delays	Speech delay	9	32.1
	Motor delay	13	46.4
	Information missing	2	7.1
Schooling			
Kindergarten	Mainstream	24	85.7
	Special developmental	3	10.7
	No kindergarten	1	3.6
Primary School	Mainstream	19	67.9
	Special developmental	7	25
	Both mainstream and special developmental	2	7.1
High School (n = 11)	Mainstream	6	54.4
	Special developmental	5	45.5
Educational progress in mainstream school			
Primary school (n = 21)	Remedial classes/tutoring/aid	13	61.9
High school (n = 6)	Remedial classes/tutoring/aid	3	50
Current school level	Achieving average or above	13	61.9
Interventional therapies	Speech	17	60.7
	Occupational	18	64.3
	Psychological	10	35.7

Note. [a]Handedness estimated by the Edinburgh Handedness Inventory (Groen, Whitehouse, Badcock, & Bishop, 2012; Oldfield, 1971). Right-handed = +40 to +100, left-handed = –40 to –100, mixed handed = –40 to +40.
AgCC = agenesis of the corpus callosum; CNS = central nervous system; WASI = Wechsler Abbreviated Intelligence Scale; WISC-IV = Wechsler Intelligence Scale for Children, 4th edition; WRAT-4 = Wide Range Achievement Test 4; BRIEF = Behavioral Rating Inventory of Executive Function; SDQ = Strengths and Difficulties Questionnaire; SSIS = Social Skills Improvement System.

Table 2. For general intellectual functioning, mean scores were in the borderline range for Full-Scale IQ and Verbal IQ, and higher, in the low average range, for Performance IQ. The overall distribution for each IQ indices was skewed toward the lower end of population expectations. The majority of children (46.4 to 66.7%) were categorized with a mild impairment for intellectual functions.

For academic functioning, mean scores were in the borderline range for Math Computation, and the low average range for Word Reading and Spelling. For Word Reading and Spelling, approximately half of the children performed in the average range or above, with impairments in Math Computation more frequent. For executive functioning in daily life, mean parent and teacher ratings on BRIEF indices were in the clinical range, with the exception of the parent rated Behavioral Regulation Index, which was in the borderline range. For behavioral functioning, mean ratings on the SDQ Total Difficulties score (parent and teacher) were above the average range (+1*SD*). For social functioning, mean parent and teacher ratings on the SISS scales were in the low average (parent ratings) to average (teacher ratings) range for the Social Skills scale, and in the average range for the Problem Behaviors scale. Of interest, a significant level of autism spectrum behaviors was reported in more than half of the sample by both parents (61.9%) and teachers (55.6%).

Table 2. Neuropsychological functioning of the pediatric agenesis of the corpus callosum cohort: comparison with normative test means, and impairment rates

	AgCC cohort				One sample t or Wilcoxon signed-rank tests		Percentage impaired		
	n	*M* (*SD*) or Mdn	Normative Test *M* (*SD*)	Mean difference	t (df) or Z	*p*-Value	Average or above	Mild	Moderate to severe
General intellectual functioning (WASI or WISC-IV)									
Full-Scale IQ	27	78.3 (15.21) Mdn = 74	100 (15)	−21.7	Z = 12.5	< .001	18.5	66.7	14.8
Verbal IQ	27	76.37 (13.45)	100 (15)	−23.63	t(26) = −9.13	< .001	29.6	48.2	22.2
Performance IQ	28	84 (18.19)	100 (15)	−16	t(27) = −4.65	< .001	39.3	46.4	14.3
Academic functioning (WRAT-4)									
Word Reading	25	89.04 (20.21)	100 (15)	−10.96	t(24) = −2.71	.012	56	24	20
Spelling	26	83.46 (18.27)	100 (15)	−16.54	t(25) = −4.62	<.001	46.2	30.7	23.1
Math Computation	27	76.04 (13.94)	100 (15)	−23.96	t(26) = −8.93	<.001	25.9	40.8	33.3
Executive functioning in daily life, parent ratings (BRIEF)									
Global Executive Composite	28	68.07 (11.91) Mdn = 65	50 (10)	+18.07	Z = 404	<.001	21.4	50	28.6
Behavior Regulation Index	28	64.82 (14.25) Mdn = 61	50 (10)	+14.82	Z = 343	<.001	42.9	28.5	28.6
Metacognition Index	28	68.29 (10.26)	50 (10)	+18.29	t(27) = 9.4	<.001	17.9	50	32.1
Executive functioning in daily life, teacher ratings (BRIEF)									
Global Executive Composite	17	71.12 (13.6)	50 (10)	+21.12	t(16) = 6.4	<.001	17.6	29.5	52.9
Behavior Regulation Index	17	67.41 (15.67)	50 (10)	+17.41	t(16) = 4.58	<.001	29.4	23.5	47.1
Metacognition Index	17	71.12 (13.39)	50 (10)	+21.12	t(16) = 6.5	<.001	23.5	17.7	58.8
							Average or above		Below average
Behavior, parent ratings (SDQ)									
Total score	25	Mdn = 15	8.2 (6.1)	+6.32	Z = 302	<.001	52		48
Behavior, teacher ratings (SDQ)									
Total score	16	13.25 (7.19)	6.5 (6)	+6.75	t(15) = 3.76	.002	56.3		43.8
Social functioning, parent ratings (SSIS)									
Social Skills	22	86.95 (20.8)	100 (15)	−13.05	t(21) = −2.94	.008	59.1		40.9
Problem Behaviors	22	104 (14.71)	100 (15)	+4	t(21) = 5.32	<.001	31.8		68.2
Autism Spectrum	22						38.1		61.9
Social functioning, teacher ratings (SSIS)									
Social Skills	18	90 (17.67)	100 (15)	−10	t(17) = −2.4	.028	94.4		5.6
Problem Behaviors	18	111 (11.77)	100 (15)	+11	t(17) = 3.97	<.001	66.7		33.3
Autism Spectrum	18						44.4		55.6

Note. Average or above = scores > −1 standard deviation (*SD*) of the test mean, Mild impairment = scores ≤ −1 to <−2 SD, Moderate to severe impairment = scores ≤ −2 SD. The number of cases differs for each outcome as not all informants provided responses for each measure. WASI, WISC-IV, WRAT-4 higher scores reflect better performance. BRIEF and SDQ: lower scores reflect better functioning. SSIS: higher scores on the Social Skills scale indicates better functioning, while lower scores on the Problem Behavior scale indicates better functioning.
WASI = Wechsler Abbreviated Intelligence Scale; WISC-IV = Wechsler Intelligence Scale for Children, 4th edition; WRAT-4 = Wide Range Achievement Test 4; BRIEF = Behavioral Rating Inventory of Executive Function; SDQ = Strengths and Difficulties Questionnaire; SSIS = Social Skills Improvement System.

Pattern of Functioning Within Neuropsychological Domains

There were some significant within group comparisons for select neuropsychological domains examined. For general intellectual functioning, Performance IQ was significantly better than Verbal IQ, $t(26) = 3.245$, $p = .003$. For academic functioning, Word Reading, $t(24) = -5.221$, $p < .001$, and Spelling $t(25) = -3.063$, $p = .005$ were significantly better than Math Computation. For executive functioning in daily life, the parent-rated Behavioral Regulation Index was better than Metacognition Index, $t(27) = -2.093$, $p = .046$.

Risk Factors Associated With Neuropsychological Functioning

Analyses revealed that some risk factors were important predictors for specific aspects of neuropsychological functioning, even after Bonferroni correction ($p < .006$), Table 3. For academic functioning, higher Social Risk Index and complete AgCC were associated with poorer Word Reading scores, together accounting for 36.2% of the variance, while higher Social Risk Index and additional CNS anomalies were associated with poorer Math Computation scores, accounting for 44.2% of the variance. For executive functioning in daily life, higher Social Risk Index, complete AgCC, and older age at testing were associated with poorer parent ratings on the BRIEF Behavior Regulation Index and Global Executive Composite, accounting for 38.6% and 35.4% of the variance, respectively, while higher Social Risk Index was associated with poorer parent ratings on the BRIEF Metacognition Index, accounting for 25.9% of the variance. For behavioral functioning, higher Social Risk Index was associated with poorer parent ratings on SDQ Total Difficulties, accounting for 55.5% of the variance, while additional CNS anomalies were associated with poorer teacher ratings on SDQ Total Difficulties, accounting for 45.3% of variance.

Table 3. Risk factors significantly associated with neuropsychological outcomes in children with AgCC

	Risk factor (predictor)	B	Standard error B	r^2	β	*p*-Value
General intellectual functioning (WASI or WISC-IV)						
Full-Scale IQ	None					
Verbal IQ	None					
Performance IQ	None					
Academic functioning (WRAT-4)						
Word Reading	Social Risk Index*	−5.08	1.9		−.53	.006*
	AgCC type	16.27	6.9	.362	.41	.028
Spelling	Social Risk Index	−3.83	1.43	.221	−.47	.015
Math Computation	Social Risk Index*	−3.48	.97		−.55	.001*
	CNS anomalies	−11.81	4.33	.442	−.41	.012
Executive functioning in daily life, parent ratings (BRIEF)						
Behavior Regulation Index	Social Risk Index*	3.45	.95	.501	.53	.001*
	AgCC type*	−14.221	4.41		−.51	.004*
	Age at testing	2.432	.96		.4	.018
Metacognition Index	Social Risk Index*	2.53	.78	.259	.54	.002*
Global Executive Composite	Social Risk Index*	3.14	.77		.57	< .001*
	AgCC type*	−10.98	3.57		−.47	.005*
	Age at testing	2.1	.77	.534	.41	.012
Executive functioning in daily life, teacher ratings (BRIEF)						
Behavior Regulation Index	Seizure disorder	−22	8.05		−.61	.016
	CNS anomalies	−15.25	7.5	.385	−.46	.061
Metacognition Index	none					
Global Executive Composite	Seizure disorder	−18.5	7.12		−.44	.021
	CNS anomalies	−12.8	6.6	.361	−.6	.074
Behavior, parent ratings (SDQ)						
Total score	Social Risk Index*	2.28	.43	.555	.75	< .001*
Behavior, teacher ratings (SDQ)						
Total score	CNS anomalies*	−10.11	2.97	.453	−.67	.004*
Social functioning, parent ratings (SSIS)						
Social Skills	Social Risk Index	−3.81	1.38		−.434	.013
	Genetic disorder	19.15	7.76		.4	.024
Problem Behaviors	none					
Social functioning, teacher ratings (SSIS)						
Social Skills	CNS anomalies	18.5	7.85	.258	.51	.031
Problem Behaviors	none					

Note. Sex had a significant impact on SSIS parent ratings and therefore sex was entered as a covariate in regression analyses. Risk factors that reached significance at the Bonferroni-corrected level ($p < .006$) are indicated with asterisks. Backward hierarchical regressions examined risk factors as predictors of each outcome, including age at testing, social risk index, AgCC type (complete vs partial), size of the anterior and of the posterior commissures (absent, reduced, normal, or enlarged), additional CNS anomalies, diagnosed genetic condition, and seizure disorder.

AgCC = agenesis of the corpus callosum; CNS = central nervous system; WASI = Wechsler Abbreviated Intelligence Scale; WISC-IV = Wechsler Intelligence Scale for Children, 4th edition; WRAT-4 = Wide Range Achievement Test 4; BRIEF = Behavioral Rating Inventory of Executive Function; SDQ = Strengths and Difficulties Questionnaire; SSIS = Social Skills Improvement System.

DISCUSSION

A major congenital brain malformation such as AgCC demonstrates the remarkable capacity of the brain for structural and functional plasticity during development. Indeed, individuals with AgCC do not exhibit the classic disconnection syndrome observed in "split-brain" patients, where absence of the CC is acquired through surgical resection for the treatment of epilepsy. Consequences of developmental absence of the CC remain imperfectly understood, largely reflecting the inherent problem of small sample studies and the important heterogeneity of this population in terms of neuroimaging profiles (complete or partial, isolated or associated AgCC), etiologies, neuropsychological difficulties, and clinical sequelae (Bedeschi et al., 2006; D'Antonio et al., 2016; Moutard et al., 2003; Shevell, 2002; Siffredi et al., 2017). This study provides the first comprehensive report of general intellectual, academic, executive, behavioral, and social functioning in a cohort of school-age children presenting for clinical services to a hospital and diagnosed with AgCC confirmed on MRI.

Our pediatric cohort performed below normative test expectations across all neuropsychological domains studied. However, it is important to note that, despite major atypical brain development, around 20% performed at the average or above average level of functioning across all domains. Overall, general intellectual functioning in our AgCC cohort was in the borderline range, and more than one standard deviation below the average test mean for the general population. As often reported in previous AgCC studies, we observed a significant variability within our pediatric cohort, with Full-Scale IQ ranging from extremely low to superior. The distributions for both verbal and performance IQs were skewed toward the lower end of the normal distribution.

Consistent with low general intellectual functioning in our cohort and previous child and adolescent AgCC studies (Siffredi et al., 2013), we observed high rates of parent-reported developmental delays, with 32% of children reported to have had speech delay and 46% motor delay. Our results reveal stronger visual-spatial than verbal abilities, a result that is specific to our cohort and might reflect the inherent heterogeneity of AgCC. For academic functioning, mathematical performance was most impaired, falling in the borderline range, with reading and spelling both in the low average range. This is consistent with previous studies showing high rates of mathematical impairment (Siffredi et al., 2013).

In regard to educational placement, more children attended mainstream school in earlier school levels, while in later school levels it was more common for children to attend special developmental school. Almost half of the children attending secondary school were attending special developmental school, while, in contrast, most of the remaining participants were reported by parents as performing at an average level at least in mainstream school (with or without the support of additional tutoring or aid). For executive functioning in daily life, children demonstrated more difficulties in metacognition (e.g., working memory, initiation) than behavioral regulation (e.g., inhibition, emotional control). Significant behavioral and social difficulties were observed in our cohort, consistent with previous studies.

Furthermore, a high rate of ASD symptoms was observed, with more than half of parents and teachers reporting clinical levels of ASD in our cohort (Paul et al., 2014, 2004). Consistent with previous AgCC studies that have reported a higher proportion of left-handers than in the general population, ranging from 24% to 56% (e.g., Chiarello, 1980; Lábadi & Beke, 2017; Sauerwein & Lassonde, 1994), in our AgCC cohort almost half of the children were left-handed. This atypical clinical observation might reflect properties of this brain malformation. It is possible that processes associated with the early development of the corpus callosum and early development of lateralization of hemispheric function in general play a role in determining handedness.

In our cohort of children with AgCC, we found social risk was a key factor in understanding functioning across academic, executive and behavioral domains, but not intellectual or social functioning domains. In typically developing children, the association between high social risk and low achievement in academic functioning, in particular mathematics, as well as low executive and behavioral functioning has been well documented (Farah et al., 2006; Jordan & Levine, 2009; Sarsour et al., 2011). This importance of social risk for understanding variability in functional outcomes for children with AgCC is consistent with Dennis' developmental framework (Dennis, 2000; Dennis et al., 2006) proposing factors likely to influence neuropsychological development.

However, in contrast to this framework, we found little evidence that the child's age at testing or a wide range of neurological factors proposed in the literature to influence neuropsychological functioning, including AgCC type, size of the anterior and posterior commissures, additional CNS anomalies, diagnosed genetic condition or seizure disorder, were consistently associated with functioning across intellectual, academic, executive, behavioral, and social domains. We note, there was some suggestion that the presence of additional CNS anomalies was associated with select aspects of academic, executive, behavior and social functioning, and complete AgCC was associated with aspects of academic and executive functioning. Future studies examining age, social risk and neurological factors associated with neuropsychological functioning in larger samples will be important.

The findings of this study should be considered in the context of its limitations. Due to our inclusion criterion for children to have the ability to engage in testing, we acknowledge that our cohort likely represents higher functioning AgCC children (see Figure 2 for participant flow). However, it is also possible our cohort is biased toward individuals with sufficient clinical need for referral for brain scan (only 35.7% were diagnosed prenatally). Given the rapid advances in neuroimaging, including ultrasound, and its growing use in obstetric populations, increased detection of patients with AgCC during fetal life through routine ultrasound screening, including those who are asymptomatic, may result in research documenting alternative profiles of neuropsychological

functioning to those that exists in the historical literature (Pisani, Bianchi, Piantelli, Gramellini, & Bevilacqua, 2006).

Moreover, we used a subjective method for reviewing MRI scans to describe neurological characteristics, in particular properties of the anterior and posterior commissures that could be involved in compensation mechanisms in individuals with AgCC (Barr & Corballis, 2002; Hannay et al., 2009; Lassonde, Sauerwein, Chicoine, & Geoffroy, 1991). The use of quantitative measures could provide new insights into compensation mechanisms in this population, such as volumetric or quality of the fibers crossing these commissures, to explore associations with neuropsychological outcomes. The use of test norms rather than a local representative comparison group of children, and the small sample of children across a relatively wide age range with a range of varying etiologies and brain abnormalities on MRI are limitations that should be considered. This study provides a broad understanding of neuropsychological functioning in children with AgCC presenting for clinical services, and future studies examining in further detail neuropsychological domains will contribute to a greater understanding of neuropsychological outcomes.

CONCLUSION

To our knowledge, this is the first cohort study to comprehensively report on general intellectual, academic, executive, behavioral, and social consequences of AgCC in school-age children who present for clinical services to a hospital. We showed that while children with AgCC perform below their peers across a range of neuropsychological domains, they demonstrate some relative strengths within domains. Specifically, we identified relative strengths in non-verbal skills, word reading, spelling, and everyday behavioral regulation. Our results do not support a clear and unique neuropsychological phenotype for AgCC in childhood, further highlighting the heterogeneity of this condition. The variability in neuropsychological functioning we observed appears to be differentially associated with individual factors, in particular social risk.

These findings have important clinical implications, suggesting that providing children and their families with a supportive social environment could promote positive neuropsychological outcomes across a range of domains, for example through school support and aid, parenting advice, access to tailored interventions according to the child's individual difficulties such as psychological, speech, or occupational interventions. Further research in a larger cohort of patients with AgCC is needed to better understand the neuropsychological outcomes in this heterogeneous population.

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Supplementary materials

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PLOS ONE

RESEARCH ARTICLE

Examining distinct working memory processes in children and adolescents using fMRI: Results and validation of a modified Brown-Peterson paradigm

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Abstract

Verbal working memory (WM) comprises different processes (encoding, maintenance, retrieval) that are often compromised in brain diseases, but their neural correlates have not yet been examined in childhood and adolescence. To probe WM processes and associated neural correlates in developmental samples, and obtain comparable effects across different ages and populations, we designed an adapted Brown-Peterson task (verbal encoding and retrieval combined with verbal and visual concurrent tasks during maintenance) to implement during functional magnetic resonance imaging (fMRI). In a sample of typically developing children and adolescents (n = 16), aged 8 to 16 years, our paradigm successfully identified distinct patterns of activation for encoding, maintenance, and retrieval. While encoding activated perceptual systems in posterior and ventral visual regions, retrieval activated fronto-parietal regions associated with executive control and attention. We found a different impact of verbal versus visual concurrent processing during WM maintenance: at retrieval, the former condition evoked greater activations in visual cortex, as opposed to selective involvement of language-related areas in left temporal cortex in the latter condition. These results are in accord with WM models, suggesting greater competition for processing resources when retrieval follows within-domain compared with cross-domain interference. This pattern was found regardless of age. Our study provides a novel paradigm to investigate distinct WM brain systems with reliable results across a wide age range in developmental populations, and suitable for participants with different WM capacities.

Introduction

The ability to maintain relevant information in mind in the presence of interference or distracting information is critical for higher cognitive functions required in daily life. Working memory (WM) is the theoretical construct used to refer to this capacity to simultaneously

required prior to release. Only de-identified data will be available.

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maintain and process information over brief periods of time according to current task goals [1–3]. Studies in children and adolescents show that WM capacity plays a crucial role in the development of many cognitive activities (e.g., learning, reasoning, problem solving, language comprehension), and also predicts academic performance and achievement [4–6]. Moreover, WM is impaired in various developmental disorders, e.g. attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) or specific language impairment (SLI), providing a crucial neuropsychological measure in several neuropsychiatric conditions and useful risk marker for cognitive development [7–9].

From a developmental point of view, WM capacity develops rapidly over childhood [10–13]. This is usually measured by the increase in the amount of information that can be retained and transformed using complex memory span tasks that require maintaining information for further recall while performing a concurrent activity [7]. An important component of WM maintenance, involving active verbal rehearsal and attentional refreshing, emerges around 7 years of age [14]. Evidence suggests that multiple mechanisms contribute to childhood development of WM, affecting all the processes involved in encoding, maintenance, and retrieval (e.g., increase in attentional capacity, process automatisation, increase in knowledge, mnemonic strategies, and so forth; see [15]).

In terms of neural substrates, development of WM ability parallels structural changes in frontal-parietal cortices affecting grey matter [16] and white matter [17]. Similar to neuroimaging findings in adult populations, this core network of fronto-parietal brain areas is consistently found to activate in children and adolescents, and is apparent as early as 5 years of age during different verbal and visuospatial tasks thought to evaluate WM functions [18–20]. One recent imaging study compared encoding and retrieval processes in a Sternberg item recognition paradigm with digits in children and adolescents from 9 to 19 years [21]. Encoding of digits activated the right prefrontal and parietal cortex, left motor areas, occipital cortex, and cerebellum; retrieval activated the left prefrontal and parietal cortex, right motor areas, as well as anterior and posterior cingulate cortex, and cerebellum. Other functional neuroimaging studies investigating WM in school-age children have used an n-back task in which a sequence of stimuli is presented to the participant who must indicate when the current stimulus matches the one from *n* steps earlier in the sequence (e.g., [22, 23]). Despite its popularity in fMRI studies, empirical evidence shows that the n-back task correlates weakly with WM span tasks, suggesting that it is unlikely that these two types of tasks reflect a single construct, and questionning the empirical validity of using n-back tasks (continuous-recognition or updating measures) as a WM task [24, 25]. Other tasks, such as the Steinberg item recognition paradigm (e.g., [12, 26]), have also been used to study WM in developmental populations. However, these tasks require the maintenance of information in short-term memory, but not the simulatenous maintenance and manipulation of information as the theorethical construct of WM specifies [3, 27]. Thus, very few developmental studies have explored the neural correlates of WM using tasks requiring not just maintenance, but also active manipulation of information [18, 19]. To our knowledge, brain activity associated with WM processes of maintenance during the simultaneous processing of a concurrent task and retrieval have not yet been studied in developmental fMRI studies.

Previous literature has identified the major challenges inherent in studying both typical and atypical development, including designing tasks that can be administered to individuals across a wide age range in both typical and atypically developing groups [28]. In this study, our aims were to design a novel WM paradigm that: i) is demanding of WM capacity but simple enough to be administered to both children and adolescents and both healthy and clinical paediatric populations (e.g., populations with mild intellectual difficulties), and for which brain activity could not be explained by difference in age or WM performance; ii) would enable investigation

of neural substrates for encoding, maintenance and retrieval WM processes during fMRI; and could identify the effect of different concurrent processing tasks on maintenance and retrieval.

Among the paradigms appropriate for measuring the impact of concurrent processing on maintenance, the Brown-Peterson task is best suited to examine encoding, maintenance, and retrieval processes in WM. The original Brown-Peterson task requires participants to encode and retrieve a string of letters with a concurrent task (i.e., counting backward by three) interposed between encoding and subsequent retrieval [29, 30]. In opposition to the immediate serial recall paradigm, the concurrent task in Brown-Peterson paradigm impairs maintenance and thus retrieval of the encoded information. Here, we designed a novel task inspired from the Brown-Peterson paradigm in which children and adolescents had to maintain verbal information (letters) while performing a concurrent task involving either verbal (lexical decision) or visual (face decision) task appropriate for children and adolescents. This design allowed us to compare not only encoding and retrieval components of verbal WM during fMRI, but also to probe for neural substrates differentially modulated by the concurrent task, both within-domain (i.e. verbal distractors) and cross-domain (i.e. visual distractors). According to the influential model of Baddeley (1986; [31]), verbal and visuo-spatial maintenance and processing involve separate and domain-specific systems, a phonological loop for verbal information and a visuospatial sketchpad for visuospatial information. Thus, processing irrelevant verbal information should produce selective interference with verbal maintenance because verbal processing would mobilize the phonological loop, thus impeding the articulatory rehearsal process in charge of verbal maintenance. By contrast, processing visuospatial information should involve the domain-specific visuospatial sketchpad and should not have any effect on verbal maintenance.

To validate this novel paradigm, we applied it in children and adolescents aged 8 to 16 years. We expected that all would successfully complete our adapted Brown-Peterson fMRI paradigm, which tailors task difficulty to each participant according to their WM capacity. We predicted that distinct activation patterns would be elicited by the two concurrent tasks (i.e. within and cross-domain), not only during the maintenance interval, but also during the subsequent retrieval period. Based on Baddeley's WM model [30], the nature of the concurrent task was expected to differentially impact verbal WM and thus modulate brain areas recruited during retrieval, despite the fact that identical verbal stimuli were encoded. Specifically, exposure to words vs faces during the maintenance interval should hamper vs favour the engagement of language-related regions in the left hemisphere during the subsequent retrieval phase.

Materials and methods

Participants

Participants were 16 healthy children and adolescents aged 8 to 16 years (8 to 10 year-old, n = 5; 11 to 13 year-old, n = 8; 14 to 16 year old, n = 3; mean age = 12.19; SD = 2.25), 9 females and 7 males, recruited though advertisements in local schools and staff at the Royal Children's Hospital. The wide age range of this sample allowed us to examine whether the adapted Brown-Peterson task was suitable for both children and adolescents. No participant had a documented history of a brain lesion, neurological disability or neurodevelopmental disorder such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD). All participants were right-handed as measured by a score between +40 and +100 at the Edinburgh Handedness Inventory [32, 33], English speaking, had a Full Scale Intellectual Quotient (FSIQ) based on the Wechsler Abbreviated Scale of Intelligence (WASI; [34]) higher than 85 (M = 116.2, SD = 10.4) and normal or corrected-to-normal vision and hearing. The study was approved by the Human Research Ethics Committee at the Royal Children's Hospital. Written

informed consent was obtained from the caregivers of the children and adolescents prior to participation.

Material and design

Participants completed an adapted version of the Brown-Peterson paradigm [29, 30] implement during functional magnetic resonance imaging (fMRI). A mixed block and event-related design allowed separate examination of specific WM processes: encoding, maintenance and retrieval. The task required a combination of verbal storage and maintenance during either verbal (within-domain) or visual (cross-domain) concurrent tasks. Each active trial consisted of three active phases (Fig 1):

1) Encoding period.

Participants were presented with a series of single upper-case letters for further recall displayed sequentially in the middle of the screen at a rate of one letter per second. All consonants of the English alphabet were used as memory items except W, which is three-syllabic. Series of two and three letters were created for within-domain and cross-domain blocks in such a way that each letter appeared with the same frequency in both blocks. Participants were asked to maintain the letters in order of appearance.

2) Maintenance delay filled with a concurrent task.

During the maintenance delay of 6 seconds, a concurrent task required to process either verbal

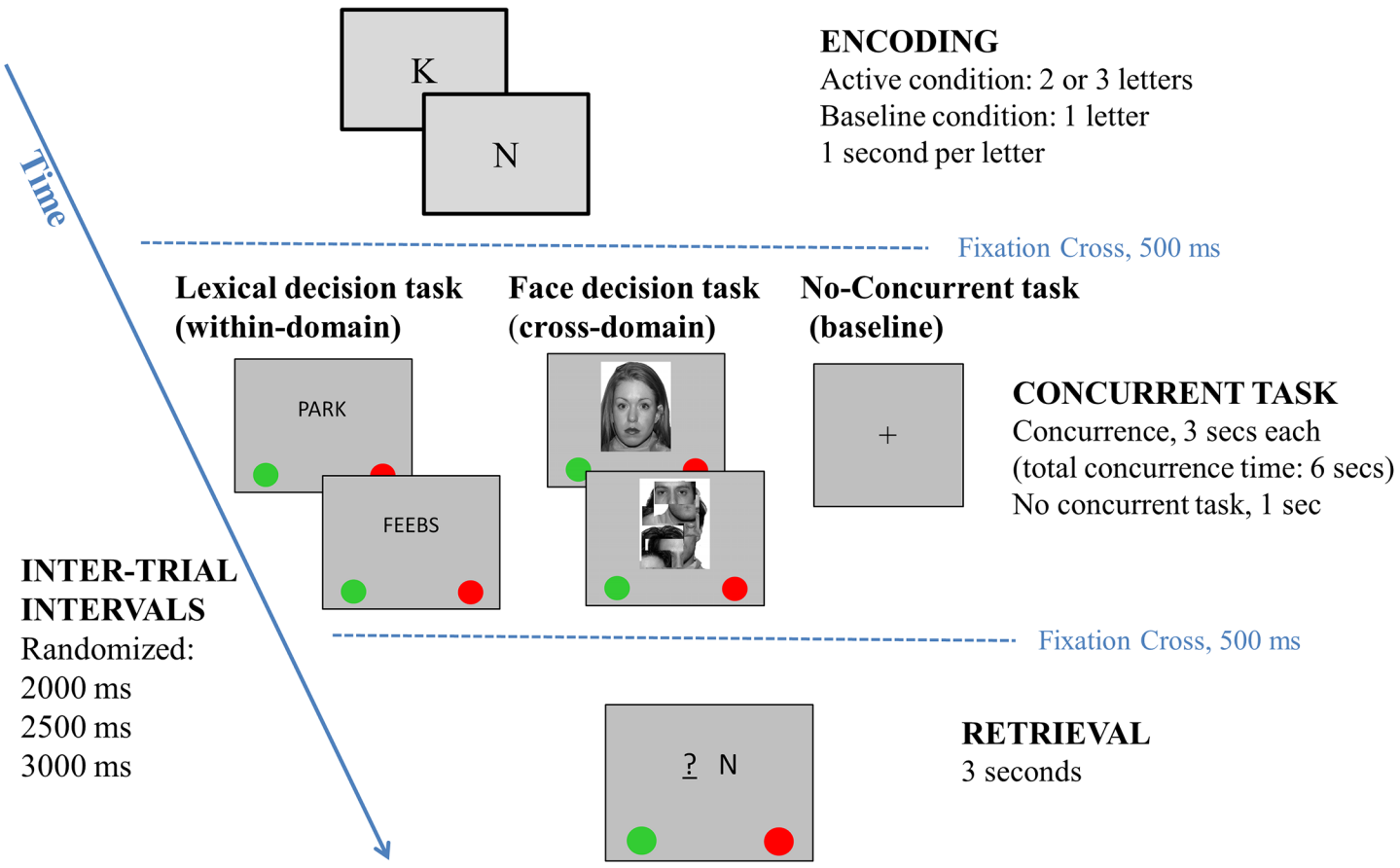

Fig 1. Adapted Brown-Peterson fMRI paradigm using within- and cross-domain concurrent tasks.

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or non-verbal stimuli involving within- or cross-domain interference respectively.
The within-domain concurrent task was a lexical decision task. Two successive letter-strings were presented for 3 seconds each and required simple motor responses (i.e. press as quickly and as accurately as possible the left-most/green button if the letter-string was a word; or the right-most/red one if it was a non-word). Words were selected from the "Oxford Wordlist", which is an Australian database of high frequency words in young children's writing and reading development [35]. Among the 307 most frequently used words, only nouns were selected based on the following search terms: any gender, any location (urban or rural), any socioeconomical status, any text type (e.g., description, discussion, narrative) and appearing during the first three years of school (40% were within 1 to 100 most frequently used words; 35% were within 101 to 200 most frequently used words; 25% were within 201–307 most frequently used words). Non-words with orthographically existing onsets and bodies were selected from the "ACR Nonword database" [36]. Three to eight letter-strings (words and non-words) were displayed centrally on the screen. Words and non-words were equally often presented.
The cross-domain concurrent task was a face decision task. Two successive pictures were presented for 3 seconds each, requiring similar motor responses (i.e. press as quickly and as accurately as possible the left-most/green button if a real face was presented; or the right-most/red one if it was a scrambled face). Ten males and 10 females faces with a neutral expression were selected from the NimStim database [37], and converted into greyscale using Matlab R2013a (The MathWorks, 2012). Scrambled faces were created from the original faces using Matlab (size of square = 300, iterations = 2). Faces and scrambled faces were equally often presented.

3) Retrieval period.
At retrieval, one single upper-case letter was presented along with either one or two placeholders (for paradigm with 2 or 3 letters to remember, respectively) made of dashes with a question mark. Participants had to decide if the single letter matched the letter that was presented in that serial position during the encoding period by giving a simple motor responses, i.e. press as quickly and as accurately as possible the left-most/green button or the right-most/red one for positive and negative responses respectively. This was done to make sure that participants memorised both item and serial order information.

In addition to the active condition, there was a baseline condition (no-concurrent task) in which participants were required to encode a single letter and recognise it after a short empty delay of 1 second. They were instructed to press as quickly and as accurately as possible the left-most/green button if the single letter was the same during encoding and retrieval; or the right-most/red one if it was a different letter.

For both the active and baseline conditions, a randomized inter-trial interval of 2000, 2500, or 3000 milliseconds was presented before the next trial. Three types of blocks of 10 trials each were created: two active blocks, one including the within-domain concurrent task and the other including the cross-domain concurrent task, and a third baseline block. The order of presentation of these three blocks was counterbalanced across participants and repeated twice for a total of six blocks of 10 trials. Within each block, half of the probes were positive (i.e., 5 trials required a "yes" response) and the position of positive and negative probes were randomized within each blocks.

Two important challenges of brain imaging studies examining cognitive development are that differences in both participant age and task performance may influence activation patterns. One concern is whether changes in neural activity reflect changes in functional maturation of the central nervous system, independently of behavioural efficiency, or whether they reflect changes in task performance consequent upon increasing age [22, 38]. For these reasons, in our paradigm, task difficulty was adapted to each participant by adapting the number

of verbal items to remember. Based on pilot testing conducted outside the scanner, participants with a backward digit span of 5 or more were presented with the version of the paradigm with 3 letters to be remembered, and those with a backward digit span lower than 5 were presented with the version of the paradigm with 2 letters to be remember. In our sample, seven participants completed the 3-letters paradigm (age range = 10 to 15 years; M = 12.53; SD = 1.44) and nine participants completed the 2-letters paradigm (age range = 8 to 16 years; M = 11.93; SD = 2.78). All participants had a retrieval accuracy of 80% or more, which suggested that task difficulty was appropriate for each participant.

Procedure

Participants completed the adapted Brown-Peterson fMRI paradigm. This fMRI paradigm was presented visually during fMRI using E-prime2 (Psychology Software Tools, PST, Pittsburgh). Initially, participants successfully completed a mock MRI scanner training protocol before the MRI. Participants were prepared for the adapted Brown-Peterson paradigm through training initially outside (5 trials for each of the three conditions described above) and then inside the scanner before starting fMRI acquisition (again 5 new trials for each of the three conditions). All participants demonstrated understanding of the paradigm before being placed in the scanner. The paradigm was projected onto a screen at the foot of the MRI bed, and participants viewed the images from a mirror attached to the head coil. To minimize head motion during scanning, a soft cloth was placed on the child's forehead, then taped to the head tray, and foam pads were inserted around the head. Responses were provided using an MRI compatible response box with four response buttons. The response box was placed centrally on the child's stomach and responses were provided by pressing the left-most/green button with the left thumb or the right-most/red button with the right thumb, respectively.

Statistical analysis of behavioural data on concurrent task and retrieval

Separate repeated measures analyses of variance (ANOVA) were conducted on accuracy measures (percent correct) for the concurrent tasks (within domain/lexical decision task and cross-domain/face decision task) and the retrieval period with the type of the previous concurrent task (within- or cross-domain) as within-subject factor. Independent-sample t tests were used to explore sex differences in accuracy. Pearson's correlation was used to study the relationship between age and accuracy. Statistical analyses were performed using SPSS Statistics V22.0 [39].

Image acquisition

MRI was performed on a Siemens 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany) at the Royal Children's Hospital. The scanner was equipped with the Syngo MR B17 software release, and a 12-channel receive-only head coil was used. T1-weighted MP-RAGE sequence (Magnetization Prepared Rapid Gradient Echo) were obtained using the following parameters: repetition time (TR) = 1900 ms, echo time (TE) = 2.71 ms, inversion time (TI) = 900 ms, flip angle (FA) = 9˚, field of view (FoV) = 256mm, voxel size = 0.7 x 0.7 x 0.7 mm. Functional images were acquired using a T2-weighted with a gradient-echo-planar imaging (EPI) sequence with 32 interleaved slices with 5% gap, voxel size = 2.6 x 2.6 x 3 mm, TR = 2400ms, TE = 35ms, FA = 90˚, FoV = 240mm.

Image analysis

fMRI data were preprocessed and analysed using SPM8 (Wellcome Department of Imaging Neuroscience, University College London, UK) implemented in Matlab R2014a. The images

of each subject were corrected for slice acquisition timing, and spatially realigned to eliminate movement artefacts. Head motions were small in any direction (Maximum translation, X = 0.39mm, Y = 0.76mm, Z = 1.69mm; Maximum rotation (converted from degrees to millimetres, 40): X = 0.04mm, Y = 0.2mm, Z = 0.01mm; Mean translation: X = 0.08mm, Y = 0.11mm, Z = 0.25mm ; Mean rotation : X = 0.004mm, Y = 0.003mm, Z = 0.002mm) and therefore no participant was excluded from further processing [40]. To allow for inter-subject comparison, data were normalized using the MNI brain template (Montreal Neurologic Institute) and resampled to 1.9 x 1.9 x 3 mm. These functional images were finally smoothed using a Gaussian filter of full width at half maximum = 8mm to increase signal-to-noise ratio.

Statistical analyses were performed using a two-step process, taking into account the intra-individual and inter-individual variance [41]. First level single subject statistics were assessed by a voxel-based statistics according to the General Linear Model implemented in SPM8. Given the high rate of correct responses across participants (above 90%, see Results section for further detail) and to guarantee an equal number of trials for each condition, brain activity was analysed pooling the correct and incorrect trials together. The onsets of each event of interest were convolved with the canonical hemodynamic response function (HRF) and used as regressors in the individual design matrix. For the encoding period, these onsets included encoding of the active condition and encoding of the baseline condition, using a boxcar function of 2 or 3 seconds for active encoding (depending of the difficulty level) and 1 second for the baseline encoding. The maintenance delay filled with a concurrent task was modelled using a boxcar function of 6 seconds for the within-domain (lexical decision) and the cross-domain (face decision) concurrent tasks. Finally, the retrieval period was modelled using a boxcar function of 3 seconds for the tree retrieval types, i.e., retrieval after within-domain concurrent task, retrieval after cross-domain concurrent task and retrieval of the baseline condition.

All six movement parameters (translation: x, y and z; rotation: pitch, roll and yaw) were included as covariates of no interest in the model. The individual statistical images from each condition were then entered in a group analysis at the second level using a flexible factorial design, which provides the flexibility to specify the different period of our mixed block and event-related paradigm. In this random-effects model, independence and unequal variance between subjects and conditions were assumed, allowing for violation of sphericity, as implemented in SPM8. Considering a possible impact of gender on brain-activation, we also added this binary variable as a covariate in the flexible factorial design [26, 38, 42, 43]. In line with guidelines used in neuroimaging studies of complex cognitive functions [44], whole-brain analysis was conducted with a significance threshold of $p < .001$ at the voxel level, uncorrected for multiple comparisons, and a minimum extent threshold of 20 voxels [26, 45]. Anatomical location of activations was verified using SPM Anatomy toolbox [46].

We performed exploratory analyses to examine age- and retrieval accuracy-related changes in brain activation during the Brown-Peterson fMRI paradigm. The largest and most relevant clusters of activation identified at the group level were used to define functional regions of interest (ROIs) for each of the different conditions using the marsBaR toolbox [47]. Beta values were extracted from each ROI, by contrasting activation during the encoding or retrieval WM conditions relative to the respective baseline conditions. Beta values from each ROI and each participant were then used to compute Pearson's correlation coefficients in order to evaluate any age- and accuracy-related effects on ROI activity using SPSS [39]. Beta values from the encoding or retrieval periods were contrasted to the baseline values (rather than to each other) to test for condition-specific effects without mixing any positive vs negative correlation with one vs the other active condition.

We also performed a whole-brain analysis where different active phases were compared (encoding vs retrieval, within-domain concurrent task vs cross-domain concurrent task,

retrieval following within-domain concurrent task vs retrieval following cross-domain concurrent task), but now including age and retrieval accuracy as covariates of interest in a multiple parametric regression design using SPM8. For these regressions, a significant threshold of $p < .001$ uncorrected for multiple comparisons with a minimum extent threshold of 20 voxels was used.

Results

Behavioural data

As far as the concurrent tasks were concerned, the percentage of correct responses was 97% (SD = 4.3) for the within-domain (lexical decision task) and 98% (SD = 3.5) for the cross-domain (face decision task). For the effect of the type of the concurrent task, assumption of normality was violated, as assessed by inspection of histograms and results of the Shapiro-Wilk test (p = .001). Therefore, related-sample Wilcoxon-signed rank test was used and showed no significant effect of the type of concurrent task ($W_s = 33$, z = .58, p = .565). Concerning retrieval of the active condition, repeated-measures ANOVA showed no effect of type of concurrent task on response accuracy, $F(1,15) = 1.278$, $p = .276$ (90.9%, SD = 8.8, and 93.4%, SD = 5.3, for the within-domain/lexical and cross-domain/face decision tasks, respectively). Hence, differences in brain activity patterns at retrieval could not be explained by differences in WM performance.

There was no significant relationship between age and response accuracy on the retrieval of the active condition whatever the type of the previous concurrent task ($r = .318$, $p = .23$, and $r = .299$, $p = .261$ for the within- and between-domain concurrent task respectively), and no significant relationship between age and response accuracy on the concurrent tasks ($r = .493$, $p = .052$, and $r = .185$, $p = .492$ for the lexical decision and face decision concurrent tasks, respectively). There was no significant gender difference for any of the measures, $ts < 1$, $ps > .50$.

Taken together, these behavioural data show good performance overall on the adapted Brown-Peterson paradigm. Moreover, this pattern was stable across the age range of our sample and gender. Therefore, from a behavioural point of view, our task appears to be suitable for a wide age range of children and adolescents.

Functional magnetic resonance imaging

Active letter encoding and retrieval vs. baseline. To delineate brain regions generally recruited during WM, we first contrasted the active encoding period relative to the baseline encoding period, regardless of the domain of concurrent task during the maintenance interval. This showed activation in a widespread network, including bilateral visual areas in the occipital lobes, parahippocampal gyri, as well as left prefrontal regions, the caudate nucleus, and the cerebellum (Table 1). Likewise, we contrasted the active retrieval relative to the baseline retrieval period, regardless of concurrent conditions, which revealed a distributed pattern of activation encompassing mainly bilateral prefrontal cortices, but also temporal and parietal areas (Table 1). These data confirm that our working memory paradigm successfully engaged brain networks associated with visual stimulus processing and executive functions.

Active letter encoding vs. letter retrieval. We next sought to identify regions selectively recruited by distinct WM processes. Encoding, as compared to retrieval (during the active task), was associated with widespread activations bilaterally in the occipital and ventral temporal lobes (inferior occipital and fusiform gyri), as well as in medial frontal areas (supplementary motor area (SMA), middle cingulate gyrus) and precentral gyrus. Smaller activation foci were found in the insula (Fig 2 and Table 2). Conversely, the retrieval phase, compared to encoding, activated bilateral dorsolateral prefrontal areas (mainly inferior and middle, but also superior

Table 1. List of activations for active encoding and retrieval compared to baseline condition.

Region		Hemisphere	Number of voxels	t value	x, y, z
ENCODING (compared to encoding baseline)					
Frontal	Inferior (BA 47)	L	108*	4.46	-38, 30, -14
	Superior and middle (BA 9)	L	160*	4.42	-27, 40, 43
	Superior and superior medial (BA10)	L	193*	4.22	-15, 57, 13
Occipital	Lingual, inferior, calcarine (BA18)	L	515*+	6.33	-25, -95, -11
				4.66	-11, -99, -8
		R	631*+	6.08	25, -91, -11
				5.89	21, -91, -2
Temporal	Parahippocampal gyrus	L	130*+	5.07	-40, -28, -11
		R	71*	4.77	13, -13, -17
Subcortical	Caudate nucleus (BA 48)	L	563*+	5.87	-17, 19, 10
	Pulvinar	R	24	3.64	13, -32, 13
	Cerebellum	L	222*	4.77	-10, -30, -14
RETRIEVAL (compared to retrieval baseline)					
Frontal	Prefrontal, putamen, middle and inferior (BA 49, 10, 44)	L	7684*+	6.10	-15, -6, 13
				6.07	-27, 8, -2
				5.83	-29, 42 19
				5.05	-61, 11, 22
	Middle and superior (BA 10, 6)	R	572*+	4.91	27, 46, 7
				4.43	28, 51, 10
			23	4.01	36, -2, 64
	Superior orbital (BA 11)	L	74*	4.77	-21, 53, -14
	Precentral gyrus (BA 6, 4)	L	268*	5.13	-34, -4, 61
		L	56	4.18	-49, 0, 40
		L	32	3.49	-36, -17, 40
	Middle cingulate (BA 24)	L	42	3.82	-17, -25, 46
Parietal	Angular (BA 39)	R	169	4.21	40, -65, 46
	Inferior and superior lobule (BA 7)	L	1813*+	5.02	-36, -55, 55
				4.92	-32, -61, 55
	Inferior lobule and postcentral gyrus (BA 40, 1)	L	404*+	4.85	-51, -25, 46
				4.19	-57, -23, 28
Temporal	Middle extending calcarine gyrus	R	189*+	5.74	32, -65, 16
	(BA23)			3.49	28, -57, 10
	Superior and middle (BA 39)	L	82	4.25	-61, -47, 19
	Middle (BA 21)	R	58	3.83	51, -34, -14
Occipital	Lingual (BA 18)	L	214	3.98	-6, -76, -2
Subcortical	Vermis	L	229	4.68	-2, -53, -5
	Cerebellum	L	156	4.32	-25, -61, -17

Note: Coordinates are in MNI space. x, y, z coordinates refer to voxels with highest statistical significance within a cluster (location of the peak coordinate).
Clusters used to define ROIs for specific subsequent analyses are marked with a sign *.
Clusters reaching a significance threshold of $p < .05$ at the voxel level, corrected for multiple comparison, are marked with a sign +. BA = Brodmann area

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frontal gyri), as well as the anterior cingulate cortex (ACC), inferior parietal lobule (angular, supramarginal, and postcentral gyri), and lateral temporal areas (superior and middle temporal gyri).

Maintenance delay filled with a concurrent task (within-domain vs. cross-domain). Comparing activations during the within-domain concurrent task (lexical decision task),

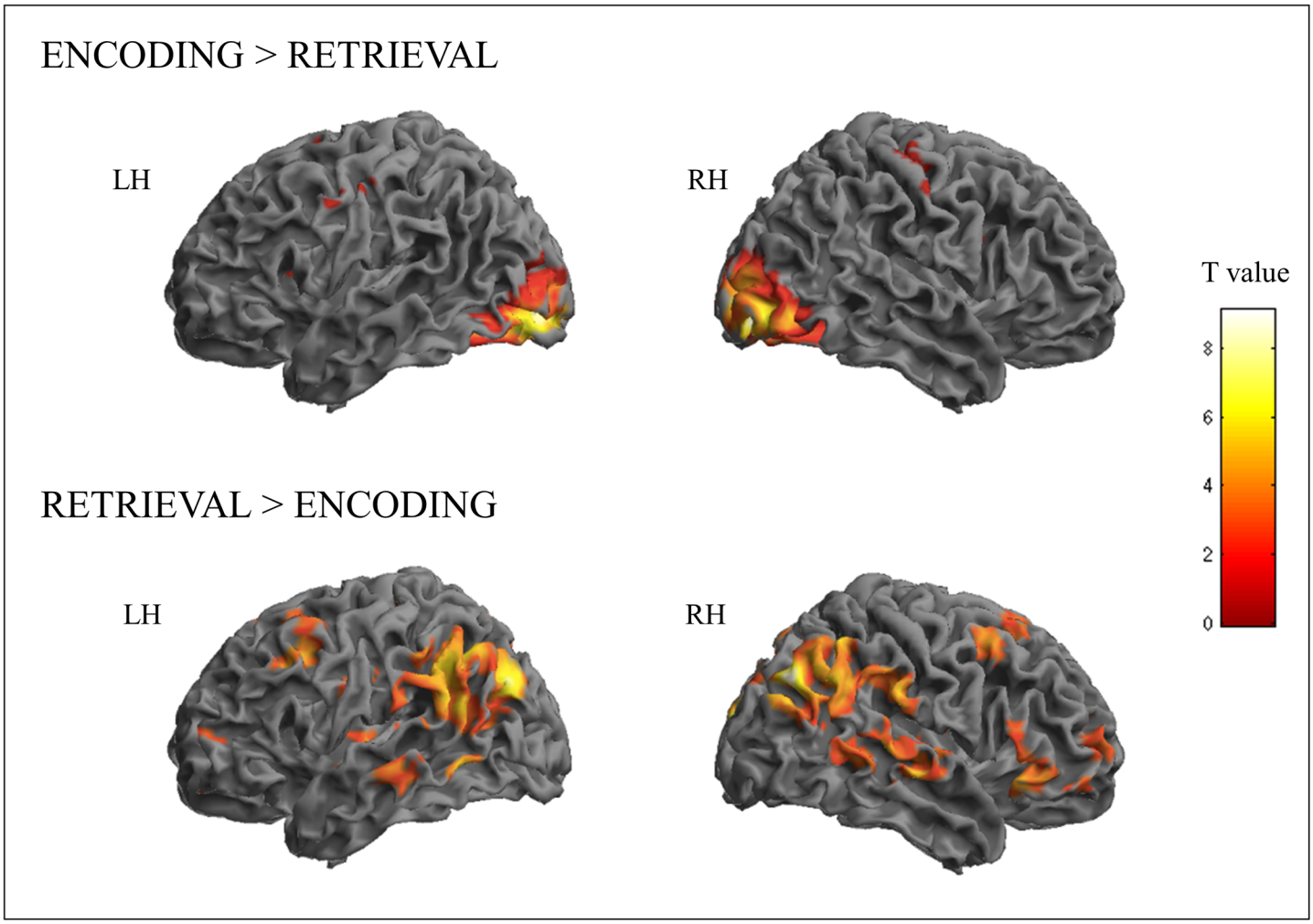

Fig 2. Activation maps related to the contrasts encoding vs retrieval.

https://doi.org/10.1371/journal.pone.0179959.g002

relative to the cross-domain concurrent task (face decision task), revealed differential increases in the right middle frontal gyrus (Brodmann area 10) and medial fusiform cortex only (Table 2 and Fig 3). Conversely, the cross-domain concurrent task (face decision task) compared to within-domain concurrent task (lexical decision task) produced a more extensive pattern of activation, particularly in bilateral visual areas, including occipital and fusiform cortex overlapping with the fusiform face areas (FFA). Activations were also found in several frontal areas (left inferior and medial frontal gyri, SMA, right middle cingulate cortex, precentral gyrus), the temporo-parietal junction, left parahippocampal gyrus, and right pulvinar. Thus, the cross-domain concurrent task appeared to recruit a more widespread network than the within-domain concurrent task, even though behavioural data show that this could not be explained by task difficulty since accuracy did not significantly differ in the two concurrent tasks.

Letter retrieval following within-domain vs. cross-domain concurrent tasks. The most critical question concerning the WM system in our paradigm is whether the nature of the concurrent task during the maintenance interval may produce different degrees of competition and thus result in different neural substrates during retrieval. We therefore tested for brain

Table 2. List of activations for contrasts of interest.

Region		Hemisphere	Number of voxels	t value	x, y, z
ENCODING > RETRIEVAL					
Frontal	SMA, middle cingulate (BA 6)	L&R	640*+	6.84	-6, 8, 49
				5.45	8,10,49
	Pre and post central gyrus (BA 4)	L	175	4.07	38, -21, 55
	Precentral gyrus (BA 6)	R	104+	5.32	46, 6, 28
	Medial (BA 11)	L	23	3.68	-0, 38, -17
Parietal	Postcentral gyrus (BA 6, 1)	L	70+	5.09	-53, -6, 49
		R	25	4.05	61, -13, 46
Occipital	Inferior (cuneus, precuneus, lingual), fusiform (BA 18, 19, 37)	L	2468*+	13.24	-23, -89, -11
				11.65	-36, -80, -11
				8.94	-36, -51, -17
		R	2692*+	13.11	27, -87, -11
				8.28	34, -49, -17
				8.25	32, -89, 10
Other	Insula (BA 13)	L	31	3.63	-30, 13, 10
RETRIEVAL > ENCODING					
Frontal	Precentral, middle (BA 8, 6) Middle (BA 8, 10)	L	500*	4.87	-36, 11, 40
				4.78	-38, 13, 37
		R	227*	4.6	40, 10, 49
		L	59	3.64	-44, 51, 10
	Inferior, middle (BA 47, 10)	R	487*	4.68	47, 23, -8
				4.27	44, 53, -11
	Superior and middle (BA 10)	R	212	4.2	30, 63, 4
	Superior, SMA (BA 8, 6)	R	242*	4.1	25, 23, 55
				4.08	9, 25, 58
	Anterior cingulate (BA 32)	R	227*	4.09	2, 36, 19
	Precentral gyrus (BA 4)	L	34	4.04	-19, -27, 55
	Middle orbital (BA 10)	L	34	3.93	-29, 57, -11
	Superior medial (BA 8)	R	24	3.57	2, 34, 40
Parieto-temporal	Angular, superior temporal, supramarginal, inferior parietal lobule (BA 39, 22)	R	3563*	7.3	46, -74, 34
				5.17	59, -19, -5
				4.94	46, -53, 49
	Angular, middle temporal, inferior parietal lobule	L	5998*	6.41	-42, -55, 40
				6.02	-55, -51, 22
				5.35	-49, -51, 37
	Postcentral gyrus (BA 4)	L	188*	4.91	-42, -13, 31
Temporal	Superior extending to putamen (BA 49)	L	301	4.7	-30, -13, 4
	Middle (BA 21)	L	190	4.18	-65, -25, -8

(*Continued*)

Table 2. (*Continued*)

Region		Hemisphere	Number of voxels	t value	x, y, z
Occipital	Lingual (BA 18)	R	25	3.8	11, -74, -8
Subcortical	Putamen (BA 49)	R	199	4.44	30, -13, 7
WITHIN-DOMAIN > CROSS-DOMAIN CONCURRENT TASK					
Frontal	Frontal pole (BA 10)	R	266*+	5.3	27, 55, 4
Occipital	Medial fusiform (BA 19)	R	36*	4.43	30, -53, -8
CROSS-DOMAIN > WITHIN-DOMAIN CONCURRENT TASK					
Occipital	Inferior (lingual, precuneus, fusiform), cuneus, including fusiform face area (FFA; BA 19, 18, 37)	R	2873*+	9.1	42, -84, -11
				8.97	34, -91, -5
				5.92	49, -53, -14
	Middle, lingual, inferior, lateral fusiform, including FFA (BA 19, 18, 37)	L	878*+	5.64	-34, -91, -5
				4.76	-44, -72, -14
				4.6	-48, -51, -17
	Precuneus gyrus (BA 7)	R	30	3.79	8, -59, 64
	Lingual (BA 18)	L	39	3.79	-0, -61, 7
Frontal	Inferior (BA 47)	L	238*+	5.11	-38, 36, -14
	Precentral (BA 4)	R	156+	4.9	38, -13, 43
	Medial frontal (BA 11)	L	92	4.79	-2, 46, -17
	Middle cingulate (BA 24)	R	92	4.22	13, -17, 49
	SMA (BA 6)	L	59	3.82	-6, -13, 55
Temporal	Inferior (BA 20)	R	39*+	5.29	47, -27, -20
	Middle (BA 21)	L	60	4.12	-61, -9, -20
	Parahippocampal gyrus	L	806*+	5.63	-29, -11, -14
Parietal	Inferior lobule (BA 40)	R	119+	5.06	57, -27, 55
	Postcentral gyrus (BA 4)	L	92	4.32	-42, -27, 64
	Angular (BA 39)	L	169	4.1	-36, -59, 22
	Superior lobule (BA 7)	R	59	4.06	25, -70, 52
Subcortical	Pulvinar	R	207*+	5.28	25, -30, 7
RETRIEVAL AFTER WITHIN-DOMAIN > RETRIEVAL AFTER CROSS-DOMAIN CONCURRENT TASK					
Occipital	Cuneus, fusiform, middle and inferior occipital (BA 18, 19)	R	3181*+	8.71	15, -101, 7
				8.44	27, -78, -8
				7.58	30, -89, 10
				7.17	42, -72, -8
	Inferior and middle occipital, fusiform, calcarine (BA 18, 37)	L	1620*+	7.15	-25, -80, -8
				6.71	-32, -61, -14
				6.62	-15, -101, 4
				5.47	-6, -91, -11
RETRIEVAL AFTER CROSS-DOMAIN INTERFERENCE > RETRIEVAL AFTER WITHIN-DOMAIN CONCURRENT TASK					

(*Continued*)

Table 2. (*Continued*)

Region		Hemisphere	Number of voxels	t value	x, y, z
Temporal	Middle and superior (BA 21)	L	27*	3.74	-40, -47, 4
		L	23*	3.39	-59, -34, 4
Occipital	Calcarine (BA 17)	R	279*	4.79	2, -91, 10
	Inferior (BA 37)	L	22*	3.83	-53, -63, -14

Note: Coordinates are in MNI space. x, y, z coordinates refer to voxels with highest statistical significance within a cluster (location of the peak coordinate). Clusters used to define ROIs for specific subsequent analyses are marked with a sign *.
Clusters reaching a significance threshold of p < .05 at the voxel level, corrected for multiple comparison, are marked with a sign +. BA = Brodmann area.

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regions that would be differentially activated during the retrieval period when following within-domain concurrent task (lexical decision) or when following cross-domain concurrent task (face decision). Greater increases following the within-domain concurrent task were found in visual areas, with large bilateral clusters in occipital cortices (bilateral middle and

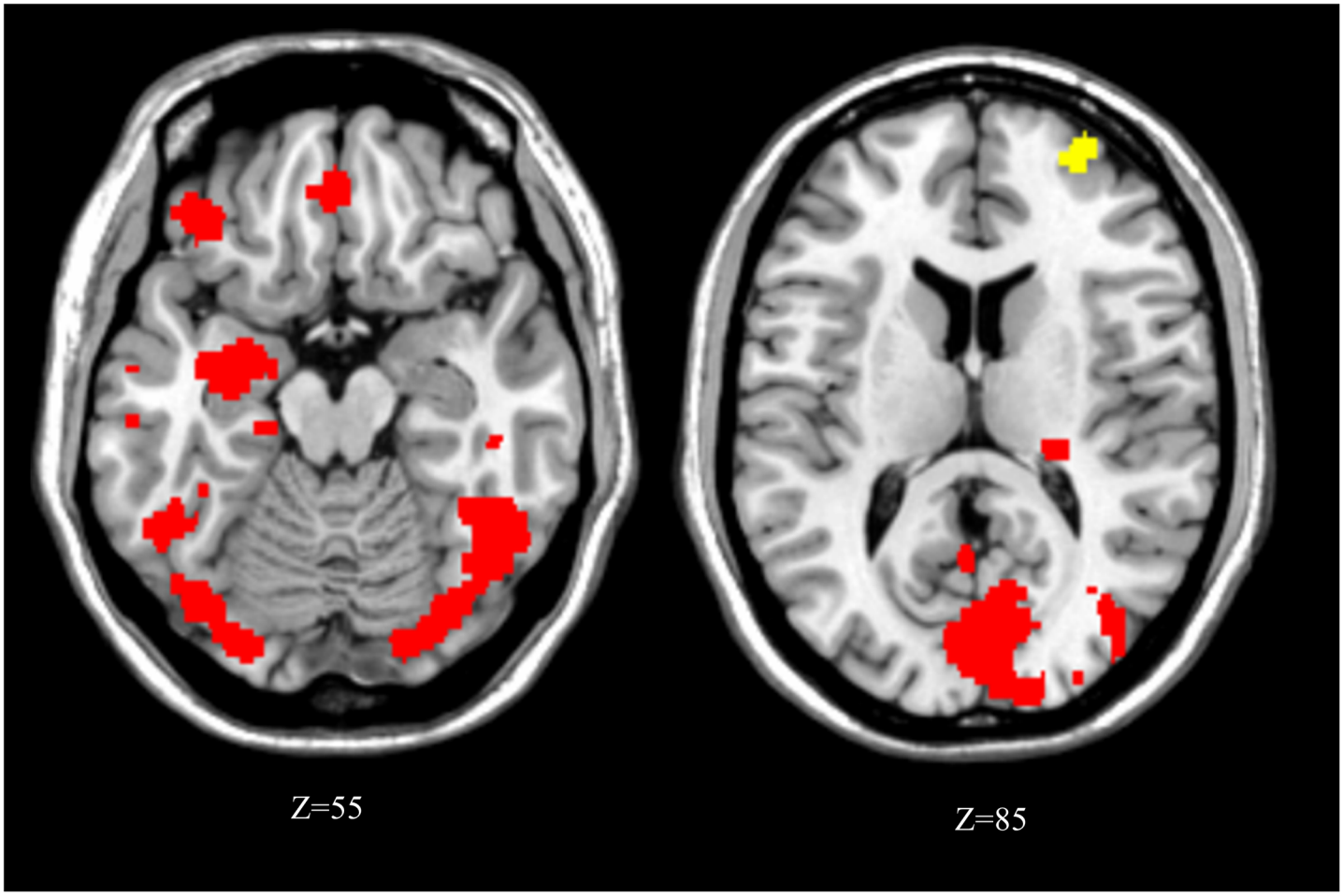

Fig 3. Activation map for the contrast within-domain vs cross-domain concurrent tasks (MRIcron reference slices). Activations in yellow: within-domain concurrent task > cross-domain. Activations in red: cross-domain concurrent task > within-domain.

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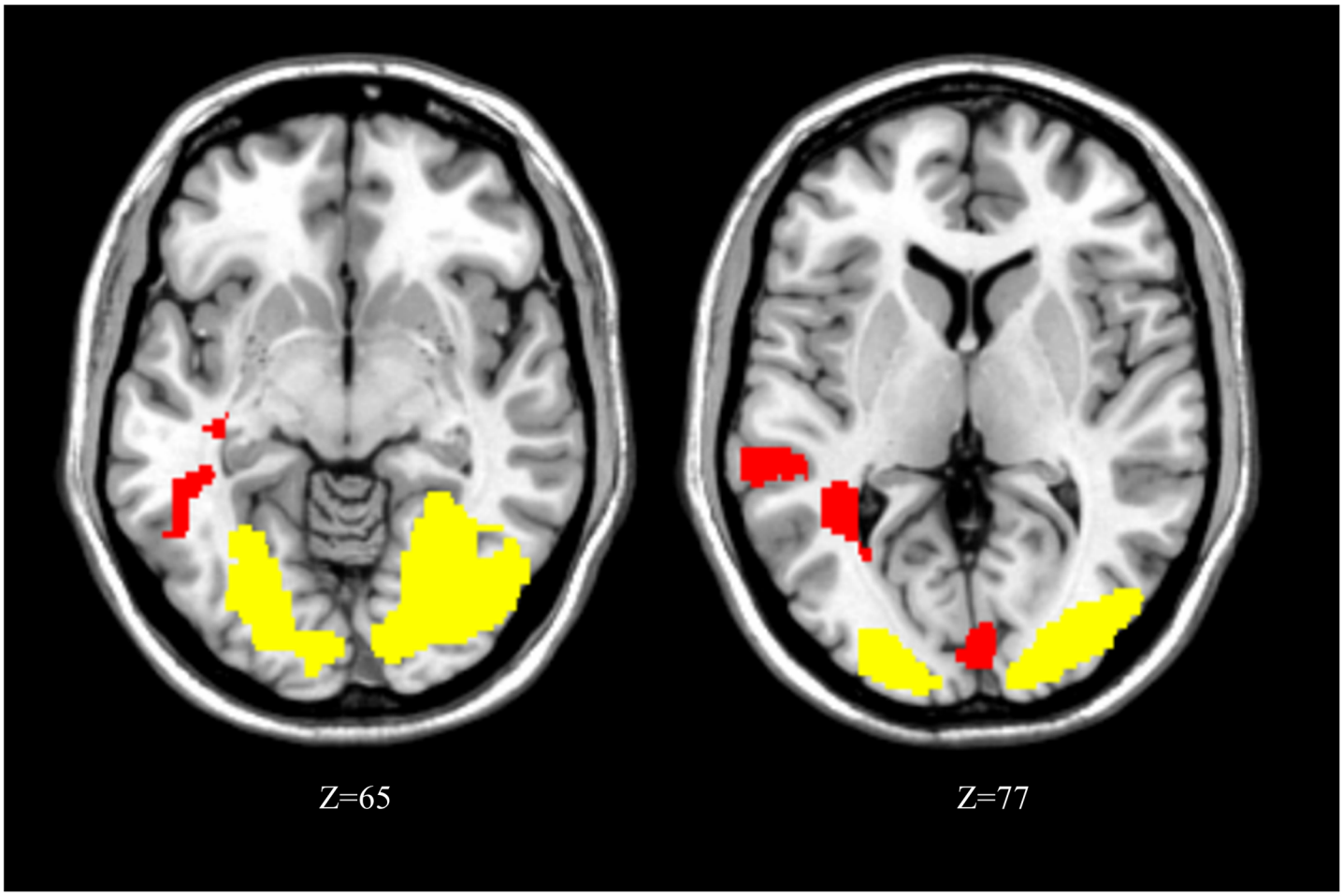

Fig 4. Activation map for retrieval following within-domain vs cross-domain (MRIcron reference slices). Activations in yellow: retrieval following within-domain concurrent task > cross-domain. Activations in red: retrieval following cross-domain concurrent task > within-domain. For illustration purpose, activations observed in retrieval following within-domain concurrent > cross-domain are represented with a threshold of p < .005 uncorrected for multiple comparisons.

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inferior occipital gyri, fusiform gyri, right cuneus and left calcarine). Conversely, greater increases were found after the cross-domain concurrent task in the left middle and superior temporal cortex, overlapping with usual location of phonological processing [48, 49], plus left calcarine gyrus and bilateral medial occipital cortex (Table 2 and Fig 4).

Age and retrieval accuracy-related activations. Several functional ROIs were defined for each of the contrast of interest described above (marked with a star in Tables 1 and 2) and used for additional analyses to examine any modulation by individual characteristics of the participants. Parameter estimates (beta values) extracted and averaged across voxels from these ROIs were then submitted to Pearson's correlation with age and WM retrieval accuracy. No significant correlation was found between encoding- or retrieval-related activation (relative to baseline activation) with neither age nor WM retrieval accuracy on the adapted Brown-Peterson paradigm for any of these ROIs. Table 3 summarizes these correlation coefficients.

We also performed an exploratory whole-brain regression analysis in SPM using (a) age; and (b) WM retrieval accuracy for the main contrasts of interest as described above (encoding vs retrieval, within vs cross domain concurrent tasks). None of these analyses revealed any significant overlap with activations identified by the main contrasts of interest reported in

Table 3. Pearson's correlations between activity of functional ROIs and (a) age or (b) retrieval accuracy.

Functional ROIs				Age		Accuracy	
Region	**Side**	**Number of voxels**	**Peak coordinates**	**r**	**P value**	**r**	**P value**
ENCODING (compared to encoding baseline condition)							
Frontal Inferior	L	108	-38, 30, -14	-.351	.183	-.275	.304
Superior and middle	L	160	-27, 40, 43	-.041	.881	-.269	.314
Superior and superior medial	L	193	-15, 57, 13	-.101	.711	-.360	.171
Occipital Lingual, inferior, Fusiform	L	515	-25, -95, -11	.322	.224	.235	.382
	R	631	25, -91, -11	.308	.245	.182	.501
Temporal Parahippocampal Gyrus	L	130	-40, -28, -11	.455	.077	.214	.426
	R	71	13, -13, -17	.225	.401	.389	.137
Subcortex Caudate Nucleus	L	563	-17, 19, 10	-.225	.402	-.111	.683
Other Cerebellum	L	222	-10, -30, -14	.241	.369	.361	.169
RETRIEVAL (compared to retrieval baseline condition)							
Frontal Inferior extending to putamen and insula	L	7684	-15, -6, 13	-.174	.519	-.100	.171
Middle and superior	R	572	27, 46, 7	-.010	.969	.055	.839
Precentral	L	268	-34, -4, 61	.242	.367	.282	.289
Superior orbital	L	74	-21, 53, -14	.030	.911	.076	.780
Temporal Middle extending to precuneus	R	189	32, -65, 16	.187	.489	.405	.120
Parietal Inferior and superior lobule	L	1813	-36, -55, 55	.395	.130	.248	.354
Inferior lobule, postcentral	L	404	-51, -25, 46	.338	.201	.381	.145

Note: Activity was measured during either encoding or retrieval periods depending on the phases recruiting each ROI. Coordinates in MNI space and number of voxels are given for each functional ROI, as well as Pearson's correlation coefficients, r, and corresponding p values.

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Table 2 indicating that all effects reported above are largely independent of age (within the range of our sample) and WM retrieval accuracy.

Discussion

We report and validate an adapted Brown-Peterson fMRI paradigm that probes for the neural correlates of different WM processes, including encoding, maintenance and retrieval, as well as the effect of within- and cross-domain concurrent tasks during maintenance. Results indicate that this paradigm can be performed equally well by children and adolescents of different ages, with reliable results across different levels of performance. To our knowledge, this is the first study to propose a paradigm to delineate distinct patterns of brain activity for the different WM processes in children and adolescents. We provide the first exploratory results on brain activity related to encoding, maintenance, and retrieval WM processes in children and adolescents, and compare verbal WM in the presence of both verbal (within-domain) and visual (cross-domain) concurrent tasks.

As expected, our adapted Brown-Peterson paradigm was successfully completed with high accuracy in the MRI scanner by typically developing children as young as 8 years of age, indicating that it is suitable to examine WM processes in children and adolescents from 8 to 16 years of age. It is important to note that task difficulty was adapted to each participant's WM capacity using a simple procedure (based on backward digit span performance, the participant completed the paradigm with two or three letters to remember), and we found no significant association between age or task performance and brain activation patterns. These findings indicate that our paradigm is well suited to examine brain systems associated with different

WM capacities in different age groups. This may be an important advantage when comparing groups with different developmental trajectories, because previous studies show that WM-related activations may increase with age in parallel with changes in performance and improvements in WM capacity [12, 18].

Secondly, our imaging results demonstrate that, while distributed networks in frontal and visual areas activated in the context of the verbal WM paradigm used here (i.e. during the active conditions compared to the baseline), distinct neural substrates were selectively recruited during the encoding and retrieval periods. The verbal encoding period induced stronger activations in posterior and ventral brain regions, with large bilateral increases in occipital, as well as parahippocampal cortices. In contrast, the verbal retrieval period induced stronger activations in more anterior and dorsal regions, in particular in prefrontal and parietal areas, and to a lesser extent in lateral temporal areas.

The predominance of activity in visual cortex together with medial temporal lobe (parahippocampal gyrus) during encoding is consistent with the need to extract discriminative visual information from the to-be-remembered stimuli and store this information into short-term memory. On one hand, ventral occipito-temporal areas differentially engaged during encoding are crucial for perceptual shape analysis, especially for letters with a letter-sensitive activation in these regions [50, 51]. We did not find selective activations corresponding to the "visual word form area" but this region is typically responsive to letter-strings or words rather than isolated letters [52–54]. Moreover, we did not find language-related activation during verbal encoding, in particular Broca's area which has been implicated in the subvocal rehearsal system [55]. However, language-related activation has been mainly found during encoding of words [56] and not during encoding of letters [57].On the other hand, the parahippocampal cortex is a key brain region at the interface between perception and memory, therefore likely to make an important contribution to efficient storage of visual information into WM [58].

As expected, predominant activity in frontal and parietal areas during retrieval is consistent with executive control and attentional focusing. The executive control system serves as an attention controller that allocates and coordinates attentional resources for cognitive tasks, such as retrieval of information encoded in working memory [59, 60]. Our findings accord with previous studies showing the involvement of frontal areas, especially prefrontal and anterior cingulate cortices, in the executive control required during WM demands [61, 62]. Focusing attention is crucial for efficient executive control [63] and recruits parietal regions [64], which were strongly implicated during the retrieval period in our study. In addition, WM retrieval of serial order is dissociable from the type of information contained in the item sequence [65] and also relies on activation in frontal and parietal activations [66].

Overall, our findings converge with those of van den Brosh and colleagues (2014), who reported a similar posterior and perceptual network during the encoding phase compared to a more anterior and executive network during the recall phase of a Sternberg item recognition paradigm (which did not include a distracting phase) in children and adolescents aged 9 to 19 years. However, these authors did not find any temporal or parahippocampal activations, possibly reflecting differences in the paradigm and material used (digits in their study vs. letters in ours). More generally, our findings of extensive fronto-parietal and visual activity during WM also dovetail with previous neuroimaging studies investigating brain systems associated with verbal WM in children and adolescents, across different kinds of verbal WM paradigms, such as the Steinberg item recognition task using letters [21, 67, 68] or n-back tasks using letters [69, 70].

Study hypotheses were supported by results revealing that brain activation patterns differ as a function of the nature of the concurrent task performed during the maintenance interval. Our design allowed us to compare the impact of within-domain (lexical decision task) versus cross-domain (face decision task) concurrent task processing during the maintenance period

intervening between encoding and retrieval, while information stored in WM itself did not differ. A lexical decision task was expected to produce within-domain interference, as it involved verbal material resembling the to-be-remembered material (i.e. letters), while a face decision task was considered to induce cross-domain interference as it relied on non-verbal visual processes.

As predicted, the within-domain and cross-domain concurrent tasks evoked distinct brain activations when compared to each other. Localised and right-sided activations in the right frontal pole (Brodmann area 10) and medial fusiform gyrus were observed during the within-domain/lexical concurrent task, whereas the cross-domain/face concurrent task elicited much more distributed activations in occipital temporal extrastriate areas, but also left parahippocampal gyrus and fronto-parietal regions. These differences could not be attributed to task difficulty (since there were no significant difference in accuracy between the within-domain/lexical and the cross-domain/face decision task) but most likely reflect the different task demands and perhaps different strategies and processes applied during the maintenance interval. Since verbal information had to be held in WM, it might have produced stronger interference and greater conflict in resource allocation during the within-domain/lexical decision task than the cross-domain/face decision task, eventually affording less efficient engagement of task-specific networks in the former condition and hence lower accuracy. The involvement of the right frontal pole (Brodmann area 10), thought to organize an optimal use of cognitive resources and overcome potential impasses [71], may reflect this conflict in resource allocation and an increase in cognitive load during a verbal concurrent task. Such recruitment of attentional control mechanisms during interference appears consistent with the time-based resource-sharing model (TBRS; [72–74]). This model postulates the existence of attention-based mechanisms involved to maintain relevant verbal information when the capacity of the verbal-specific system (comparable to the phonological loop in Baddeley and Hitch's model) is exceeded [75]. Alternatively, greater activation of visual and fronto-parietal areas as well as temporal regions, including parahippocampal gyrus, during the cross-domain/face decision task might reflect the dual process of face decision task and active maintenance of verbal information.

Critically, and in keeping with our hypotheses, the two concurrent tasks (within- and cross-domain) elicited distinct patterns of brain activity during the subsequent retrieval phase, despite the fact that identical stimuli were encoded, maintained and retrieved from WM. This indicates that partly different processes mediated retrieval after within- and cross-domain interference, and thus WM retrieval differed according to the nature of the preceding concurrent task. Large bilateral occipital activations were engaged during retrieval after the within-domain/lexical concurrent task, whereas only limited activity was observed in medial occipital cortex in addition to left superior and middle temporal cortex during retrieval after the cross-domain/face concurrent task. Interestingly, the latter cluster in temporal cortex overlapped with regions often reported in phonological tasks and associated with language networks [48, 49]. A plausible explanation for such difference would be that the maintenance of letters relied on a preferentially visual format when a concurrent verbal task had to be performed (i.e., within-domain concurrent task), hindering the use of the phonological loop for maintenance. On the other hand, the visual concurrent task may not prevent maintenance in the phonological loop, explaining a lesser involvement of visual cortex but conversely greater recruitment of language-related areas (left superior and middle temporal) during retrieval. These interpretations would accord with Baddeley and Hitch's model previously mentioned, and the proposed effect of articulatory suppression on verbal WM [59, 76, 77].

The current study is not without limitations. The study sample size could be considered relatively small. We note, however, that it is comparable with previous studies exploring neural correlates of WM [12, 67, 78]. Even if our data showed no hint of any systematic modulation

of brain activity patterns by age or retrieval accuracy, correlation and regression analysis performed here can be sensitive to small size. Nevertheless, by design, our procedure of tailoring task difficulty to each participant according to their WM capacity precisely aimed at avoiding age related effects and minimizing confounding effects due to individual differences in performance. We acknowledge that the lack of variability and the high retrieval accuracy resulting from this procedure may have limited the sensitivity of our study to activations modulated by age or other individual factors. Another limitation is that our paradigm did not test the reverse situation of verbal versus visual concurrent tasks on visual information held in WM. Examining both verbal and visuospatial WM in the presence of verbal and visuospatial interference could map more precisely how the different processes subserving verbal and visuospatial WM are influenced by different kinds of concurrent tasks.

Conclusions

Our study provides new insights into WM-related brain activity. We show a greater role of perceptual brain systems for encoding processes, and a fronto-parietal attentional network for retrieval processes. More critically, we show that a concurrent task during maintenance in WM produced distinct activations not only during the concurrent task itself, but also during subsequent retrieval. We conclude that the specific demands of the concurrent task affect the way memory items are maintained in WM, selective verbal interference resulting in greater reliance on visual cortex for retrieval, whereas visual interference leaves verbal systems of maintenance unaffected, hence resulting in the involvement of language-related areas in left temporal cortex for retrieval. These data accord with WM models postulating differentiated cognitive processes, with distinct neural substrates, according to the concurrent material interfering in verbal WM [59, 76, 77]. In addition we show that these activation patterns are robust across different ages and different WM capacities. More generally, our work validates a new WM paradigm derived from the Brown-Peterson task allowing us to probe for the neural correlates of different WM processes. Because the difficulty of the task was adapted to each participant and results were stable across age, this fMRI paradigm may be usefully applied in developmental populations with a wide age range and also feasible in clinical paediatric population (e.g., populations with mild intellectual difficulties).

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Neural correlates of working memory in children and adolescents with agenesis of the corpus callosum: An fMRI study

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ABSTRACT

The ability to temporarily maintain relevant information in mind in the presence of interference or distracting information, also called working memory (WM), is critical for higher cognitive functions and cognitive development. In typically developing (TD) children, WM is underpinned by a fronto-parietal network of interacting left and right brain regions. Developmental absence (agenesis) of the corpus callosum (AgCC) is a congenital brain malformation resulting from disruption of corpus callosum formation. This study aims to investigate functional organisation of WM in children and adolescents with AgCC using functional magnetic resonance imaging (fMRI). Nine children with AgCC and a comparison group of sixteen TD children aged 8–17 years completed an fMRI WM paradigm designed to enable investigation of different WM processes, i.e., encoding, maintenance and retrieval. We found that AgCC children recruited globally similar brain regions as the TD comparison group during the WM task, despite significant disparity in brain development, i.e., bilateral occipito-frontal activations during verbal encoding, and bilateral fronto-parietal executive control network during retrieval. However, compared to their TD peers, children with AgCC seemed less able to engage lateralised brain systems specialised for particular memory material (i.e. less supramarginal activations for verbal material and less fusiform activations for face processing) and particular memory process (i.e. absence of right-predominant activations during retrieval). Group differences in the pattern of activation might also reflect different cognitive strategies to cope with competition in processing resources with different susceptibility to concurrent tasks (verbal vs visual), such as differential recruitment of associative visual areas and executive prefrontal regions in the AgCC compared with the TD group depending on the concurrent task completed during maintenance. This study provides a first step towards a better understanding of functional brain networks underlying higher cognitive functions in children with AgCC.

1. Introduction

The corpus callosum (CC) is the largest cerebral commissure in the brain and a major white matter pathway that connects homologous structures between both halves of the central nervous system (Paul et al., 2007; Raybaud, 2010). In typical development, this bundle of fibres is a major conduit that transfers information between the two hemispheres, and also contributes to the integration of information across hemispheres for various cognitive and sensorimotor tasks (Bloom and Hynd, 2005; Chiarello, 1980).

Developmental absence, or agenesis, of the CC (AgCC) is a congenital brain malformation that results in the complete or partial failure of callosal fibres to form connections between cortical areas of the two hemispheres (dos Santos et al., 2002). Diagnosis of AgCC can be made prenatally or postnatally based on characteristic neuroimaging changes using ultrasound, computerised tomography (postnatally) or magnetic resonance imaging (MRI), including fetal MRI (Tang et al., 2009). Improvements in neuroimaging techniques, such as higher field strength

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for MRI, its growing use in paediatric populations as well as the growing use of routine prenatal ultrasound have resulted in increased rates in the detection of patients with AgCC (Moutard et al., 2003; Pisani et al., 2006). In the general population, its estimated prevalence is ~1–7 in 4000 live births (Glass et al., 2008; Wang et al., 2004). AgCC can be complete, with interruption of callosal development occurring at early stage in embryological development before 6 gestational weeks (Edwards et al., 2014), or partial, with disruption occurring slightly later in gestation (Huang et al., 2009; Paul, 2011; Richards et al., 2004). It may present as an isolated condition with other common secondary effects including colpocephaly, Probst bundles and cingulate gyrus absence (Booth et al., 2011). It may also be associated with other brain malformations including hydrocephalus, grey matter heterotopia, holoprosencephaly, interhemispheric cysts, gyral abnormalities (Bedeschi et al., 2006), and neurological sequelea such as epilepsy, macro or microcephaly, hearing and vision impairments (Moes et al., 2009). The causes are heterogeneous, however, genetic conditions including single-gene and chromosomal abnormalities are reported (Edwards et al., 2014). Consistent with the variability in presentation and aetiology of this brain malformation, previous studies have reported cognitive abilities ranging from "normal", with children attending mainstream school and adults having a conventional career (Caillé et al., 1999), to severe cognitive difficulties, with individuals attending special developmental school and requiring assistance in daily living activities (Graham et al., 2003, 2008). In a systematic review of neuropsychological functioning in AgCC (n = 110 patients), mean intellectual functioning was described to be in the low average range for adults (IQ: Mean = 88.2, SD = 15.18, n = 41) and in the borderline range for children (IQ: Mean = 76.4, SD = 30.12, n = 48; Siffredi et al., 2013). Therefore, studying this brain malformation has been a challenge as the heterogeneity is inherent to this clinical population. In contrast to split-brain patients (acquired destruction of the CC), individuals with AgCC show very little, if any, evidence of interhemispheric disconnection, and do not present with the typical disconnection deficits (Jea et al., 2008; Lassonde and Jeeves, 1994; Siffredi et al., 2013; Vuilleumier, 2001). This suggests that brain organisation and functions are capable of major plasticity, and determine long-term neurodevelopmental outcomes (Anderson et al., 2011).

In children and adolescents, working memory (WM) is a fundamental cognitive system that involves actively storing and manipulating information over brief periods of time (Baddeley, 1986) and relies on distributed brain networks across the two hemispheres. WM is considered a building block for the development of other higher cognitive functions, such as reasoning, language, social cognition and academic performance (e.g., Alloway et al., 2004; Barrouillet et al., 2008; Gathercole et al., 2004). WM capacity, as measured by the amount of information that can be retained and transformed in complex memory span tasks, develops dramatically across childhood and adolescence (Klingberg et al., 2002). In typically developing (TD) children and adolescents, a core bilateral fronto-parietal network is known to underpin verbal and visuo-spatial WM (e.g., Kwon et al., 2002; O'Hare et al., 2008; Spencer-Smith et al., 2013; van den Bosch et al., 2014). Intrahemispheric as well as interhemispheric connectivity, mostly supported by the CC, is likely to play a crucial role in WM processes by promoting efficient functional integration between brain areas (Hillary et al., 2011; Koshino et al., 2005; Schlösser et al., 2006). Indeed, in typically developing children, a significant correlation between visual WM performance and development of white matter in the anterior corpus callosum has been described (Nagy et al., 2004). In brain-injured children, microstructural integrity of the CC has been associated with variance in verbal and visuospatial WM capacity (Treble et al., 2013). As a consequence, in AgCC a disruption of normal functional connectivity between the two hemispheres would be expected to impact on WM processes (Quigley et al., 2001). However, WM and concomitant interhemispheric interactions have not previously been studied in AgCC individuals. To our knowledge, two case studies have been published examining WM abilities in AgCC, both adults. However, results are contradictory, with impaired performance on a 2-back task in one case (Simon et al., 2008), and average performance on auditory-verbal and visual WM tasks in the second case (Reddy et al., 2010). In addition, Sauerwein and Lassonde (1994) reported working memory performance below the average range but not significantly different from the control group in 9 individuals with AgCC from 10 to 29 year-old.

Our study aimed to investigate the functional organisation of WM in children and adolescents with AgCC compared with TD children using fMRI. We designed an fMRI WM paradigm developmentally appropriate for participants across a wide age range and with different WM capacities (Siffredi et al., 2017). Specifically, our paradigm was adapted from the Brown-Peterson task (Brown, 1958; Peterson and Peterson, 1959), which allows us to: 1) explore brain systems recruited by different verbal WM processes: encoding, maintenance and retrieval; and 2) investigate the effect of different concurrent tasks (verbal and visual) during maintenance and retrieval. As hemispheric lateralisation of verbal versus visual processing and communication between hemispheres might differ in the context of AgCC, we expect that brain networks in AgCC children will show different patterns of activation compared with TD children during the fMRI WM paradigm.

2. Materials and methods

2.1. Participants

Nine participants with AgCC diagnosed on MRI were recruited from clinics and radiology records at The Royal Children's Hospital in Melbourne, Australia, as part of the "Paediatric Agenesis of the Corpus Callosum Study" at the Murdoch Children's Research Institute. Individuals with a diagnosis of AgCC confirmed on MRI were aged 9–17 years at assessment. In addition to a diagnosis of AgCC on MRI. Further inclusion criteria were: English speaking, and ability to engage in the assessment. A comparison group of 16 typically developing (TD) children and adolescents was recruited through advertisement in local schools and through staff at The Royal Children's Hospital. TD participants were aged 8–16 years at assessment, English speaking, with no documented history of a brain lesion, neurological disability or neurodevelopmental disorders. Participants from the AgCC and TD groups had normal or corrected-to normal vision and hearing.

2.2. Descriptive measures

Verbal working memory capacity was estimated using the standard scores of the Digit Span Backward subtest from the Wechsler Intelligence Scale for Children 4th edition (WISC-IV; Wechsler, 2003) and from the Wechsler Adult Intelligence Scale 4th edition for the 17 year-old participant (WAIS-IV; Wechsler, 2010; M = 10, SD = 3). Participants listened to a sequence of digits, which they were required to repeat in the reverse order. Full-Scale Intelligence Quotient (IQ) was estimated using the 4-subtests version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Handedness was estimated using the Edinburgh Handedness Inventory (EHI), a ten-item self-report questionnaire assessing preferred hand for daily life activities (Oldfield, 1971).

2.3. Neuroimaging

2.3.1. Image Acquisition

MRI was performed on a Siemens 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany) at the RCH. The scanner was equipped with the Syngo MR B17 software release, and a 32-channel receive-only head coil was used. T1-weighted MP-RAGE sequence (Magnetisation Prepared Rapid Gradient Echo) were obtained, TR = 1900 ms, TE = 2.71 ms, TI = 900 ms, FA = 9°, FoV = 256 mm, voxel size = 0.7 × 0.7 × 0.7 mm. Functional images were acquired using a T2*-weighted

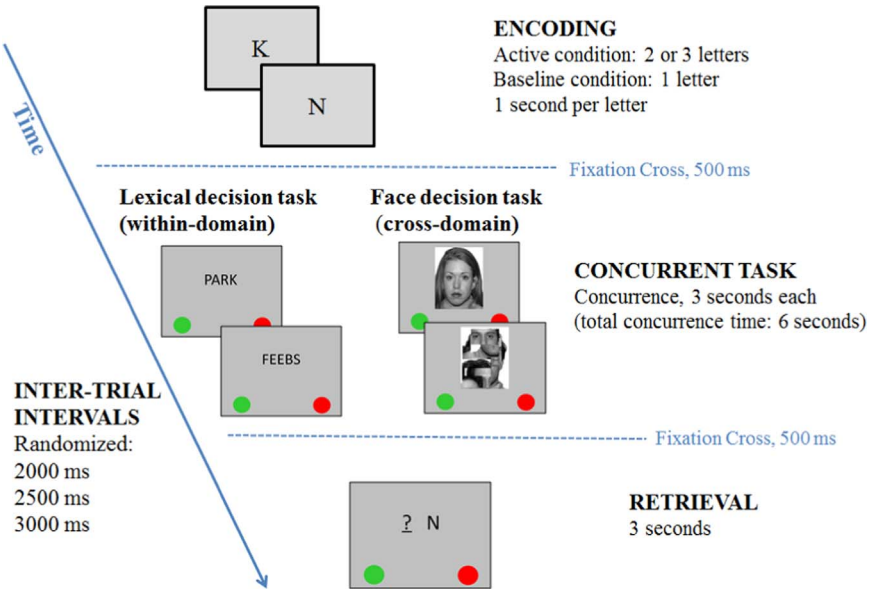

Fig. 1. Adapted Brown-Peterson fMRI WM paradigm.

gradient-echo-planar imaging (EPI) sequence with 32 interleaved slices with 5% gap, voxel size = 2.6 × 2.6 × 3 mm, TR = 2400 ms, TE = 35 ms, FA = 90°, FoV = 240 mm.

2.3.2. Scan coding

Using a revised coding system for brain malformations (Leventer et al., 1999), sagittal T1- and coronal T2-weighted structural MR images were qualitatively reviewed by a paediatric neurologist (RJL). Absence of the CC was classified as complete if no callosal tissue was present or partial only a part of the callosum was absent. Any associated brain anomalies were noted.

2.3.3. fMRI paradigm

Participants completed an adapted version of the Brown-Peterson paradigm (Brown, 1958; Peterson and Peterson, 1959) previously described in Siffredi and colleagues (2017), presented visually during fMRI using E-prime2 (Psychology Software Tools, PST, Pittsburgh). A mixed block and event-related design allowed us to separately examine different processes of WM. The task required a combination of verbal encoding and maintenance during either verbal (within-domain) or visual (cross-domain) concurrent tasks. Each trial consisted of three parts, Fig. 1: 1) an encoding period during which participants were presented with a series of single upper-case letters for further recall displayed sequentially in the middle of the screen at a rate of one letter per second; 2) a maintenance delay of 6 s filled with a concurrent task requiring to process either verbal or visual stimuli involving within- or cross-domain interference respectively (see below); and 3) a letter retrieval period of 3 s during which participants were presented with one single upper-case letter among one (paradigm with 2 letters to remember) or two (paradigm with 3 letters to be remembered) dashes with a question mark in the middle of the screen. Participants have to indicate as quickly and as accurately as possible whether this letter matched the letter previously seen in that serial position, by pressing the green key [left side] for yes (same letters and same order) or the red key [right side] if not. This was done to make sure that participants memorised both the item and order of information. The within-domain concurrent task was a lexical decision task. Two successive letter-strings were presented for 3 s each and required a simple motor response (i.e. press as quickly and as accurately as possible the green key if the letter-string was a word or the red one if it was a non-word). The cross-domain concurrent task was a face decision task of two successive pictures presented for 3 s each, requiring a motor responses (i.e. press as quickly and as accurately as possible the green key if a real face was presented or the red key if it was a scrambled face).

A randomised inter-trial interval of 2000, 2500, or 3000 ms was used before the next trial. Two types of blocks of 10 trials each were created: one including the within-domain concurrent task and the other including the cross-domain concurrent task. The order of presentation of these two blocks was counterbalanced across participants and repeated twice for a total of four blocks of 10 trials. Within each block, half of the probes were positive (i.e., 5 trials required a “yes or green” response) and the position of positive and negative probes were randomized within each blocks.

Because a challenge of brain imaging studies examining cognitive development is that differences in both age and task performance may influence activation patterns, the memory load in our fMRI WM paradigm was tailored to each participant. At issue is whether changes in neural activity reflect changes in functional maturation of the central nervous system, independently of behavioural efficiency, or whether they reflect changes in task performance naturally associated with increasing age (Kwon et al., 2002; Schweinsburg et al., 2005). Therefore, in our paradigm, task difficulty was adapted to each participant by adapting the number of verbal items to remember, while keeping the protocol similar to avoid other issues related to differences in the timing and sampling of brain activity measures. Consistent with our previous study (Siffredi et al., 2017), children with a backward digit span of 5 or more were presented with 3 letters to be remembered, whereas children with a backward digit span lower than 5 had only two letters to remember. In the AgCC group, seven participants completed the 2-letters paradigm (age range = 9–17.08, M = 12.21, SD = 2.78), and two completed the 3-letters paradigm (age range = 9.67–15.58, M = 12.63, SD = 4.18). In the TD comparison group, 10 participants completed the 2-letters paradigm (age range = 8.33–16.42, M = 11.97, SD = 2.63), and six completed the 3-letters paradigm (age range = 10.92–15.08, M = 12.57, SD = 1.58). There was no significant group difference between the numbers of participants who completed the 2-letters or 3-letters versions of the paradigm ($p = 0.661$, Fisher's exact test).

2.4. Procedure

This study was approved by The Royal Children's Hospital Human Ethics in Research Committee. Written informed consent was obtained from the caregivers prior to participation in the study. Children completed a mock MRI scanner training protocol. They were prepared extensively for the fMRI task through training outside and inside the

scanner. The fMRI WM paradigm was projected onto a screen at the foot of the MRI bed, and participants viewed the images from a mirror attached to the head coil. Responses were provided using an MRI compatible response box with four response buttons, which was placed centrally on the child's stomach.

2.5. Statistical analysis

2.5.1. fMRI WM paradigm behavioural data

To examine differences in performance accuracy between the within- and cross-domain concurrent tasks and following retrieval, Wilcoxon signed-rank tests were performed (given that the assumption of normality was violated for the accuracy measure in all conditions in both groups as assessed by inspection of histograms and results of the Shapiro-Wilk test, ranging from $p < 0.001$ to $p = 0.003$). Group differences in performance accuracy were explored using Kruskal-Wallis tests. To examine the effect of the concurrent tasks on retrieval in the two groups, linear regressions were performed. Regression plots presenting various residual values were inspected to establish the validity of regression assumptions. Statistical analyses were performed in SPSS (IBM, Released, 2013).

2.5.2. Image analysis

fMRI data were preprocessed and analysed in SPM8 (Wellcome Department of Imaging Neuroscience, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in Matlab R2014a. Images of each subject were spatially realigned to eliminate movement artefacts, and corrected for slice acquisition timing. As noted by Tyszka et al. (2011), morphological differences between AgCC and TD individuals are minimal on the lateral cortical surfaces, but are pronounced around the midline and ventricles due to the absence of the CC, and the presence of Probst bundles, mesial cortical reorganisation and colpocephaly. Therefore, we created a customised template using the DARTEL algorithm following the procedure outlined by Salami et al. (2014), which is close to the procedure used by Tyszka et al. (2011). First, individuals' T1-weighted images were segmented into grey and white matter using the toolbox "New Segment". Secondly, a group-specific template ($n = 25$) was created using Exponentiated Lie Algebra (DARTEL). Grey and white matter tissue class images were imported using the normalisation parameter yielded during the segmentation step followed by resampling to isotropic voxels ($1.5 \times 1.5 \times 1.5$ mm). Then, the imported images went through and interactive procedure that began by producing an initial template as a mean of grey and white matter across all participants. Deformation from the initial template to each individual's grey and white matter images was computed and the inverse of the deformation was applied to each individual's images. A second template was created as the mean of the deformed individuals' grey and white matter images across all participants, and this procedure was repeated until a sixth template was created, Fig. 2. Finally, the realigned and resliced fMRI images and the flow field grey matter image were nonlinearly normalised to the sample-specific template for each individual independently (voxel size of $1.9 \times 1.9 \times 3$ mm); and affine-aligned into MNI space. These functional images were finally smoothed using a Gaussian filter of full width at half maximum = 8 mm to increase signal-to-noise ratio.

Statistical analyses were performed using a two-step process, taking into account the intra-individual and inter-individual variance (Friston et al., 1995). First level single subject statistics were assessed by a voxel-based statistics according to the General Linear Model implemented in SPM8. Activity was analysed pooling across the correct and incorrect trials together. The onsets of each event of interest, i.e., verbal encoding, lexical decision task (within-domain concurrent task), face decision task (cross-domain concurrent task), retrieval following within-domain concurrent task, retrieval following cross-domain concurrent task, were convolved with the canonical hemodynamic response function (HRF) and used as regressors in the individual design matrix. The letter encoding period was modelled using a boxcar function of 2 or 3 s (depending of the difficulty of the task); the maintenance delay filled with one of the concurrent task was modelled using a boxcar function of 6 s; and finally, the letter retrieval period was modelled using a boxcar function of 3 s.

All six movement parameters (translation: x, y and z; rotation: pitch, roll and yaw) were included as covariates of no interest in the model. The individual statistical images from each condition were then entered group-averaged at the second level using a flexible factorial design, with a main-effect of subject and an interaction of conditions and groups. In this random-effects model, we modelled independent levels for subject and group, but dependent levels for conditions. For the three factors, we modelled unequal variances, which allows for violation of sphericity, as implemented in SPM8. In line with guidelines used in neuroimaging studies of complex cognitive functions (Lieberman and Cunningham, 2009), whole-brain analysis was conducted with a significance threshold of $p < 0.001$ at the voxel level, uncorrected for multiple comparisons, and a minimum extent threshold of 20 voxels. Conjunction analysis was performed to define regions commonly activated in both groups (Friston, 1999). Between group contrasts were conducted to define regions differentially activated in the two groups. The condition x group interaction was masked by the main effect of this same condition in one group to identify condition-specific effects for the given group. We used inclusive masks of within group contrast with an uncorrected mask p-value of 0.05 and a significance threshold of $p < 0.001$ at the voxel level, uncorrected for multiple comparisons, and a minimum extent threshold of 20 voxels. Anatomical location of activations was verified using SPM Anatomy toolbox (Eickhoff et al., 2005) and xjView (Cui, 2007). In addition, results in AgCC were reviewed individually to make sure that the locations of group activations corroborate activations at the individual level.

A series of multiple regressions with retrieval accuracy as the covariate and the factor group as the regressor was conducted for the whole brain in the AgCC and the TD groups separately during encoding, retrieval following within-domain concurrent tasks and following cross-domain concurrent tasks. Similarly, multiple regressions were used to explore any association between brain activations with WM capacity measured by Digit Span Backward or IQ scores. In the AgCC group, multiple regressions were used to investigate association between brain activity and handedness or extent of agenesis (complete or partial). For these regressions, a significant threshold of $p < 0.001$, and a minimum extent threshold of 20 voxels was used. To explore the impact of potential covariates on the activation pattern, analyses were initially conducted without any covariates and then repeated with the following covariates: IQ scores, Digit Span Backward scores, handedness and sex.

3. Results

3.1. Sample characteristics

The AgCC group was similar to the TD comparison group in age ($t(23) = 0.111$, $p = 0.312$), sex ($X^2(1, n = 25) = 2.71$, $p = 0.1$) and Digit Span Backward standard scores ($t(23) = -1.43$, $p = 0.17$), Table 1. Six children had complete AgCC, and three had partial AgCC, Table 2. Six of the nine children with AgCC and all TD children were right-handed. Full-Scale IQ was significantly lower in the AgCC than the TD group ($t(10.17) = -4.05$, $p = 0.002$).

3.2. fMRI WM paradigm – behavioural findings

Percentages of correct trials (i.e., accuracy) were calculated for the different conditions, Fig. 3. For the concurrent tasks, accuracy was similar on the cross-domain and within-domain tasks for the total sample ($Ws = 121.5$, $z = 1.59$, $p = 0.113$), the AgCC group ($Ws = 29.5$, $z = 1.62$, $p = 0.106$) and the TD group ($Ws = 33$, $z = 0.58$, $p = 0.565$). On the within-domain concurrent task, the AgCC group performed less

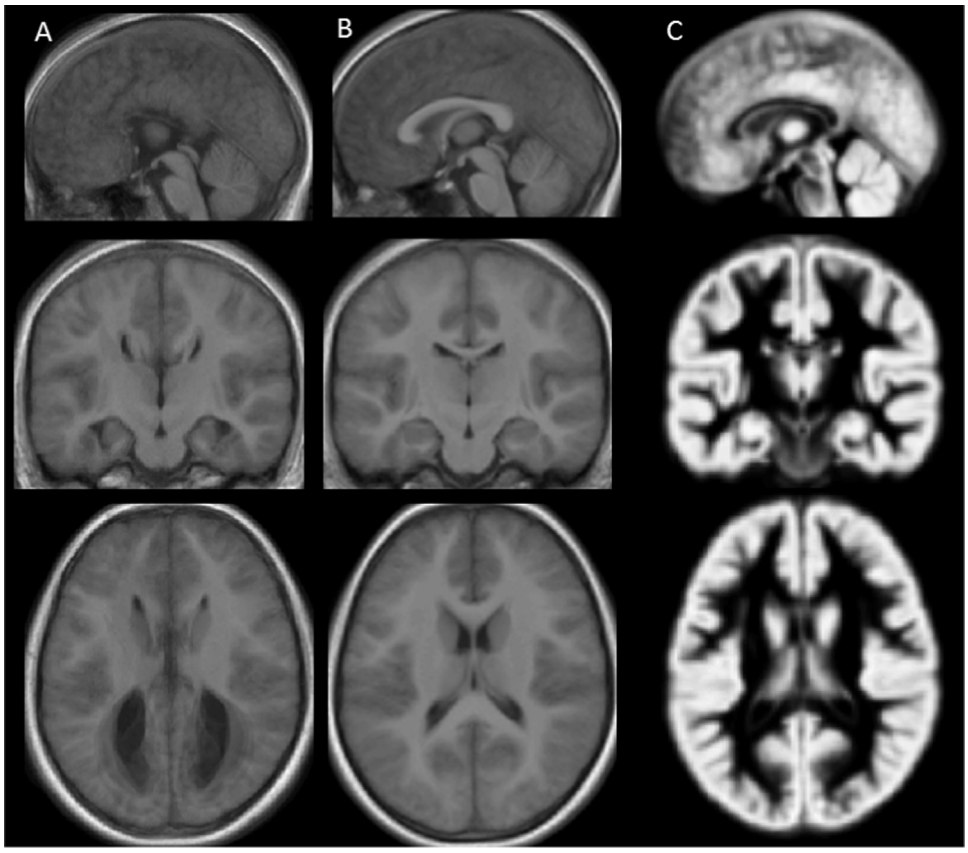

Fig. 2. Creation of a customised template using DARTEL: (a) Mean T1-weighted image of the AgCC group; (b) Mean T1-weighted image of the TD comparison group; (c) Customised template created using DARTEL based on structural images from the total sample of AgCC and TD children (6 iterations).

Table 1
Characteristics of the agenesis of the corpus callosum (AgCC) and typically developing (TD) groups.

	AgCC	TD
n	9	16
Mean age in years	12.31 (SD = 2.83)	12.19 (SD = 2.25)
Sex	7 males, 78%	7 males, 44%
Handedness	6 right-handed, 67%	16 right-handed, 100%
Mean Full-Scale IQ	85.44 (SD = 21.42)	116.19 (SD = 10.4)
Mean Digit Span Backward standard score	9 (SD = 3.61)	11.1 (SD = 3.38)

accurately than the TD group (H(1) = 5.86, p = 0.015) but similar to the TD group on the cross-domain concurrent task (H(1) = 0.13, p = 0.716). For the retrieval period, retrieval accuracy was similar after the cross-domain concurrent task and within-domain concurrent task in the total sample (Ws = 103, z = 0.78, p = 0.439), the AgCC group (Ws = 18.5, z = 0.071, p = 0.943) and the TD group (Ws = 36.5, z = 0.93, p = 0.352). The AgCC group performed similar to the TD group differences in retrieval accuracy after the cross-domain (H(1) = 2.33, p = 0.127) or within-domain (H(1) = 1.45, p = 0.229) concurrent task. Performance on the concurrent task did not predict performance on the retrieval period in the total sample (F(1;1198) = 2.35, p = 0.126), in the AgCC group (F(1;518) = 0.491, p = 0.484) or the TD group (F(1;678) = 2.74, p = 0.98). There was no significant association between age and performance accuracy for the different tasks in the AgCC group or the TD group (r ranging from −0.126 to 0.493).

Table 2
Demographic and neuroimaging details of children with agenesis of the corpus callosum (AgCC).

ID	Age	Sex	H	FSIQ	C/P	CC details	AC	PC	PB	CO	Associated MRI findings
102	12.67	M	R	70	C	Absent	+ +	+	+	+	None
103	11	M	R	76	C	Absent	+	Tiny	+	+	None
104	15.58	M	L	113	P	Part of genu Present	+	+	+	+	None
105	14.42	M	R	67	C	Absent	+	+	+	+	None
106	11.33	M	L	67	C	Absent	+	+	+	+	Cortical dysplasia in L frontal lobe
109	9.67	F	R	126	P	Genu and anterior body present, thin rostrum	+	+	+	+	History of haemorrhagic cerebral AVMdue to hereditary haemorrhagic telangiectasia
110	9	M	L	95	C	Absent	+	+	+	+	L interhemispheric cyst with septation, malformed cortex around cyst
112	17.08	M	R	82	P	Rostrum present	-	+	+	+	Frontonasal dysplasia, sphenoidal encephalocele
113	10	F	R	73	C	Absent	+	+	+	+	None

Note: ID study identification number; Age in years; Sex: F female, M male; H Handedness: L left, R right; P/C: P partial AgCC, C complete AgCC; CC details: corpus callosum structural properties details; AC: anterior commissure, and PC: posterior commissure: - absent, + present and normal size, + + enlargement; PB: Probst bundles, and CO: colpocephaly: + present, - absent; Associated MRI findings: L left, R right.

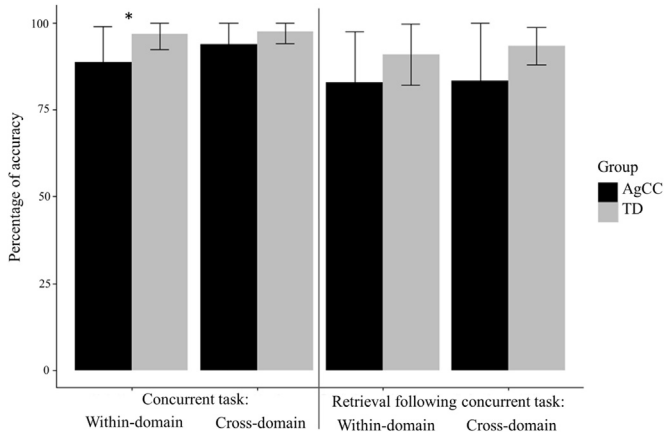

Fig. 3. Percent of accurate performances on the fMRI WM paradigm conditions for the AgCC and TD groups. * Significant group differences, $p < 0.05$.

3.3. fMRI WM paradigm – neuroimaging findings

3.3.1. Movement

Head motions were small in any direction and therefore no participant was excluded from further processing: Maximum translation: AgCC group X = 0.68 mm, Y = 1.08 mm, Z = 1.44 mm and TD group X = 0.39 mm, Y = 0.76 mm, Z = 1.69 mm; Maximum rotation (converted from degrees to millimetres; Power et al., 2012): AgCC group X = 0.03 mm, Y = 0.04 mm, Z = 0.008 mm and TD group X = 0.04 mm, Y = 0.2 mm, Z = 0.01 mm; Mean translation (considering absolute values): AgCC group X = 0.35 mm, Y = 0.56 mm, Z = 1.77 mm and TD group X = 0.08 mm, Y = 0.11 mm, Z = 0.25 mm; Mean rotation: AgCC group X = 0.03 mm, Y = 0.02 mm, Z = 0.004 mm and TD group X = 0.004 mm, Y = 0.003 mm, Z = 0.002 mm. Overall, the mean largest translational motion across the X, Y, and Z head directions (taken from realignment parameters) was 1.77 mm (SD = 0.52) for the AgCC group and 0.84 mm (SD = 0.17) for the TD group; and the mean largest rotation motion across X, Y, Z was 0.02 mm (SD = 0.008) for the AgCC group and 0.01 mm (SD = 0.004) for the TD group. Finally, movement for the AgCC group was similar to the TD group (translation X: $t(23) = 0.506$, $p = 0.126$; Y: $H(1) = 0.051$, $p = 0.821$; Z: $H(1) = 2$, $p = 0.157$; Rotation X: $t(23) = -0.485$, $p = 0.632$; Y: $t(23) = 1.466$, $p = 0.156$; Z: $t(23) = 1.566$, $p = 0.131$).

3.3.2. Activations during encoding vs. retrieval

We first compared activations shared for the AgCC group with the TD comparison group during encoding compared to the retrieval period using a conjunction analysis, which revealed large occipital and frontal activations bilaterally. Group comparisons identified some differences in the pattern of activations in these regions. Specifically, the AgCC group showed increased right-lateralised activations in occipital regions, prefrontal ventrolateral regions (BA 44 and 47) and superior temporal regions (limits of BA 40), while the TD group showed amplified activation in bilateral lingual and inferior occipital regions, Tables 3, 4, Figs. 4A and 5.

For the retrieval compared to the encoding period, conjunction analyses showed shared activations across the AgCC and TD groups in bilateral frontal areas (middle and inferior) and anterior cingulate, as well as temporo-parietal cortex (angular and middle temporal) and occipito-parietal cortex (angular, middle occipital, cuneus and precuneus). Group comparisons again identified some differences in the pattern of activations in these regions. Specifically, the AgCC showed a small significant left-lateralised activation in the posterior cingulate gyrus and the TD group showed right-lateralised activation in ventrolateral prefrontal, middle and superior temporal, and calcarine regions, as well as a left-lateralised activity in supramarginal regions, Fig. 4B.

3.3.3. Activations during concurrent tasks (within-domain vs. cross-domain)

Conjunction analyses for activations during the lexical decision concurrent task (within-domain) compared to the face decision concurrent task (cross-domain) revealed no significant similarities between the AgCC and TD groups. Group comparisons indicated increased activity in the AgCC group in the right fusiform cortex, as well as bilateral orbital (BA10) and ventrolateral (BA45) prefrontal areas, plus a small cluster in the left middle temporal gyrus. In TD children, differential activations were found in left anterior cingulate regions, Tables 3, 4, Fig. 4C.

For the face decision concurrent task (cross-domain) compared to the lexical decision concurrent task (within-domain), conjunction analyses showed shared activations across the AgCC and TD groups in bilateral occipital and inferior temporal areas. Group comparisons revealed differential increases in anterior cingulate regions in the AgCC group, while the TD group showed significantly stronger activity in a large right-lateralised fusiform cluster, overlapping with reported location for the right occipital face area (Minnebusch et al., 2009), as well as smaller increases in prefrontal (BA10), temporal, and subcortical areas, Fig. 4D.

3.3.4. Activations during retrieval following within-domain vs. cross-domain concurrent tasks

Finally, we tested whether the nature of the concurrent task during the maintenance interval produced different activations during the retrieval period, and whether these effects differed between groups. For retrieval following within-domain (lexical decision) compared to retrieval following cross-domain concurrent task (face decision), conjunction analyses showed shared activations across the AgCC and TD groups in large occipital areas. Group comparisons identified some differences in the pattern of activations in these regions. The AgCC group showed increases in the right calcarine and left precuneus, while the TD group showed a large increase in right occipito-temporal regions (middle occipital, fusiform, and inferior temporal). Notably, the TD group also showed differential increases in the right dorsolateral prefrontal cortex, Tables 3, 4, Fig. 4E.

Conversely, for retrieval after the cross-domain concurrent task (face decision), conjunction analyses revealed shared activations across the AgCC and TD groups in small bilateral medial frontal regions. Group comparisons revealed more anterior activations in prefrontal areas (right dorsolateral and cingulate) for the AgCC group, and significant increase in bilateral posterior areas (occipital cortex and precuneus) for the TD group, Fig. 4F.

3.3.5. Association between fMRI activations and fMRI task performance, cognitive scores, extent of agenesis, and handedness

To test for any systematic modulation of brain activation patterns by individual factors, we performed additional exploratory whole-brain analysis using a parametric regression design in SPM with covariates of interest reflecting several potentially relevant differences in participants with AgCC compared with the TD group (with a significance threshold of $p < 0.001$ and a minimum extent threshold of 20 voxels). For both the AgCC and TD groups, we observed no significant associations between brain activations during either encoding or retrieval with WM retrieval accuracy during fMRI, nor with IQ or verbal WM scores from neuropsychological tests. Furthermore, in the AgCC group, no significant association was observed with the extent of callosal agenesis (complete versus partial) or handedness.

4. Discussion

This study aimed to investigate the functional organisation of WM in children with AgCC using fMRI. The few previous functional imaging studies in individuals with AgCC have largely focused on activations in response to simple motor (Lum et al., 2011) or sensory stimuli (e.g.,

Table 3
Conjunction analyses between the AgCC and TD comparison groups for the comparisons of interest.

Region		Hemisphere	Number of voxels	t value	x,y,z
Encoding > Retrieval					
Occipital	Inferior	R	1701 *	9.22	32 −82 −9
	Lingual			9.14	21 −89 −9
	Fusiform			5.55	38 −51 −15
	Inferior	L	1355 *	7.79	−34 −84 −12
	Fusiform			7.28	−38 −55 −15
	Calcarine			5.54	−8 −97 −6
Frontal	Anterior cingulate	R	348 *	5.17	6 4 48
		L		4.53	−8 11 39
	Inferior	R	45 *	4.27	44 9 27
	Precentral Gyrus	R	84	4.07	42 −15 54
Retrieval > Encoding					
Frontal	Middle	R	88 *	4.24	38 11 45
	Anterior cingulate	L	176 *	3.41	0 36 15
	Superior medial			3.91	0 32 48
	Middle	L	33	4.05	−40 9 45
	Inferior	R	32	3.87	49 36 −9
Parieto-temporal	Angular	R	478 *	6.06	40 −72 36
	Middle temporal			4.66	55 −51 18
Occipito-parietal	Angular	L	632 *	5.31	−44 −57 33
	Middle occipital			4.86	−40 −72 30
	Precuneus	R	1529 *	5.42	4 −68 48
	Precuneus	L		5.08	−9 −51 36
	Cuneus	R		4.78	4 −78 39
	Cuneus	L		4.61	−4 −91 21
Temporal	Middle	L	47	3.97	−65 −32 −9
Within-domain Concurrent Task > Cross-domain					
No suprathreshold cluster					
Cross-domain Concurrent Task > Within-domain					
Occipital	Calcarine	R	92	3.9	4 −89 12
Temporal	Inferior	L	22 *	4.05	−51 −48 −6
Retrieval after within-domain > Retrieval after cross-domain concurrent task					
Occipital	Fusiform	R	831 *	6.43	30 −76 −9
	Cuneus			5.44	13 −97 6
	Lingual			4.77	13 −80 −9
	Fusiform	L	701 *	6.03	−23 −80 −12
	Inferior			3.64	−40 −80 −9
	Calcarine	L	67 *	5.34	−2 −91 −9
	Middle	L	28 *	4.14	−40 −82 15
Retrieval after cross-domain > Retrieval after within-domain concurrent task					
Frontal	Medial	R	150	4.03	8 15 48
	Posterior-medial	L		3.41	0 9 57

Coordinates are given in MNI space. x, y, z coordinates refer to voxels with highest statistical significance within a cluster (location of peak coordinate). Analyses conducted with and without covariates (i.e., IQ scores, Digit Span Backwards scores, sex and handedness) showed very similar pattern of activations but at a much smaller threshold in general when the covariates were added to the model. Therefore, clusters reaching the significant threshold of $p < 0.001$, and a minimum extent threshold of 20 voxels when the covariates were added to the model, are marked with a sign *.

Duquette et al., 2008; Paiement et al., 2010), language lateralisation (e.g., Pelletier et al., 2011) or emotionally laden information (Lungu and Stip, 2012). To our knowledge, this is the first study to explore brain activity related to WM in this population. Understanding WM functioning in children with AgCC is crucial as WM might be an important contributor to difficulties in everyday activities, including academic achievement (e.g., Alloway et al., 2009; Gathercole et al., 2004).

Although children with AgCC have a major abnormality of early brain development, they recruited globally similar regions as our comparison group of TD children during both the encoding and retrieval phases of our verbal WM paradigm. Nevertheless, group differences in activation patterns were observed. These findings did not depend on the fMRI task performance, IQ or WM scores in either of the AgCC or TD groups, or handedness and extent of agenesis (complete or partial) in children with AgCC.

4.1. Verbal encoding and retrieval

During verbal encoding compared to retrieval, both AgCC and TD children recruited widespread visual areas bilaterally, consistent with their role in perceptual shape analysis, including those involved in letter processing (Flowers et al., 2004; Garrett et al., 2000). There were, however, group differences in the pattern of occipital regions, with larger right-lateralised increased activations in children with AgCC but greater left-lateralised activations in the TD group. These differences presumably reflect less visual word form than letter specific processing in AgCC compared to TD children, conversely to the typical lateralisation of the “visual word form area” (Cohen et al., 2000). This might point to differential hemispheric dominance patterns in visual cortical areas in AgCC, subsequent to atypical interhemispheric interactions. In addition to occipital activations, both groups recruited large bilateral frontal areas during encoding (anterior cingulate, ventrolateral, and precentral). These findings corroborate previous results showing involvement of these regions during encoding and maintenance of different kinds of information in WM and long-term memory (Axmacher et al., 2009; Chein and Fiez, 2001; Rastle et al., 2002).

During retrieval compared to encoding, activations were observed in AgCC as well as the TD children in extensive bilateral fronto- and parieto-temporal regions. These findings are consistent with previous studies showing involvement of frontal-parietal regions (dorsolateral prefrontal, anterior cingulate, and parietal angular regions) in attention and executive control systems during WM, especially during retrieval of information (Crone et al., 2006; Marshuetz et al., 2000; Osaka et al.,

Table 4
Between group comparisons for encoding, concurrent tasks and retrieval using an inclusive contrast mask for each group.

Region		Hemisphere	Number of voxels	t value	x,y,z
Encoding > Retrieval					
TD group					
Occipital	Lingual	L	504*	6.51	−19 −87 −12
	Inferior			6.25	−21 −89 −3
	Lingual	R	29	4.13	23 −84 −12
	Middle	R	21	3.76	30 −67 30
AgCC group					
Occipital	Calcarine	R	143 *	5.28	8 −91 6
Frontal	Inferior	R	149*	4.4	53 13 6
	Inferior	R		4.31	51 19 0
	Inferior	R	27	3.51	34 28 3
Temporal	Superior	R	31 *	3.93	61 −21 15
Retrieval > Encoding					
TD group					
Frontal	Inferior	R	159 *	4.4	53 13 6
	Inferior	R		4.31	51 19 0
Temporal	Rolandic Operculum	R	109	3.97	53 −27 21
	Superior	R		3.93	61 −21 15
	Middle	R	69	3.96	61 −36 6
	Middle	R	24 *	3.69	57 −19 −6
Parietal	Supramarginal	L	48 *	3.7	−57 −49 24
Occipital	Calcarine	R	105 *	5.28	8 −91 6
AgCC group					
Parietal	Posterior cingulate	L	66	3.84	0 −38 33
Within-domain concurrent task > Cross-domain					
TD group					
Frontal	Anterior cingulate	L	56	3.94	−8 21 27
AgCC group					
Occipital	Fusiform	R	78	5.05	32 −78 −12
Frontal	Superior medial	L	53	4.57	−8 63 12
		R	36	3.98	10 61 12
	Inferior	R	23	3.62	46 32 15
Temporal	Middle	L	26	4.4	−61 −25 −18
Cross-domain concurrent task > Within-domain					
TD group					
Occipital	Fusiform	R	306 *	5.05	32 −78 −12
	Inferior Occipital	R		4.56	38 −86 −15
Frontal	Superior Medial	L	39	4.57	−8 63 12
Temporal	Middle	L	32	4.4	−61 −25 −18
Limbic	Putamen	L	27	4	−28 −10 3
AgCC group					
Frontal	Anterior cingulate	L	45	3.94	−8 21 27
Retrieval following within-domain > Retrieval following cross-domain concurrent task					
TD group					
Occipito-temporal	Middle occipital	R	698 *	7.06	30 −86 9
	Inferior temporal			4.98	48 −53 −12
	Fusiform			4.3	30 −49 −15
	Middle occipital	L	86	4.43	−23 −93 3
Frontal	Inferior	R	64 *	4.12	49 40 6
AgCC group					
Occipital	Calcarine	R	168 *	5.95	6 −91 3
Parietal	Precuneus	L	22	3.8	0 −49 60
Retrieval following cross-domain > Retrieval following within-domain concurrent task					
TD group					
Occipital	Calcarine	R	97 *	5.95	6 −91 3
Parietal	Precuneus	L	38 *	3.8	0 −49 60
AgCC group					
Frontal	Inferior	R	82 *	4.12	49 40 6
	Anterior cingulate	L	30	3.67	−15 17 33
		R	37	3.48	2 25 30

Coordinates are given in MNI space. x, y, z coordinates refer to the voxels with highest statistical significance within a cluster (location of the peak coordinate). Analyses conducted with and without covariates (i.e., IQ scores, Digit Span Backwards scores, sex and handedness) showed very similar pattern of activations but at a much smaller threshold in general when the covariates were added to the model. Therefore, clusters reaching the significant threshold of $p < 0.001$, and a minimum extent threshold of 20 voxels when the covariates were added to the model, are marked with a sign *.

2007). Group differences were observed, however, in the extent of these activations, with reduced right-lateralised activations in lateral prefrontal and temporal areas for children with AgCC compared to TD children. In healthy individuals, recruitment of ventrolateral prefrontal regions is commonly associated with the active retrieval of information (Petrides et al., 2002; Wager et al., 2014). Right-predominant activation observed in our comparison group of TD children during retrieval is also consistent with the Hemispheric Asymmetry Encoding-Retrieval (HERA) model (Habib et al., 2003; Nyberg et al., 1996). Such hemispheric specialisation might be less present in AgCC children. The AgCC group also differentially activated the left posterior cingulate cortex during retrieval, a region recognised to play a central role in episodic memory retrieval and monitoring task outcome (Heilbronner and Platt, 2013; Leech and Sharp, 2014). In contrast, the TD group differentially

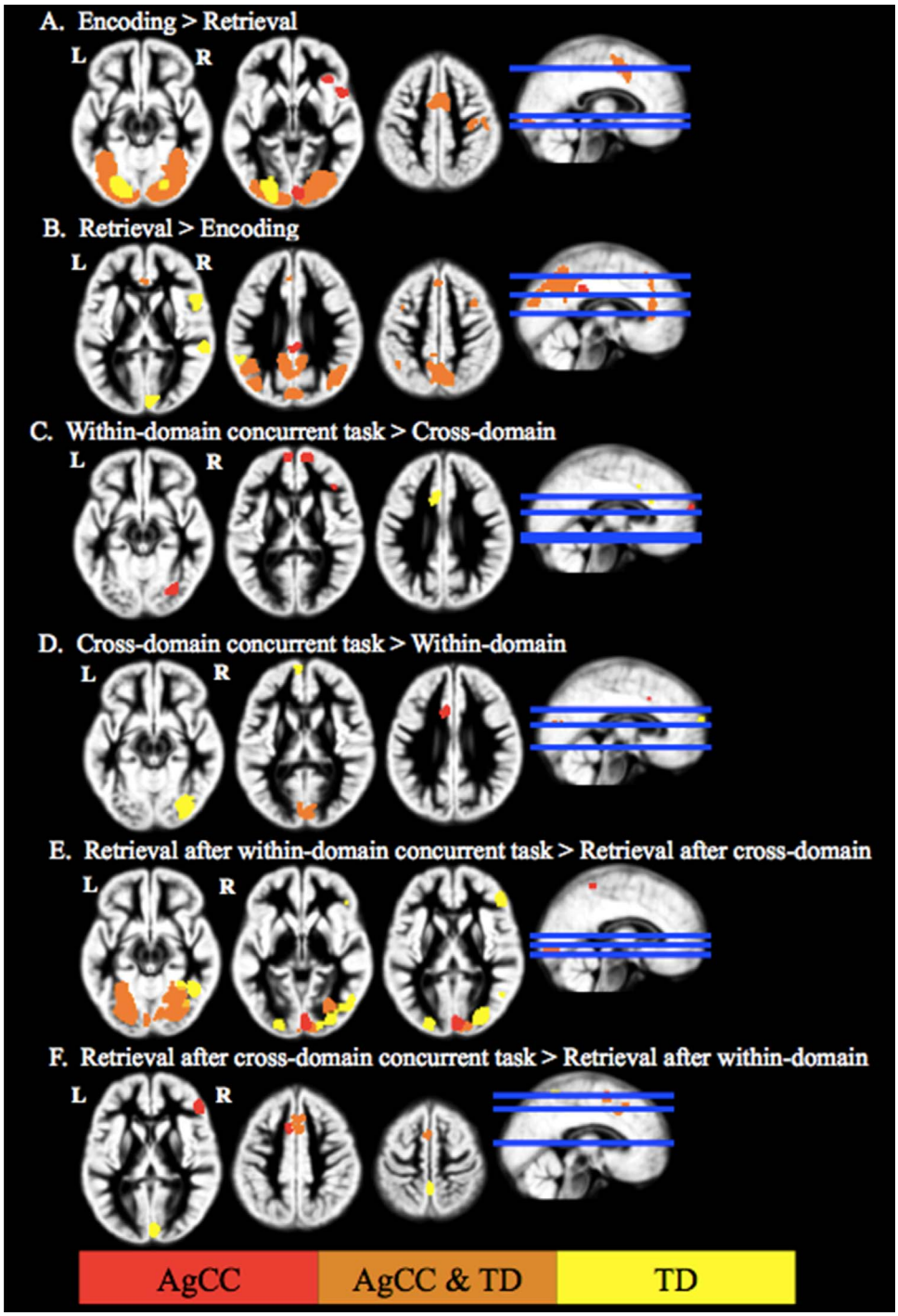

Fig. 4. Activation maps for the comparisons of interest.

recruited the left-lateralised supramarginal region, implicated in language processing (Hartwigsen et al., 2010; Stoeckel et al., 2009), indicating that they could more efficiently recruit regions specialised in the retrieval of verbal information. This could possibly reflect the use of different retrieval strategies in the two groups.

Together, our findings highlight important similarities in brain activation for children with AgCC and their TD peers, with bilateral occipito-frontal activity during verbal encoding, and involvement of bilateral fronto-parietal executive control network during retrieval. Nevertheless, group differences in activation patterns were observed that presumably reflect different hemispheric lateralisation as well as different cognitive strategies to encode and retrieve verbal information. Overall, children with AgCC seemed less able to engage lateralised brain systems specialised for particular memory material (e.g. verbal) and particular memory process (encoding and retrieval) compared to their TD peers.

4.2. Consequences of the nature of the concurrent tasks on maintenance and retrieval

We investigated the impact of the nature of the concurrent tasks (verbal versus visual) on maintenance and retrieval of verbal information. According to the influential model of Baddeley (Baddeley and Hitch, 1974; Baddeley, 1986; Baddeley et al., 2011), maintenance of information involves separate and domain-specific systems: a phonological loop for verbal information and a visuospatial sketchpad for

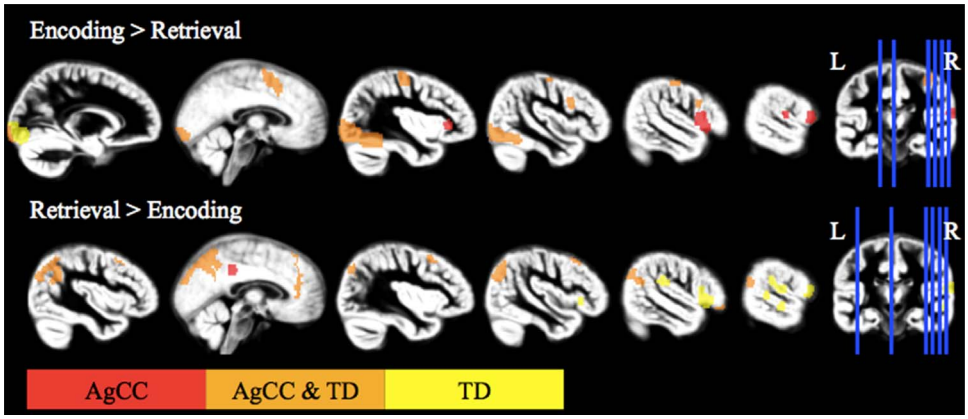

Fig. 5. Activation maps for the comparisons of the encoding vs retrieval periods showing more precisely frontal activations.

visuospatial information. Thus, processing irrelevant verbal information should produce greater interference on verbal maintenance because verbal processing would mobilise the phonological loop, thus impeding the rehearsal process in charge of verbal maintenance. In contrast, processing visuospatial information should involve the visuospatial sketchpad and thus have a reduced effect on verbal maintenance and retrieval. For retrieval performance, our behavioural results did not identify any difference between the within- and cross-domain conditions or between the AgCC and TD groups. Nevertheless, weaker within-domain concurrent task performance (lexical decision) was observed in children with AgCC, suggesting that they were less able to deal with verbal material or resist competition between the verbal encoded items and verbal concurrent items.

During the maintenance interval for the within-domain concurrent task, there was no evidence of similarities in regions activation for the AgCC and TD groups, suggesting different processing of verbal material during maintenance. For the cross-domain concurrent task, only small bilateral occipital clusters were commonly activated in the two groups, in line with the visual shape processing demands of this condition (face decision task). Moreover, differences in processing concurrent stimuli during maintenance were reflected by distinct activation patterns in right extrastriate visual areas and anterior cingulate cortex.

A region in the right fusiform area showed greater activation during the word lexical decision task in children with AgCC, while in the TD children greater activation was observed in this region during the face decision task, as typically reported in healthy populations (Minnebusch et al., 2009). This again suggests atypical hemispheric lateralisation of word and face processing in AgCC individuals (as also observed during the encoding period). Anterior cingulate responses further pointed to a different impact of verbal and visual interference during maintenance in the AgCC compared with TD children. Children with AgCC demonstrated increased activations in this region during the cross-domain concurrent task. Conversely, in TD children, we observed greater recruitment of this region during within-domain concurrence, in accordance with higher conflict for processing resources in this condition and its well-known role in the management of conflict and competition for cognitive resources (Badre and Wagner, 2004; van Veen et al., 2001). It is possible that children with AgCC present differential susceptibility to interference.

In keeping with these differences in brain activity during the maintenance interval, activity during retrieval was also influenced by the nature of the preceding concurrent task. Retrieval following within-domain concurrent task (verbal) elicited large bilateral occipital activations in AgCC as well as TD children. These results suggest greater reliance on visual information when retrieval of letters takes place after distraction by verbal material (i.e., within-domain concurrent task). In contrast, retrieval after cross-domain interference (visual) elicited medial frontal activations in AgCC as well as TD children, consistent with a role of this region in decision and response selection processes (Harrington et al., 2010). Furthermore, retrieval periods after within- and cross-domain interference showed group difference in activations in the right dorsolateral prefrontal cortex. This region, implicated in executive control and WM (Ciesielski et al., 2006), was more strongly recruited in children with AgCC during retrieval after the cross-domain task; whereas TD children recruited this region more during retrieval after the within-domain concurrent task (i.e., condition with higher competition for resources), presumably reflecting different degrees of conflict produced by verbal and visual material during maintenance in AgCC and TD groups. Right prefrontal activation in the TD group corroborates expectation of the model of Baddeley (Baddeley, 1996), i.e., increased executive control in the context of high competition for resources when a verbal concurrent task interferes with to-be remembered verbal items. This was not the case in children with AgCC, which might reflect the use of different cognitive strategies in this group, and possibly less segregated processing of verbal and visual material during the concurrent task, leading to distinct patterns of activation in executive regions during retrieval. This interpretation also accords with our finding of larger and right-predominant occipital activations in TD children after the cross-domain concurrent task, presumably reflecting more efficient retrieval of encoded information due to weaker processing competition with the concurrent tasks in the maintenance interval.

In summary, children with AgCC demonstrated similar activation to TD children in primary occipital areas during the cross-domain concurrent task and retrieval after within-domain concurrent task. However significant group differences in activation patterns were observed in associative visual areas and executive prefrontal regions, which might reflect different susceptibility to interference by the concurrent tasks and different cognitive strategies engaged to cope with competition in processing resources for AgCC compared with TD children. These differences could reflect different degrees of hemispheric lateralisation with AgCC children who seemed less able to recruit specialised brain systems during maintenance and thus differentially resist to verbal and visual interference during WM.

4.3. Potential study limitations

A limitation of our fMRI study is the relatively small sample of children with AgCC. Nevertheless, functional neuroimaging studies in this population are sparse, and their sample size is usually smaller than in the present study and include a much wider age range of participants (e.g., Lum et al., 2011; Quigley et al., 2003; Riecker et al., 2007). Increasing the sample size would allow a more systematic and representative comparison of AgCC with TD children, which would require a multi-centre approach. Another challenge in studying this brain malformation is the high heterogeneity of both clinical and anatomical presentations. A larger sample size would thus also allow for more thorough examination of the role of specific factors within the AgCC

population, such as complete versus partial agenesis, as well as more thorough investigation of the potential impact of additional neuroanatomical and genetics factors. As extra-callosal anomalies are frequent, if not systematic, in AgCC (e.g. large ventricles or cingulate gyrus alteration), these might contribute to group differences not only in brain activation patterns but also in cognitive outcomes. Again, a larger sample size might help to disentangle these factors more clearly. Another possible limitation concerns the interpretation of localisation of functional activations in the AgCC group. First, a customised anatomical brain template was created using DARTEL, but, again, a bigger sample size might allow for a more representative and reliable template. Second, even though activation sites seen on each individual's anatomy showed high consistency with the anatomical localisation of functional activations observed at the group level, group differences in anatomo-functional organisation cannot be completely excluded, especially for areas around the midline such as the anterior cingulate cortex. From a clinical perspective, the inherent heterogeneity in our sample of AgCC children is an important advantage of our study because it gives a representative picture of the AgCC population, including higher and lower functioning individuals rather than focusing on isolated AgCC as most previous studies have.

4.4. Conclusion and implications

Our study reveals globally similar regions of activation for AgCC and TD children demonstrating that the functional brain architecture may develop in a relatively typical way despite the absence or partial absence of the corpus callosum. To some extent, many areas in visual and fronto-parietal networks were found to exhibit normal functional specificity during our WM task, independent of callosal agenesis. Alternative neural pathways for intra-hemispheric and/or inter-hemispheric transfer might compensate for the developmental absence of the corpus callosum. Interestingly, however, differences in activations were observed that suggest the use of different cognitive strategies during WM tasks in AgCC and TD children, with different degrees of hemispheric lateralisation during the processing of concurrent material and distinctive patterns of brain activity during subsequent retrieval. These differences in brain activation patterns for AgCC and TD children were found despite similar retrieval performance overall. Our results will need to be confirmed and extended with further behavioural and neuroimaging testing, but give novel insight into possible ways to promote and improve WM capacity in children with AgCC. Considering the crucial role of WM in cognitive development, more effective implementation of targeted WM interventions could enhance the everyday functioning of individuals with AgCC. In addition, beyond WM, other cognitive functions might be differentially susceptible to functional integration of information and processing competition in widespread networks across the two hemispheres, and therefore more sensitive to absence of the corpus callosum, such as social or mathematics abilities.

In conclusion, individuals with AgCC and other early brain malformations present an exceptional opportunity to study the capacity and limits of brain plasticity and compensation mechanisms during development. This study provides a first step towards better understanding functional brain systems underlying higher cognitive functions in children with AgCC (apart from language functions). We report a WM paradigm that children with AgCC could successfully complete in the scanner, with overall performance controlled to be comparable to TD individuals across a wide age range. We showed that AgCC children recruit globally similar brain regions as their TD peers during encoding and retrieval periods of a WM task, despite marked differences in brain development. Our findings also highlight notable differences in brain activation patterns for AgCC compared TD children that might reflect different cognitive and executive strategies during the WM task, which are likely to be associated with different hemispheric lateralisation of memory material and processes. These activation patterns were stable across children with complete and partial agenesis, left and right handed children with AgCC, as well as stable across differences in behavioural WM performance and IQ in both groups, Further studies are needed to better understand how functional and structural connectivity may contribute to determine to brain plasticity in this atypically developing brain condition, and how these factors contribute to cognitive abilities and daily functioning during childhood and adolescence.

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