Cortical thickness and its neurodevelopmental correlates in adolescents who were born very preterm

Nam, Kie Woo

Awarding institution:
King's College London

Cortical thickness and its neurodevelopmental correlates in adolescents who were born very preterm

Thesis submitted for the degree of Doctor of Philosophy

Institute of Psychiatry

King's College London

Kie Woo Nam

Abstract

Alterations in cortical thickness following very preterm birth have been associated with neuropsychological/behavioural impairments. Here I investigated cortical thickness development in individuals who were born very preterm (gestational age < 33 weeks) between adolescence (15 years old, Time 1) and adulthood (20 years old, Time 2). Using univariate approaches, I compared cortical thickness in preterm-born individuals and controls cross-sectionally, and also assessed cortical thickness changes between Time 1 and Time 2 within each group as well as comparing them between groups. Using a multivariate approach (support vector machine, SVM), I examined spatially distributed between-group differences in cortical thickness at Time 1, and based on this, I predicted group membership of brains scanned at Time 2. Results showed that (1) at Time 1 preterm born adolescents showed greater cortical thickness compared to controls predominantly in occipitotemporal and prefrontal areas as well as temporal poles, differences which decreased by early adulthood; (2) at both time points preterm-born participants showed smaller cortical thickness compared to controls in parahippocampal regions. Longitudinal decrease, but not increase of cortical thickness was observed in all lobes, with the preterm group showing more extensive and widespread changes. SVM identified temporal, occipitotemporal, parietal and prefrontal cortices to be best discriminating between the groups at Time 1 and classified group membership at Time 2 with an accuracy of 86.5%. Longitudinal changes in cortical thickness in left temporal pole, right occipitotemporal gyrus and left superior parietal lobe were significantly associated with executive function scores. To summarise, alterations in cortical thickness development in preterm-born individuals last into early adulthood, with implications for high-order cognitive processing. The proposal, put forward by some

previous studies that preterm individuals would developmentally catch up with the control group was consistent with the results from univariate analysis, but not with those from multivariate analysis.

Acknowledgements

I very much appreciate the patience and constant support from my supervisors Dr Chiara Nosarti, Dr Andy Simmons and Dr Matthew Allin. I would not have been able to complete this project without them, particularly through difficult times.

I am also grateful to Seán Froudist Walsh, Dr Nazareth Castellanos, Dr Slava Karolis, Dr Muriel Walshe, Dr Jonathan O'Muircheartaigh and Dr Thomas White for their help with data and analysis. Things have been easier also due to emotional and professional support from my current and former teammates of the Preterm Research Group, for which I am grateful to each and every one of them. Of course, I owe a great deal to all my new and old friends as well, staying close by or far away.

My special thanks go to Dr Owen O'Daly and Dr Inês Pessoa Baptista, who encouraged me and provided guidance before starting my PhD, and to Dr Chiara Nosarti once again for believing in me and offering me the opportunity for this PhD.

Lastly, I wish to express my utmost gratitude to my father, mother and brother for their constant love and support.

Abbreviations

ADHD	attention deficit hyperactivity disorder
ANOVA	analysis of variance
ANT	Attention Network Test
ASD	autism spectrum disorders
BOLD	blood-oxygen-level dependent
BSID	Bayley Scales of Infant Development
BW	birth weight
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBCL	Child Behaviour Checklist
CGAS	Children's Global Assessment Scale
CLASP	constrained laplacian anatomic segmentation using proximity
COWAT	Controlled Oral Word Association Test
CT	cortical thickness
CV	cortical volume
CVLT	California Verbal Learning Test
DMN	default mode network
DRB	Detour Reaching Box

DTI	diffusion tensor imaging
EC	Euler characteristic
EF	executive function
ELBW	extremely low birth weight
fMRI	functional magnetic resonance imaging
FSIQ	full-scale intelligence quotient
FWHM	full width at half maximum
GA	gestational age
GM	grey matter
HSCT	Hayling Sentence Completion Test
ICBM	International Consortium for Brain Mapping
IQ	intelligence quotient
LBW	low birth weight
MDI	Mental Developmental Index
MINC	Medical Imaging NetCDF
MNI	Montreal Neurological Institute
MPC	Mental Processing Composite
MR	magnetic resonance
MRI	magnetic resonance imaging
NO-PVH	without periventricular haemorrhage

PET	positron emission tomography
PIQ	performance intelligence quotient
PVH	periventricular haemorrhage without complications
PVH+DIL	periventricular haemorrhage and ventricular dilatation
RFT	random field theory
ROCFT	Rey-Osterrieth Complex Figure Test
ROI	region of interest
SD	standard deviation
SPGR	spoiled gradient recalled
SVM	support vector machine
TMT	Trail Making Test
UCLH	University College London Hospital
UNC	University of North Carolina
VBM	voxel-based morphometry
VIQ	verbal intelligence quotient
VLBW	very low birth weight
WAIS	Wechsler Adult Intelligence Scale
WAIS-R	Wechsler Adult Intelligence Scale Revised
WASI	Wechsler Abbreviated Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children

WISC-R	Wechsler Intelligence Scale for Children Revised
WM	white matter
WMS	Wechsler Memory Scale
WMS-R	Wechsler Memory Scale-Revised

Table of contents

List of Tables

List of Figures

Chapter 1: Introduction

1.1 Preterm birth

1.1.1 Definition

Preterm birth is defined as birth taking place before 37 weeks of pregnancy (WHO, 2013). Depending on the gestational age (GA) at birth, preterm birth can be sub-categorised into extremely, very, moderately and late preterm birth (GA in weeks < 28, 28 to <32, and 32 to <37, respectively) (WHO, 2013). In the literature, "low-birth-weight" (LBW): < 2500g; very low birth weight (VLBW): < 1500g; extremely low birth weight (ELBW): < 1000g) is often used interchangeably with "preterm" as some concordance exists between the definitions, only about two thirds of LBW infants are born preterm. The remaining are term-born infants who are small for GA (Tucker & McGuire, 2004).

1.1.2 Epidemiology

Around 1 in 8 deliveries in the USA are regarded as being preterm, and this accounts for 3 out of 4 perinatal deaths (Ananth & Vintzileos, 2006). In developed countries, the frequency is known to be 1-2 in 20 births (Goldenberg, Culhane, Iams, & Romero, 2008). In England and Wales, between 2009 and 2011 7.1-7.3% of all babies were born

preterm, of whom 1.3-1.5% were born very preterm (Statistics, 2011). However, the mortality rate of preterm infants has decreased by 11% between 2006 and 2011.

There are two types of preterm births: indicated and spontaneous preterm births. Indicated preterm births refer to labours induced by medical interventions due to pregnancy complications (Behrman & Butler, 2007), including pre-eclampsia or eclampsia, intrauterine growth (Goldenberg et al., 2008), problems affecting the placenta, haemorrhage before the date of delivery, and kidney disease (Behrman & Butler, 2007). Spontaneous preterm births are induced by several causes such as inflammation or infection , vascular problems, and overdistension of the uterus (Goldenberg et al., 2008). Spontaneous preterm births refer to naturally occurring births due to beginning of labour before full-term gestation or premature breach of foetal tissues (Behrman & Butler, 2007) and are more common in women who have had a previous preterm delivery, in those with an African and Afro-Caribbean ethnicity, gum disease, and a low body-mass index (Goldenberg et al., 2008). Spontaneous preterm births are best predicted by a short length of the cervix and a high concentration of fetal fibronectin in the cervix (Goldenberg et al., 2008). Regardless of the type, preterm births can also be caused by maternal stress and heavy physical work (Steer, 2005).

The consequences of preterm birth are as follows. First, because the antioxidant enzyme system is enhanced during the last 15% of gestation, its interruption by preterm birth can expose infants to an excess of oxidants, thus increasing the risk of injuries such as bronchopulmonary dysplasia (lung), periventricular leukomalacia (brain), and retinopathy of prematurity (eye) (Davis & Auten, 2010). Other deficits observed in some preterm born infants include cerebral periventricular haemorrhage and ventricular

dilatation which have been found to be associated with structural alterations of the brain. Such alterations of the brain in preterm individuals are present at term equivalent age (Counsell et al., 2006) and known to continue during childhood (Soria-Pastor et al., 2009), adolescence (Nosarti et al., 2008) and adulthood (Fearon et al., 2004). Structural alterations in the preterm brain are associated with behavioural and cognitive problems (e.g. Peterson et al., 2000).

1.2 Neurodevelopmental and behavioural outcomes

This section describes the types of neurodevelopmental and behavioural outcomes often studied in preterm born individuals. These include intelligence, executive function, memory and psychiatric outcome. Here a general overview of these outcome measures will be described, whereas studies referring specifically to preterm born individuals will be reviewed in chapter 2.

In A Dictionary of Psychology, cognition is defined as "the mental activities involved in acquiring and processing information" (Colman, n.d.). Similarly, The Psychology Dictionary defines cognition as "the mental processes involved in gaining knowledge and comprehension" (Cherry, 2014a). Cognition can be considered to include processes such as knowing, problem-solving, remembering, thinking, and judging (Cherry, 2014a) which are high-level cognitive functions involving perception, language, planning and imagination (Cherry, 2014a). This section considers the impact of preterm birth on cognition, thus using the term "cognitive outcome".

1.2.1 Intelligence

Intelligence can be defined as "the ability to acquire and apply knowledge and skills" ("intelligence: definition of intelligence in Oxford dictionary (British & World English)," 2014), comprised of sub-domains such as memory, problem solving, and logic. Intelligence is commonly measured by intelligence quotient (IQ) scores, the mean of which is 100 with a standard deviation of 15 (Cherry, 2014b). The most commonly used IQ tests are Wechsler intelligence scales such as Wechsler Adult Intelligence Scale (WAIS) for adults aged 16-90 years, Wechsler Intelligence Scale for Children (WISC) for children aged 6-16 years. Also, a commonly used shorter version is Wechsler Abbreviated Scale of Intelligence (WASI) for individuals aged 6-90 years.

There are four different versions of the WAIS: WAIS (1955), WAIS-R ("R" for "Revised") (1981), WAIS-III (1997) and WAIS-IV (2008). The original WAIS (1955) included verbal and non-verbal (performance) subtests, and the WAIS-R comprised six verbal (Information, Comprehension, Arithmetic, Digit Span, Similarities, and Vocabulary) and five performance (Picture Arrangement, Picture Completion, Block Design, Object Assembly, and Digit Symbol) subtests. The WAIS-III included most of these subdomains, as well as a few new subtests, which together comprised four indices: verbal comprehension, working memory, perceptual organisation and processing speed indices (Figure 1-1). Both the WAIS-R and the WAIS-III yielded verbal IQ (VIQ), performance IQ (PIQ) and full-scale IQ (FSIQ), based on the subtests. The WAIS-IV (Wechsler, 2008) consisted of similar indices and subtests similar to those in WAIS-III, and the subtests were categorised as either core or supplementary ones (Table 1-1). FSIQ or general ability index are produced by combining different sets of core subtests.

The WASI produces an estimated FSIQ and contains only four subtests (vocabulary, similarities, block design and matrix reasoning subtests which are described in Table 1-1) similar to those of the WAIS. It takes about half an hour to complete the WASI whereas the WAIS requires 60-90 minutes to complete core subtests.

Similarly to the WAIS, the WISC has been produced in four versions (WISC (1949), WISC-R (1974), WISC-III (1991) and WISC-IV (2003) and yields VIQ, PIQ and FSIQ. The WISC-IV consists of the same four indices as well as similar subtests as those in WAIS. Verbal comprehension index includes vocabulary, similarities, comprehension, information and word reasoning subtests, the last of which is not included in the WAIS. Perceptual reasoning includes a picture concepts subtest, which is not included in the WAIS, and block design, matrix reasoning, picture completion subtests. Working memory index comprises digit span, arithmetic and letter-number sequencing subtests, while processing speed index consists of symbol search, coding and cancellation subtests.

Figure 1-1

Structure of the Wechsler adult intelligence scale, third edition. This figure has been adopted from http://en.wikipedia.org/wiki/Wechsler_Adult_Intelligence_Scale. For detailed description of the subtests, see Wechsler (1997).

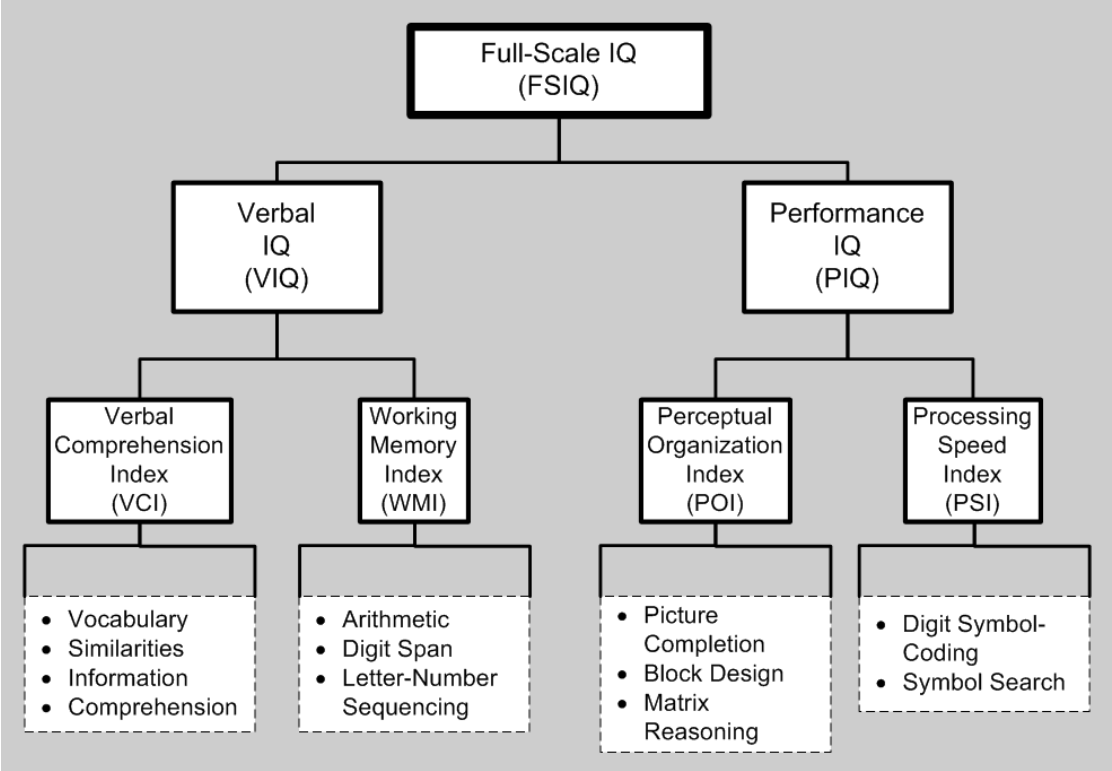


Table 1-1

Subtests of Wechsler Adult Intelligence Scale, fourth edition. Core subtests are in bold font. The non-bold ones are supplementary subtests. Different sets of core subtests (marked with "X") combine to form full-scale IQ (FSIQ) or general ability index. This table has been adopted from http://en.wikipedia.org/wiki/Wechsler_Adult_Intelligence_Scale.

	Subtests	FSIQ	General Ability Index	Proposed abilities measured
Verbal Comprehension	Similarities	X	X	Abstract verbal reasoning
	Vocabulary	X	X	The degree to which one has learned, been able to comprehend and verbally express vocabulary
	Information	X	X	Degree of general information acquired from culture
	Comprehension			Ability to deal with abstract social conventions, rules and expressions
Perceptual Reasoning	Block Design	X	X	Spatial perception, visual abstract processing, and problem solving
	Matrix Reasoning	X	X	Nonverbal abstract problem solving, inductive reasoning, spatial reasoning
	Visual Puzzles	X	X	Spatial reasoning
	Picture Completion			Ability to quickly perceive visual details
	Figure Weights			Quantitative and analogical reasoning
Working Memory	Digit span	X		Attention, concentration, mental control
	Arithmetic	X		Concentration while manipulating mental mathematical problems
	Letter-Number Sequencing			Attention, concentration, mental control
Processing Speed	Symbol Search	X		Visual perception/analysis, scanning speed
	Coding	X		Visual-motor coordination, motor and mental speed, visual working memory
	Cancellation			Visual-perceptual speed

FSIQ measured by the Wechsler intelligence tests reflects overall broad cognitive and intellectual skills (Caplan, DeLuca, & Kreutzer) and is made up of VIQ and PIQ (Wechsler, 1999). FSIQ is used in the current study (Chapter 6). VIQ measures general verbal abilities, which include attention to verbal information, acquired knowledge, and the capacity to manipulate verbal material (Caplan, DeLuca, & Kreutzer), while PIQ assesses general visual and spatial abilities, such as visuo-spatial processing, fluid reasoning, focused attention, and visuo-motor integration (Caplan, DeLuca, & Kreutzer).

IQ is known to generally increase from childhood to adolescence (Baldwin & Stecher, 1922) or adulthood (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Kangas & Bradway, 1971). Considering that FSIQ and its subscales (i.e. PIQ and VIQ) are associated with measures of brain maturation (Gale, O'Callaghan, Bredow, & Martyn, 2006; Gale, O'Callaghan, Godfrey, Law, & Martyn, 2004; Shaw et al., 2006) which occurs substantially in the periods encompassing childhood and adolescence (Giedd et al., 1999; Lenroot & Giedd, 2006, both as cited in Lange, Froimowitz, Bigler, Lainhart, & Grp, 2010), such increase in IQ along with age could reflect processes of brain development.

Structural brain measures associated with IQ include volume and thickness. For example, IQ was found to be correlated positively with total grey matter (GM) volume in 5- to-17-year-old children (Reiss, Abrams, Singer, Ross, & Denckla, 1996). Findings in adults aged between 18 and 84 years also indicated positive associations between IQ and GM volume in the temporal, parietal, occipital and predominantly in frontal lobes, as well as with white matter (WM) volume in the right middle temporal gyrus (Haier,

Jung, Yeo, Head, & Alkire, 2004). Higher IQ in adults (age 17-44 years) was also shown to be linked with greater cortical thickness (CT) in frontal cortex (anterior–ventral section of the prefrontal and fronto-polar cortices) and temporal cortex (inferior temporal cortex, fusiform gyrus, and parahippocampal gyrus) bilaterally (Narr et al., 2007). Although these studies indicate that higher IQ is correlated with more brain tissue, Shaw et al. (2006) reported such an association not during early childhood (age = 3.8–8.4 years), but only during late childhood and young adulthood (age range: 8.6–29 years). They found that higher IQ was first associated with thinner cortices during early childhood and then with thicker cortices in late childhood and young adulthood predominantly in frontal and temporal cortical regions. The positive correlation between CT and IQ was strongest during late childhood and then weakened in later periods. So, Shaw et al.'s (2006) results suggest that the relationship between IQ and CT changes at different ages.

1.2.2 Executive function

'Executive function' (EF) is an umbrella term referring to high-order cognitive skills which are crucial for purposeful behaviour (Lezak et al., 2004, as cited in Burnett, Scratch, & Anderson, 2013), and is closely associated with IQ (Arffa, 2007). There is no consensus regarding which abilities comprise EF (Burnett, Scratch, et al., 2013), but it operates based on a set of abilities: searching long-term knowledge stores, abstraction and planning, decision-making, initiation, self-monitoring, mental flexibility, and inhibition of immediate responses required to achieve longer-term goals (Palmer & Heaton, 2000).

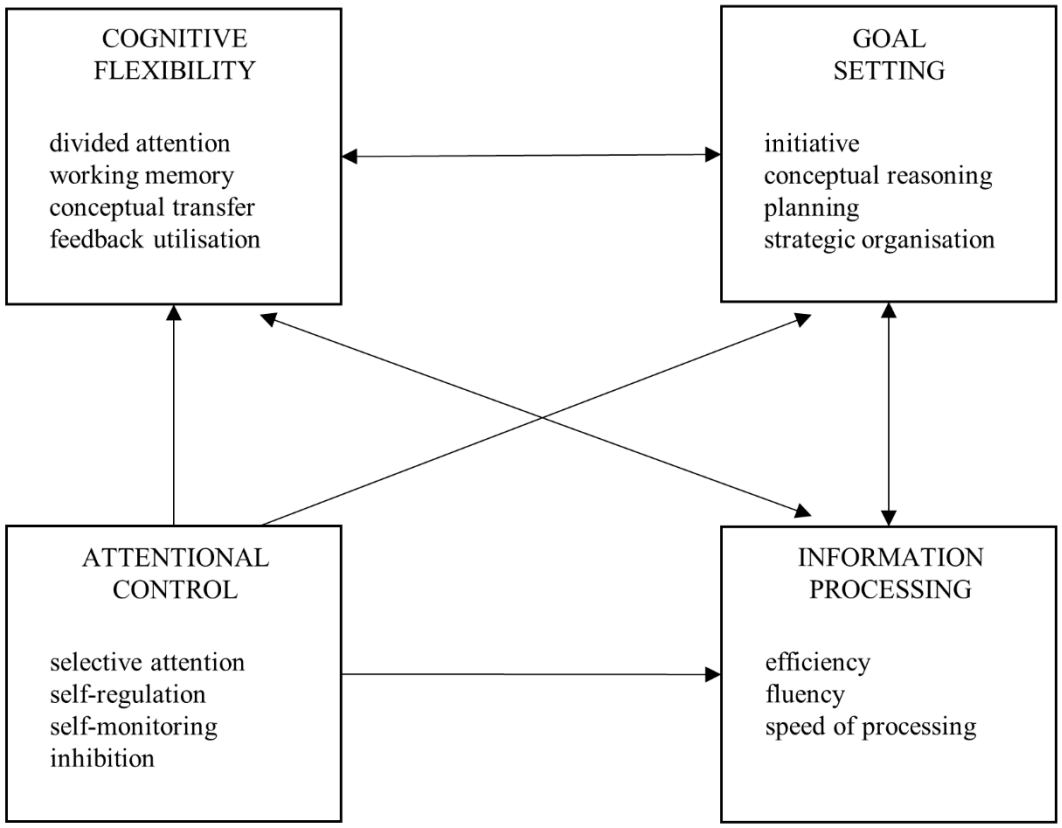
1.2.2.1 Executive function – proposed models

A number of models have been proposed to explain the EF. In this section I will summarise a few of the most widely used: Executive Control System framework, Supervisory Attentional System model and working memory model.

According to the Executive Control System framework, EF is considered to be an overall control system comprising four distinct domains (attentional control, cognitive flexibility, goal setting, and information processing) working together integratively (Anderson, 2002) (Figure 1-2). Specifically, information processing, cognitive flexibility, and goal setting domains are related to and depend on one another. On the other hand, attentional control exerts influence on these three domains. The following paragraph is the elaboration of each domain given in (Anderson, 2002).

Figure 1-2

"Proposed model of executive function" (Adopted from (Anderson, 2002))



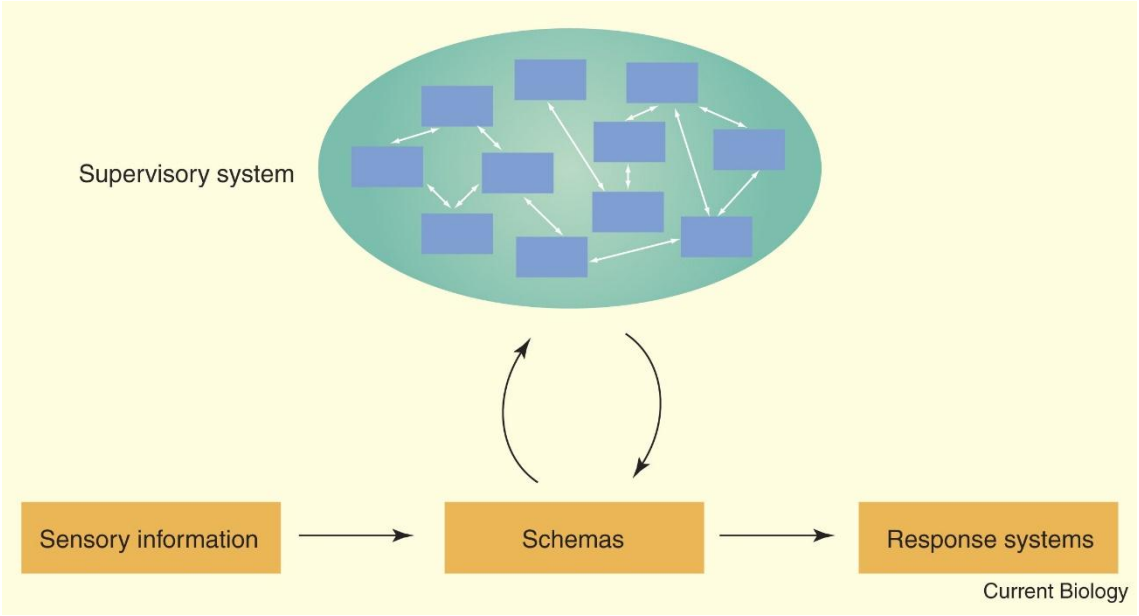
Attentional control includes selective attention and response inhibition. It also includes self-regulation and self-monitoring which enables correct execution of plans, error identification and goal achievement. Impairment in this domain results in impulsivity, lack of self-control, failing to complete tasks or correct mistakes, and inappropriate responses. Information processing regards fluency, efficiency and processing speed. This domain reflects the efficiency of neural connections and the functional coherence of frontal brain networks. Measures of information processing are reaction times, output quantity and quality. When this domain is impaired, it results in poorer output, longer reaction times and hesitation. Cognitive flexibility enables shifting between different sets of responses, learning from errors, use of different strategies, dividing attention, and simultaneous processing of multiple pieces of information. When an individual shows little cognitive flexibility, they can experience rigidity, difficulty in adopting changed procedures and perseverative behaviour such as repeatedly making the same mistakes. Goal setting abilities include having new plans and ideas, planning actions for the future, and carrying out tasks strategically. Deficits in goal setting leads to poor ability to solve problems, which is indicated by suboptimal planning, lack of organisation, problems in developing different tactics, and diminished abstract reasoning.

Another model is the Supervisory Attentional System model proposed by Norman and Shallice (1986) (Figure 1-3). The following is a description put forward by Gilbert and Burgess (2008). According to this model, a 'schema' controls behaviour. A schema refers to pre-learned specific responses (actions and cognitions) to particular environmental inputs. In other words, a schema is a set of more or less automatic responses to familiar environmental input (e.g. input and response could be red traffic light and stepping on brakes, respectively). Therefore, schemas are activated when

exposed to familiar environmental input. However, when the situation is novel or the usual schema is inappropriate, a ‘supervisory system’ modulates the schema. If the supervisory system is damaged, novel stimuli would lead to excessive distractibility while, if an inappropriate schema is activated, it will fail to be inhibited, thus leading to rigid responses.

Figure 1-3

Supervisory Attentional System model by Norman and Shallice (1986). This figure has been adopted from Gilbert and Burgess (2008).



On the other hand, the working memory model proposed by Baddeley & Hitch (1974, as cited in Baddeley, 1992) comprises the central executive, phonological loop and visuospatial sketch pad. The following explanations are from Baddeley (1992) and McLeod (2008). The central executive coordinates information to and from two subordinate systems, which are phonological loop and visuospatial sketch pad, and also carries out cognitive operations (e.g. mental arithmetic and problem solving). The visuospatial sketch pad is like an "inner eye" and is assumed to hold visual information while creating and manipulating visuospatial imagery. The phonological loop holds spoken or written verbal information, and comprises a phonological store and articulatory control processes. The phonological store is like an "inner ear" which is related with speech perception and retains verbal information for 1-2 seconds. The articulatory control process is like an "inner voice" related with speech production and is involved in rehearsal and storage of verbal information from the phonological store.

Overall, all three models (Executive Control System framework, Supervisory Attentional System model and working memory model) commonly have a superior component which influences or controls the others (attentional control component of Executive Control System framework, supervisory system of Supervisory Attentional System model, and central executive component of working memory model). This appears to reflect that, in a sense, the executive function refers to 'controlling' different functions. Also, they all have a component dealing with environmental inputs rather than just focusing on internal processes. The models are, however, different in terms of their focus. Internal processes and environmental inputs are dealt with by all models, but the Supervisory Attentional System and working memory model seem to be more specifically focused on processing environmental inputs.

1.2.2.2 Executive function and the brain

It is important to consider the brain in relation with EF because, as will be mentioned in section "2.1.3" below, brain development and EF are closely interrelated: neurodevelopment affects EF, but experience, i.e. EF, could also drive both structural and functional brain changes. While a number of studies demonstrated that the frontal lobes were responsible for EF, some studies showed the involvement of temporal and parietal regions as well. Those studies are discussed in this section.

Early lesion studies showed that EF is largely subserved by the prefrontal cortex. For example, lesions in the frontal area are often associated with perseveration (or cognitive inflexibility, referring to inability to change behaviour when required due to, for example, rule changes) (Halstead, 1947; Luria, 1973; Luria, Pribram, & Homskaya, 1964; Nichols & Hunt, 1940, all as cited in Stuss & Benson, 1984). Perseveration was reported to occur across different tasks including those involving motor manipulation, use of verbal material, sorting operations, drawings, writing, and attention "tracking" tests (Stuss & Benson, 1984). Attention problems and other deficits are also believed to be caused by tumours in the frontal lobe (Hecaen, 1964, as cited in Stuss & Benson, 1984). Similar outcomes could result from frontal trauma (Goldstein, 1936, 1944, both as cited in Stuss & Benson, 1984) or frontal lobectomy (Angelergues, Hecaen, & Ajuriaguerra, 1956; Rylander, 1939, all as cited in Stuss & Benson, 1984). The attention deficits were indicated by subnormal test performance (Stuss & Benson, 1984).

However, EF appears to rely not only on the prefrontal brain area (Critchley, 1953; Hecaen & Albert, 1975, both as cited in Stuss & Benson, 1984). For instance, the size, rather than location of the lesion could be important for perseveration (Goodglass & Kaplan, 1979, as cited in Stuss & Benson, 1984). This observation was made in respect to elementary motor perseveration (i.e. being unable to stop a movement once started), which was associated with lesion in areas encompassing the premotor area, extending into the basal ganglia (Luria, 1973, as cited in Stuss & Benson, 1984). Additionally, although perseveration is often related with frontal damage, it is also observed in individuals without frontal lesions; conversely, frontal lesions do not always result in perseveration (Stuss & Benson, 1984). Some studies also reported intact attention after frontal lesion from gunshot (Feuchtwaiiger, 1923; Teuber, 1964, as cited in Stuss & Benson, 1984), unimpaired EF (measured as digit span performance) after disease (Benson, Gardner, & Meadows, 1976; Stuss, Alexander, Lieberman, & Levine, 1978, as cited in Stuss & Benson, 1984) prefrontal leucotomy (i.e., prolonged mental activity, inhibition of conflicting stimuli, and tracking) (Benson et al, 1981; Stuss, Benson, Kaplan, Weir, & Delia Malva, 1981, as cited in Stuss & Benson, 1984).

Other studies found that the brain regions involved in EF include the temporal and parietal lobes, as well as specific subdivisions of the frontal cortex such as the anterior cingulate, dorsolateral prefrontal and orbitofrontal cortex, as revealed in functional and structural imaging as well as lesion studies. An early functional magnetic resonance imaging (fMRI) study showed that anterior cingulate and dorsolateral prefrontal cortex was activated by selective attention and task management processing (Smith & Jonides, 1999). fMRI is a commonly used technique to study how the brain works during

processing of cognitive information, and detects brain activity by measuring blood flow changes. When neurons fire, they require oxygen, which is supplied by the blood. To meet task demands, blood flow increases temporarily and this results in changes in blood-oxygen-level dependent (BOLD) signals. Apart from this fMRI study finding, a lesion to the dorsolateral prefrontal circuit (i.e. Brodmann areas 9 and 10, and part of basal ganglia) was also associated with deficits in verbal and design fluency, motor programming, set shifting, learning and memory retrieval, and problem solving (Cummings, 1993). Another study reported that the ability to resolve cognitive interference was negatively correlated with CT in two groups of regions (Westlye, Grydeland, Walhovd, & Fjell, 2011): (1) lateral superior temporal gyrus extending into the insular cortex, inferior frontal gyrus, and the temporoparietal junction and (2) lateral and medial aspects of the temporal lobe extending into the temporoparietal junction, inferior parietal cortex, and lateral inferior frontal areas. Damage to orbitofrontal circuit was also found to be associated with disinhibition (Cummings, 1993). On the other hand, Yuan & Raz (2014) found that better executive performance (measured by Wisconsin Card Sorting Test, Trail Making Test (TMT), fluency, working memory, interference and composite score) was correlated with greater prefrontal CT as well as with greater cortical volumes in medial and lateral, but not orbital prefrontal cortex.

Some researchers consider the prefrontal cortex as a whole when investigating EF (Banich, 2009). For example, Duncan & Owen (2000, as cited in Banich, 2009) claimed that the lateral prefrontal cortex is involved in various operations that involve EF. However, others attributed different components of EF to distinct regions of the prefrontal cortex (Banich, 2009). Petrides (2005) argued that mid-dorsolateral prefrontal cortex is involved in stimuli monitoring and manipulation whereas mid-ventrolateral prefrontal cortex is required for more basic executive processes such as active selection,

comparison and judgment of stimuli held in short-term and long-term memory. Christoff and Gabrieli (2000) argued that EF in the prefrontal area is hierarchically organised: dorsolateral prefrontal region is involved in processing externally generated (i.e. from the environment) information and frontopolar region in processing internally generated information. In addition, lesion studies have suggested that some EF are distributed in three regions (Stuss & Alexander, 2007). Initiation and sustaining of responses depend on the superior medial frontal region, task setting relies on the left lateral frontal region, and monitoring requires the right lateral frontal region (Stuss & Alexander, 2007). All in all, these studies have well demonstrated the need to consider specific subregions in the frontal cortex when investigating the relationship between the brain and executive function.

1.2.3 Memory

Memory generally refers to the ability to retain and retrieve information. This ability is required for and is a proof of learning and therefore of significant importance in human development.

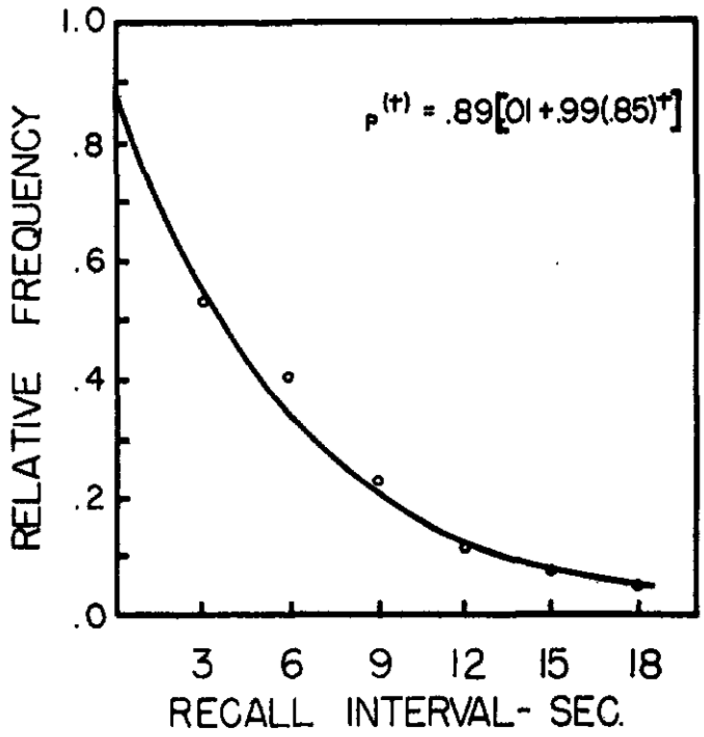
Memory is generally categorised into short-term and long-term. Short-term memory is temporary, considered to last between a few seconds (Figure 1-4a) to hours (Figure 1-4b). Long-term memory is permanent and refers to encoding and retrieving information after a period of time which exceeds the capacity of short-term memory. There are 2 types of long-term memory: explicit (or declarative) and implicit (or non-declaritive or procedural), where the former is related to recollection and the latter concerns behavioural change (Squire, 1992). Explicit memory can be retrieved to consciousness

(e.g. meaning of words) – “perceptible” in a sense – whereas implicit memory is not (e.g. how to drive a car).

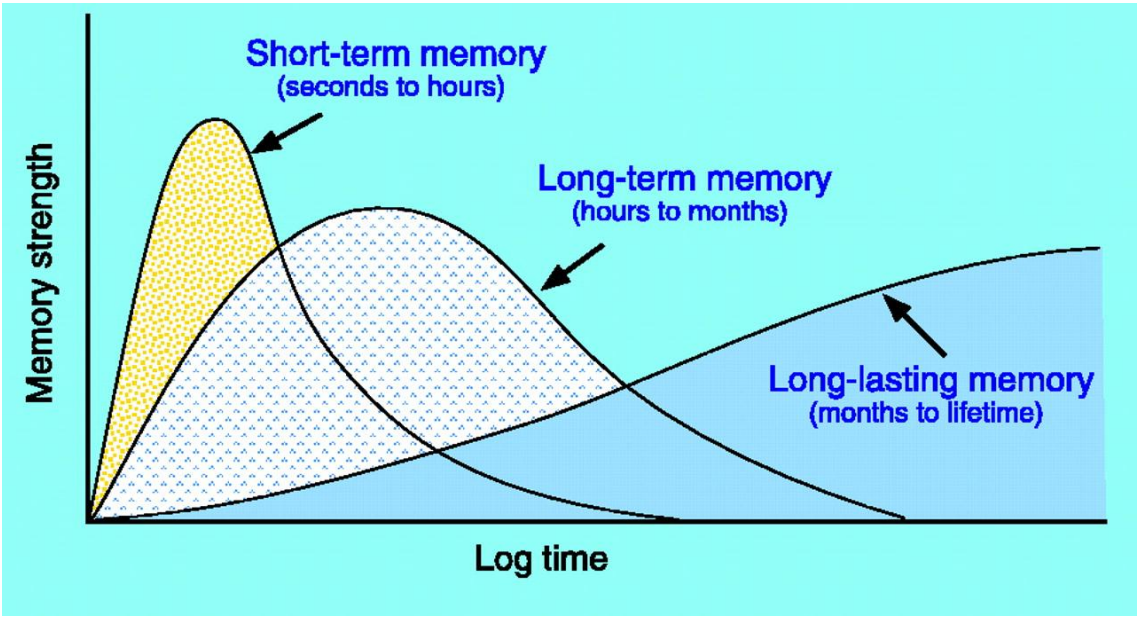
Figure 1-4

Span of short-term memory. (a) “Correct recalls with latencies below 2.83 sec. as a function of recall interval.” (Adopted from Peterson and Peterson (1959)). (b) “Memory consolidation phases.” (Adopted from McGaugh (2000))

(a)



(b)



It has been suggested that one important component of short-term memory is working memory (Seamon & Kenrick, 1994, as cited in Engle, Tuholski, Laughlin, & Conway, 1999). In the literature a distinction is often made between working memory and short-term memory (e.g. Engle et al., 1999; Kibby & Cohen, 2008). While short-term memory merely refers to temporary storage of information (Seamon & Kenrick, 1994, as cited in Engle et al., 1999), working memory can be defined as "a brain system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning, and reasoning" (Baddeley, 1992, p. 556). In other words, working memory refers to the ability to hold and manipulate information. Working memory also serves as temporary storage of information retrieved from long-term memory (Atkinson & Shiffrin, 1968) and is crucial for long-term learning (Baddeley, Papagno, & Vallar, 1988). However, some studies have suggested that short-term and long-term memories involve independent processes, as described by McGaugh (2000).

This paragraph describes the development of working memory between infancy and adolescence as described in (Tau & Peterson, 2010). A basic level of memory can be observed as early as 6 months of age, but a full memory capacity is developed later in life (Brody, 1981; Diamond, 1990; Millar and Watson, 1979, as cited in Tau & Peterson, 2010). At 7-8 months of age, infants can successfully perform Piaget's A-not-B task (Piaget, 1954, as cited in Tau & Peterson, 2010) during which a baby watches an item being hidden in one of two possible places and is required to take it out (Diamond, 1990, as cited in Tau & Peterson, 2010). The 7-8-month-old babies were unable to perform the task with delay, but this became possible at 9 months of age (Diamond, 1990, as cited in Tau & Peterson, 2010). Although working memory completely develops by age 5-6 years (Tsujimoto et al, 2004, as cited in Tau & Peterson, 2010), it can be attenuated

in children while trying to manipulate information or when distractors are present (Davidson et al, 2006; Hitch, 2002, both as cited in Tau & Peterson, 2010). On the other hand, working memory performance becomes more stable during adolescence (Davidson et al, 2006; Demetriou et al, 2002; Luciana and Nelson, 1998; Luna et al, 2004; Scherf et al, 2006; Swanson, 1999, all as cited in Tau & Peterson, 2010).

Memory function involves a number of brain regions. In the 20th century, the frontal lobe was believed to be crucial for memory function. Early animal studies suggested a link between memory and the frontal lobe because monkeys with frontal lesions could normally perform immediate discrimination tasks, but not delayed response tasks (Jacobsen, 1935, 1936, both as cited in Stuss & Benson, 1984). In humans with frontal lobe damage too, learning deficits were shown during maze learning (Corkin, 1965; Milner, 1965; Walsh, 1960, all as cited in Stuss & Benson, 1984) and recency judgement tasks (Milner, 1971, 1974; Ladavas, Umilta, & Provinciali, 1979, as cited in Stuss & Benson, 1984). Gross and Weiskrantz (1964, as cited in Stuss & Benson, 1984) claimed that this reflected an inability to retrieve memories rather than memory loss. Stuss & Benson (1984) also suggested that the frontal damage indirectly impairs memory function. For example, a frontal lesion could lead to a binary deficit, failing to create stable intention to remember and deficiency in shifting recall from one trace to another (Luria, 1971, 1973, as cited in Stuss & Benson, 1984).

More recent findings indicate that working memory relies on frontoparietal regions, as well as the cerebellum (Ravizza et al., 2006). Functional neuroimaging studies have demonstrated that working memory tasks mainly activate parietal (Cabeza & Nyberg, 2000) and prefrontal regions (Cabeza & Nyberg, 2000; D'Esposito et al., 1995) or, in

particular, dorsolateral and left inferior regions of prefrontal area (Braver et al., 1997). Working memory also involves attentional processes which are linked with a lateral and superior frontoparietal network that include superior frontal sulcus, ventrolateral prefrontal cortex, intraparietal sulcus, and supramarginal gyrus (Champod and Petrides, 2007; Corbetta et al, 2008; Corbetta and Shulman, 2002; Posner and Petersen, 1990, all as cited in Tau & Peterson, 2010).

As described by Tau and Peterson (2010), frontoparietal regions are activated during working memory tasks already during childhood (Casey et al, 1995; Crone et al, 2006; Durston et al, 2006; Geier et al, 2009; Klingberg et al, 2002; Konrad et al, 2005; Kwon et al, 2002; Luna et al, 2001; Scherf et al, 2006; Thomas et al, 1999, all as cited in Tau & Peterson, 2010), but the activated areas are altered during online manipulation of information (Crone et al, 2006; Konrad et al, 2005; Olesen et al, 2007, as cited in Tau & Peterson, 2010)) or in the presence of distractors (Olesen et al, 2007, as cited in Tau & Peterson, 2010). Unlike adolescents, children rely on ventromedial regions, such as caudate nucleus, and insula while performing more complex working memory tasks (Casey et al, 1995; Crone et al, 2006; Durston et al, 2006; Geier et al, 2009; Klingberg et al, 2002; Konrad et al, 2005; Kwon et al, 2002; Luna et al, 2001; Scherf et al, 2006; Thomas et al, 1999, all as cited in Tau & Peterson, 2010). Also adults, compared to adolescents, recruit more focal regions of frontal and parietal cortices during working memory performance (Durston et al, 2006; Konrad et al, 2005; Scherf et al, 2006, as cited in Tau & Peterson, 2010), which suggests that working memory processing recruits frontoparietal regions more fully and consistently with increasing task difficulty between childhood and adolescence, and that this is spatially refined between adolescence and adulthood.

Regarding long-term memory, explicit and implicit memory develop through separate processes in different brain regions. Exlpicit memory is believed to depend on the hippocampus which integrates different cortical regions involved in storing memories. Specifically, explicit memory involves, at the time of learning, neocortical regions sending two thirds of information onto medial temporal structures such as parahippocampal gyrus and perirhinal cortex (Insausti et al., 1987, as cited in Squire, 1992) and the remaining information to other structures (Squire, 1992). Then, the information is passed onto the entorhinal cortex and then to the hippocampus, which processes the information and projects it back to the neocortex (Squire, 1992). Implicit memory depends on the neostriatum, cerebellum, amygdala as well as the posterior neocortex. In implicit memory, information is taken as 'changes' in particular perceptual or response systems and is independent from memory for the prior encounters which resulted in behavioural change (Squire, 1992). Different types of implicit memory rely on different brain regions: skill learning and habits rely on the neostriatum (Heindel et al., 1988; Heindel et al., 1989; Packard et al., 1989; Saint-Cyr et al., 1988; Wang et al., 1990, all as cited in Squire, 1992), conditioning of skeletal musculature relies on the cerebellum (Thompson, 1986, as cited in Squire, 1992), emotional conditioning depends on the amygdala (Davis, 1986; LeDoux, 1987), and certain types of priming rely on early-stage processing systems in posterior neocortex (Squire et al., in press).

1.2.4 Psychiatric outcome

Most commonly reported psychiatric problems in preterm sample are attention deficit hyperactivity disorder (ADHD) (e.g. Botting, Powls, Cooke, & Marlow, 1997), autism-spectrum disorders (e.g. Johnson et al., 2010), depression and anxiety (e.g. Walshe et al., 2008).

ADHD refers to a group of behavioural problems including poor attention (short attention span or high distractibility), hyperactivity (restlessness, constant fidgeting or overactivity) and impulsiveness, possibly accompanied by sleep and anxiety disorders ("Attention deficit hyperactivity disorder (ADHD) - NHS Choices," 2014). These problems begin appearing usually before age 7 years, and persist across development (Barkley, 1990; Hinshaw, 1994; Weiss & Hechtman, 1993, all as cited in Barkley, 1997). ADHD is also more common in boys (Barkley, 1990; Szatmari, 1992, as cited in Barkley, 1997). As individuals with ADHD grow up, they are more likely to experience poor academic achievement and school performance, repetition of school grades, suspensions and expulsions from school, poor peer and family relationships, anxiety and depression, aggression, conduct problems and delinquency, substance misuse, motor accidents and speeding violations, as well as difficulties in forming adult social interactions, marriage, and employment (Barkley, 1990; Barkley, Fischer, et al., 1990; Barkley, Guevremont, Anastopoulos, DuPaul, & Shelton, 1993; Barkley, Murphy, & Kwasnik, 1996, in press; Biederman, Faraone, & Lapey, 1992; Hinshaw, 1994; Murphy & Barkley, in press; Nadeau, 1995; Weiss & Hechtman, 1993, all as cited in Barkley, 1997). Many of these problems become more pronounced when coupled with comorbid aggression–conduct problems (Barkley, Fischer, et al., 1990; Barkley et al., 1993; Hinshaw, 1987, 1992, 1994, all as cited in Barkley, 1997). Also, ADHD in adolescence can be a precursor of psychosis at adulthood (Jandl, Steyer, & Kaschka, 2012). ADHD is often treated by the parents, teachers and the extended family, parent and teacher

guidance using behaviour management techniques; special education resources; and pharmacotherapy (Barkley, 1990, as cited in Barkley, 1997).

Autism spectrum disorders (ASD) are a range of conditions that share core impairments in reciprocal social interaction, communication, and a pattern of restricted/repetitive behaviours or interests (Johnson et al., 2010). The name "spectrum" reflects that, while autistic individuals share certain difficulties (i.e. problems in reciprocal social interaction and communication as well as a pattern of restricted/repetitive behaviours or interests (Johnson et al., 2010)), they experience additional symptoms which differ among one another. For example, around 75% of autistic individuals were estimated to experience learning disabilities (see O'Brien & Pearson, 2004). Other possible symptoms of autism include sensory and motor abnormalities as well as sleep disturbance (see Geschwind, 2009). Diagnosis of autism is made based on social interaction, communication, and flexible imaginative functions (Happe & Ronald, 2008), commonly called "triad of impairments".

Depression is characterised by a range of symptoms, from persevering sorrow and hopelessness to loss of interest in the things one used to enjoy and feeling very tearful. In many cases, depression is accompanied by anxiety. Additionally, physical symptoms have been reported in depression, including feeling always tired, sleeping problems, lack of appetite or sex drive, and various aches and pains. Depression could cause low spirits when mild, but also suicidal impulse when severe. Depression is treated with medication or counselling, or both. This description of depression was summarised from ("Clinical depression - NHS Choices," 2012).

Anxiety can be seen as uncontrollable worries and is the main symptom of conditions such as panic disorder, phobias, post-traumatic stress disorder and social anxiety disorder (social phobia). Generalised anxiety disorder is a long-term condition causing one to feel constantly anxious and have not only psychological (e.g. restlessness or worrying, and problems concentrating or sleeping), but also physical symptoms (e.g. dizziness, shortness of breath and headache). Treatments of generalised anxiety disorder include psychological therapies (e.g. cognitive behavioural therapy) and medication (e.g. selective serotonin reuptake inhibitors). This description of anxiety was summarised from ("Generalised anxiety disorder - Symptoms - NHS Choices," 2014).

Chapter 2: Literature review - Neurodevelopmental and behavioural outcome in adolescence/adulthood following preterm birth

Several studies have suggested an association between preterm birth and cognitive changes and psychiatric problems in childhood and later in life. In this chapter, I will summarise developmental studies investigating cognitive (intelligence, executive function (EF) and memory) outcomes in preterm born individuals as well as behavioural/psychiatric problems associated with preterm birth.

2.1 Intelligence

2.1.1 Intelligence in preterm born individuals

A common tool used to estimate babies' intelligence in the pediatric literature is the Bayley Scales of Infant Development (BSID). There are 2 versions of the scale which have been widely used in studies with preterm infants (e.g. Spittle et al., 2010; Thompson et al., 2008). The first is the BSID-II (Bayley, 1993) which calculates a Mental Developmental Index (MDI), measuring language, memory, and reasoning skills ("Definition of MDI," 2012). BSID-II MDI was not found to be significantly different between preterm and control groups at 8 months (from term-equivalent time point)

(Petrie Thomas, Whitfield, Oberlander, Synnes, & Grunau, 2012) and 1 year (Hughes, Greisen, Arce, & Thornton, 2014). However, these findings should be considered with caution because, in LBW individuals (811 ± 125 g; GA = 26.4 ± 2 weeks), MDI at 20 months corrected age was shown to poorly predict IQ scores (measured as Mental Processing Composite (MPC) score of Kaufman Assessment Battery for Children) at age 8 years (Hack et al., 2005). Hack et al. (2005) divided their study participants into (1) those with or without neurosensory impairment (i.e. major neurologic problems (e.g., cerebral palsy) and/or who were blind or deaf), and also into those with subnormal (< 70) or normal MDI scores. Their findings showed that, within the neurologically impaired subgroup, only 20% of those with subnormal MDI score at age 20 months had subnormal MPC scores at age 8 years. This rate for the neurologically normal group was 61%. Therefore, it may be hypothesised that BSID-II MDI underestimates cognitive ability in infancy.

Another version of the BSID is the BSID-III (Bayley, 2006), which assesses abilities in five domains: Adaptive Behaviour, Cognitive, Language, Motor and Social-Emotional. The BSID-III was also often used to assess preterm babies' development (Chorna, Solomon, Slaughter, Stark, & Maitre, 2014; Sansavini et al., 2014). For example, Sansavini et al. (2014) used the BSID-III to assess language (at 12, 18, 24, 30 and 36 months), and motor and cognitive skills (at 12, 24 and 30 months). Receptive and expressive communications subscales were used for language assessment, fine and gross motor skills subscales for motor assessment and cognitive skills subscale for cognitive assessment. Sansavini et al. (2014) observed that preterm infants (GA ≤ 28 weeks) scored significantly lower than controls at all time points. The difference

between the groups in the rate of score increase was not significant for language and cognitive skills, but significantly different for motor skills.

However, research findings suggest problems in interpreting BSID-II MDI and BSID-III scores in relation with each other, although BSID-II MDI and BSID-III cognitive and language scores are highly correlated (Acton et al., 2011; Moore et al., 2012, as cited in Johnson, Moore, & Marlow, 2014). One problem is that the BSID-III scores are as much as 10 points higher than the BSID-II MDI scores (Acton et al., 2011; Moore et al., 2012; Vohr et al., 2012, as cited in Johnson et al., 2014), and therefore, as Johnson et al. (2014) explains, the BSID-III could underestimate developmental delays. One potential solution to this problem is to raise the cut-off (between normal and "impaired" subgroups) when using BSID-III scores. One study raised it by 15 points (Askie et al., 2011, as cited in Johnson et al., 2014), while another suggested that 10-point increase maximally matches scores on the BSID-III and BSID-II MDI (Moore et al., 2012, as cited in Johnson et al., 2014). On the other hand, Johnson et al. (2014) demonstrated that varying cut-offs had differential impacts among different BSID-III measures. They administered the BSID-II MDI and the BSID-III cognitive and language scales to preterm individuals (GA 22-26 weeks; corrected age: 29-49 months). For the BSID-III, there were five measures: (1) cognitive composite, (2) language composite, (3) cognitive or language composite, (4) cognitive and language composite, and (5) combined BSID-III score (average of cognitive and language composites). They compared the proportion of children having BSID-II MDI < 70 (indicating moderate-to-severe neurodevelopmental delay) with those having BSID-III measures < 70, <80 and <85. The best correspondence with the BSID-II MDI < 70 was shown by the BSID-III 'Cognitive and language composite < 85' (98.9% agreement) and 'combined BSID-III score < 80' (97.8% agreement), and the worst correspondence shown by 'Cognitive and

language composite < 70' (93.0% agreement). Therefore, Johnson et al.'s (2014) findings suggest that not only should the cut-off be adjusted to make the BSID-III compatible with the BSID-II MDI, but also one should consider how to combine the subscores. Further research is required in order to obtain more generalisable and specific solutions to tackle the incompatibility between the BSID-II MDI and the BSID-III.

During childhood, studies tend to show that preterm individuals have subnormal IQ compared to controls. Some studies showed significantly lower intelligence level in preterm born children compared to age-matched controls using the Stanford-Binet test (Terman & Merrill, as cited in Caravale, Tozzi, Albino, & Vicari, 2005; Thorndike, Hagen, & Sattler, 1986). Study participants were assessed at age 3 to 4 years (Caravale et al., 2005) and 5 years (Kilbride, Thorstad, & Daily, 2004). Studies using the McCarthy Scales have also showed that preterm groups obtain subnormal scores in most domains tested. Delahunty et al. (2010) showed that preterm children at age 5.5 years also had significantly lower scores compared to controls on the McCarthy scales' (McCarthy, 1972) general cognitive, motor, memory, verbal and perceptual performance domains, but not in the quantitative domain which assesses mathematical abilities (e.g. numerical memory, and counting and sorting). Similarly, preterm children at age 7 years scored significantly lower than controls on McCarthy scales' measuring general cognitive, motor, verbal and perceptual performance domains, whereas no significant between-group difference was found in the memory domain (Halsey, 1996). However, it should be noted that McCarthy scales measure cognitive abilities rather than intelligence (Van et al., 2008, as cited in "McCarthy Scales of Children's Abilities", 2013)) – in other words, McCarthy scale scores are not the same as IQ. To avoid confusion with IQ, McCarthy scale scores use a t-score with a mean of 50 and standard

deviation (SD) of 10 ("McCarthy Scales of Children's Abilities", 2013). At age 8 years, another study (Lewis et al., 2002) using a tool designed to assess children's IQ, the WISC-III (Weschsler, 1991) found that VIQ, PIQ and FSIQ were significantly lower in two preterm groups (one with bronchopulmonary dysplasia and the other without it) compared to controls.

In contrast, a few studies have reported non-significant group differences in childhood IQ. For instance, Pearl & Donahue (1995) found no significant difference in intelligence level between 4.5-year-old preterm individuals and controls. They measured intelligence using Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1989). Briscoe et al. (1998, as cited in van Noort-van der Spek, Franken, & Weisglas-Kuperus, 2012) also observed a non-significant difference in IQ between preterm and control groups aged 3 to 4 years, using the Raven's Coloured Progressive Matrices. However, this finding may be unreliable because Raven's Coloured Progressive Matrices is designed for 5-year-old or older individuals.

Several studies during the adolescent period have reported that preterm individuals had lower IQ than term-born controls. For example, FSIQ, VIQ and PIQ at ages 15.3 years (measured with the WISC-Revised (WISC-R) (Wechsler, 1974, as cited in Allin et al., 2008)) and 19.5 years (measured with the WASI) were significantly lower in the preterm group (GA < 33 weeks) than in controls. Healy et al. (2013) also revealed a significant difference in FSIQ between controls and preterm adolescents (GA < 33 weeks) at age 15 years, using WISC-R. Significantly lower FSIQ in preterm group compared to controls at 18 years (GA = 27 (1.0) weeks) was also found by Hallin, Hellstrom-Westas, & Stjernqvist (2010), using the WAIS.

Such subnormal IQ in preterm individuals has also been observed during adulthood (Lohaugen et al., 2010; Nosarti et al., 2007; Skranes et al., 2013), but some studies demonstrated preterm individuals' recovery over times. Ninteen-to-20-year-old VLBW adults (mean 1217g, SD 233g; GA: mean 29.1 weeks, SD 2.5 weeks) had significantly lower FSIQ, VIQ and PIQ compared to controls (Lohaugen et al., 2010). Additionally, high FSIQ scores (>1SD above control group mean) were observed only in the control group (18%) and low FSIQ scores (> 1SD below control group mean) were more prevalent in the preterm group (53%) than in the controls (15%) (Lohaugen et al., 2010). Nosarti et al. (2007) found that preterm adults (GA < 33 weeks) had significantly lower VIQ and FSIQ than controls at a mean age of 22-23 years. In contrast, preterm individuals had significantly lower IQ compared to controls in childhood (age 5 years), but neither IQ nor educational performance was significantly different from those of controls in adolescence (age 16 years) (Peng et al., 2007). Similarly, preterm adolescents (age 16 years) showed impaired educational performance, which increased to control levels at adulthood (age 19 years) (Tideman, 2000).

In summary, the results of studies investigating IQ in preterm samples are mixed during infancy, childhood and adulthood, whereas adolescent findings consistently showed lower intelligence level in the preterm group. Measurement of IQ at infancy and childhood was problematic because of the incompatibility between different versions of tests or the validity of the test. Mixed results at adulthood suggest that preterm born individuals might reach normal levels general intellectual functioning, after demonstrating domain-general delays earlier in development.

2.1.2 Intelligence in preterm born individuals – moderating factors

IQ depends on many factors. Preterm birth is one important factor, as described in the previous section, but the relationship between preterm birth and IQ can be affected by other factors as well. Such factors range from neonatal (GA, birth weight) to cognitive (processing speed, memory) and environmental factors (e.g. parental education and parenting style), and their influence on the relationship between IQ and preterm group birth varies at different ages.

Around infancy, GA and parenting style turned out to be an important moderating factor. The extent of prematurity itself was shown not to affect intelligence at age 3 years (Shah, Robbins, Coelho, & Poehlmann, 2013), when the preterm group was subdivided into very (GA < 30 weeks), moderately (GA: 33-33$^{6/7}$ weeks) and late preterm birth (GA: 34-36$^{6/7}$ weeks) groups. This study also measured parenting style with the Parent Child Early Relational Assessment (Clark, 1985, as cited in Shah et al., 2013), which included 3 subscales, each assessing the extent of positive parenting (positive affect, involvement and verbalisations), negative parenting (negative affect and behaviour (e.g. rage and lack of appreciation)) and intrusive parenting (intrusiveness, insensitivity and inconsistency). Study results showed that IQ was not significantly affected by parenting style on its own on. However, there was an interaction between prematurity and negative style of parenting, that is, children exposed to more negative parenting had lower IQ in the very preterm group, but not in the moderately or late preterm groups. There was no such interaction between prematurity and other styles of parenting (i.e. positive and intrusive parenting). These results suggest that those preterm infants with lower GA are especially susceptible to the adverse effects of negative parenting, and therefore should be reared with greater care.

During middle childhood, GA and birth weight seem to affect IQ. Wolke, Schulz and Meyer (2001, as cited in Johnson, 2007) studying a sample of children in middle childhood, also reported a positive association between GA and IQ from 27 to 32 weeks GA, but no correlation was found for GA from 33 to 42 weeks. Consistently, in 7-year-old children, lower birth weight (and lower GA) groups had lower IQs (Hack et al., 1994). The IQs for the < 750g (GA = 25.7 ± 2 weeks) group, 750g-1499g (GA = 29.4 ± 2 weeks) group and term-born controls were 87 ±15, 93 ±14 and 100 ±13, respectively. IQ was measured with Kaufman Assessment Battery for Children Mental Processing Composite Short Form (Kaufman & Applegate, 1988, as cited in Hack et al., 1994). Additionally, IQ impairment rates defined as (standard score < 70) were also higher in lower birth weight groups: above 20% in <750g group, above 5 % in 750g-1499g group and below 5% in term-born controls. However, these differences were not statistically tested and therefore the impact of these findings is limited. On the other hand, total IQ, VIQ and PIQ, which were significantly lower in the preterm group (GA < 32 weeks) than in controls, significantly and positively correlated with gestational age and birth weight (Foulder-Hughes & Cooke, 2007). Participants' ages were 7-8, and IQ was measured with the WISC-III. These results show an adverse impact of low GA or LBW on the general intellectual functioning of preterm individuals.

In adolescence, on the other hand, preterm individuals' IQs appear to be affected by processing speed and memory (Rose & Feldman, 1996) as well as parental education level (Weisglas-Kuperus et al., 2009). GA (Whitaker et al., 2006, as cited in Johnson, 2007) and social acceptance (Yau et al., 2013; Healy et al., 2013) was also discussed, but the evidence is inconclusive for both. Processing speed and memory were reported

to account for about 60% of the IQ difference between preterm children (GA = 31.2 (1.8) weeks) and controls at 11-12 years of age (Rose & Feldman, 1996). That is, IQ difference (lower in preterm group) was 10.31, but it reduced to down to 4.21 after controlling for the processing speed and memory scores. IQ was measured with WISC-R, and memory and processing speed were assessed with the Cognitive Abilities Test (Detterman, 1988, 1990, as cited in Rose & Feldman, 1996) and Colorado Specific Abilities Test (Rose & Feldman, 1995, as cited in Rose & Feldman, 1996).

At 15 years, being bullied (assessed by a self-report questionnaire) was significantly associated with low IQ in an ELBW group (< 1000g; GA = 26 ± 2 weeks) (Yau et al., 2013), demonstrating a link between social rejection and low intelligence level in preterm populations. On the other hand, no link was found between IQ and social immaturity (measured with Child Behaviour Checklist (CBCL)) at age 15 years in both controls and preterm individuals (Healy et al., 2013). This could suggest that social rejection, which could be caused by social immaturity, does not affect IQ. However, a direct inference regarding relationship between IQ and social rejection cannot be made based on these finding and needs to be investigated further.

A study in 16-year-old LBW adolescents also revealed no link between GA and IQ after controlling for several risk factors (Whitaker et al., 2006, as cited in Johnson, 2007). However, this finding may be limited, in terms of generalisability, by the fact that the cut-off for birth weight was 2000g and not 1500g and the authors controlled for many GA-related variables in their analyses, such as intraventricular haemorrhage, periventricular leukomalacia, days on ventilator (Johnson, 2007).

Parental education was another important predictor of IQ in 19-year-old preterm individuals (GA = 31 (2.5) weeks; birthweight = 1314 (283) g) (Weisglas-Kuperus et al., 2009). Preterm adults with higher-educated parents (higher vocational education or university) had 14.2 points higher IQ than those with lower-educated parents (primary school or junior secondary vocational education). Those who had intermediate-educated parents (general or senior secondary education) also had 6.1 points higher IQ than those with low-educated parents. In this study, IQ was measured with Multicultural Capacity Test–Intermediate Level (Bleichrodt, 2000, as cited in Weisglas-Kuperus et al., 2009).

2.1.3 Intelligence in preterm born individuals – relationship with brain correlates

It is important to study IQ in relation with brain measures because the two are closely related (Lange et al., 2010; Shaw et al., 2006). For example, IQ is associated with CT differentially at different age groups (Shaw et al., 2006). For instance, a negative association was observed between IQ and CT (i.e. higher IQ was associated with thinner CT) in early childhood (age 3.8-8.4 years), whereas a positive association was found in late childhood (age 8.6-11.7 years), adolescence (11.8-16.9 years) and early adulthood (17-29 years). The positive association was strongest during late childhood. Another example is the association between FSIQ and volumes of temporal GM and WM and frontal WM (Lange et al., 2010). Intuitively, brain appears to affect IQ rather than the other way round although I speculate that, during development, level of IQ could reinforce certain ways of brain usage and affect the brain as well. This section and the whole thesis is based on this assumption that the brain affects cognitive functions. The following studies used both cross-sectional (e.g. Peterson et al., 2000; Soria-Pastor et al., 2009) and longitudinal approaches (e.g. Isaacs et al., 2004; O'Brien, 2004; Beckwith &

Parmelee, 1986), measuring group difference in GM and WM structures and their associations with IQ.

Longitudinal studies have shown contradictory IQ development trajectories between controls and preterm individuals. While the normative population showed increasing IQ over time (e.g. between 5 and 16 years (Baldwin & Stecher, 1922); between 2-5.5 years and 40-43.5 years (Kangas & Bradway, 1971)), preterm born individuals without neurological abnormality showed both increase of IQ during early childhood (Beckwith & Parmelee, 1986) and decrease in VIQ and PIQ between mid-childhood and adolescence. Beckwith & Parmelee (1986) demonstrated that IQ at age 8 years (measured with the WISC-R) was higher than IQ at age 5 years (assessed with Stanford-Binet test) in preterm born children (GA ≤ 37 weeks). On the other hand, Isaacs et al. (2004) measured IQ in preterm children (GA: 26-30 weeks) at ages 7.5 and 15.3 years with the WISC-R and the WISC-III, respectively. The results showed significant decrease in VIQ and PIQ from childhood to adolescence, before and after adjusting the scores of the WISC-III to account for possible difference from the scores of the WISC-R (Isaacs et al., 2004). When subtests were examined, significant decrease was observed in all (Similarities, Arithmetic, Block Design and Object Assembly) but the Vocabulary subtest, reported to be relatively unaffected by neural deficit (Yates, 1954, as cited in Isaacs et al., 2004). Also, the size of decline in VIQ, but not PIQ correlated with age at test in adolescence, suggesting different declining trajectories between the two types of IQs in preterm individuals (Isaacs et al., 2004). O'Brien (2004) also showed significant decrease in FSIQ and VIQ (measured with Wechsler Intelligence Scales for Children – Revised) of preterm individuals (GA: 24-32 weeks) between ages 8 and 15 years. Decrease in PIQ was non-significant, which is consistent with Isaacs et al.'s (2004)

suggestion that VIQ and PIQ decline differently. These generally contrasting results between controls and preterm individuals could be explained as follows. The preterm brain sustains neural injury prenatally or perinatally, as proposed by Isaacs et al. (2004). So, one possibility is that the injured areas do not affect IQ in early life, but only later when they mature (Isaacs et al., 2004). Another possibility is that early brain damage disrupts the rate of development during childhood, especially as the cognitive demands become increasingly complex.

Preterm individuals' deviation in their trajectory of IQ development could reflect structural maturational alterations, as already mentioned, as well as changes in functional development following preterm birth. For example, brain volume, which is one of the most commonly investigated structural measures of the brain, has often been reported as being smaller in preterm individuals compared to controls (Kesler et al., 2008; Ment et al., 2009; Nosarti et al., 2002; Soria-Pastor et al., 2009; Zubiaurre-Elorza et al., 2011). Several studies have investigated the association between regional brain volumes and IQ in preterm samples at different stages of development. Peterson et al. (2000) reported that IQ in preterm infants was positively associated with regional cortical volumes of middle temporal and sensorimotor cortices, which were also significantly smaller in the preterm group compared to term-born controls. Similar findings have been described in school-age preterm children, who showed reduced GM volumes in middle temporal and postcentral gyri compared to controls, which were positively correlated with IQ (Soria-Pastor et al., 2009). Preterm adolescents had significantly smaller volumes of total brain tissue (i.e. total intracranial volume), GM, WM, thalamus, basal ganglia, cerebellum, hippocampus and amygdala, and all these volumes were also positively associated with IQ (Cheong et al., 2013). These three studies suggest that IQ is (1) significantly lower in preterm group than controls and (2)

positively associated with brain volume (regional or whole brain). Reflecting on the positive association between IQ and the total cerebral volume in normative population (Haier et al., 2004; Reiss et al., 1996) mentioned earlier, this seems to show that the general relationship between brain volume and IQ remains similar in preterm individuals as in controls.

In addition to brain volume, alterations in CT and their relationship with IQ were also studied in preterm samples. At adolescence, low IQ in the preterm group (defined as 2 SD below the control group's mean) was associated with thinner bilateral parahippocampal cortices, which were also significantly thinner in the preterm group compared to controls (Martinussen et al., 2005). Another study using the same cohort also found significant positive associations between IQ and CT in entorhinal cortex (measured in the preterm group only) where CT was significantly smaller in the preterm group (Skranes et al., 2012). In addition, preterm adults had higher IQ when their CT was greater in ventro-lateral frontal, parietal and temporal areas, most of which showed no group difference in CT (Bjuland, Lohaugen, Martinussen, & Skranes, 2013). In both controls and preterm adults (GA < 33 weeks; mean age 20 years), WM volume deficit in left inferior frontal gyrus (where volume was smaller in preterm group than controls) and the right lingual gyrus (where volume was larger in preterm group than controls) explained 18% of the variance in FSIQ (Nosarti et al., 2014). Preterm young adults had significantly lower FSIQ than controls (Nosarti et al., 2014).

Overall, both positive and negative relationships were found between CT in widely distributed regions and IQ in preterm samples, although cortical thickness in selective regions in which significant structure-function associations were observed did not

always show group differences in cortical thickness. Observation of both positive and negative associations between IQ and structural brain measures could reflect long term alterations in brain and/or IQ development because normative populations tend to show a positive link between IQ and structural brain measures. For example, CT in prefrontal (anterior-ventral prefrontal and frontopolar areas) and temporal areas (inferior temporal, fusiform, and parahippocampal cortices) was observed in normative samples (Narr et al., 2007). Additionally, low, but significant correlations were found between FSIQ and various brain measures (total brain volume, GM volume, WM volume, intracranial cavity and head circumference) (Lange et al., 2010). Also, Shaw et al. (2006) showed positive associations between IQ and CT at late childhood, adolescence and early adulthood although the association was negative at early childhood.

Studies investigating WM revealed micro- and macro-structural alterations in preterm individuals, as well as significant associations between WM measures and IQ. Most studies measured WM volume, fractional anisotropy (FA) or mean diffusivity (MD). Fractional anisotropy indicates directionality (i.e. if FA is higher, water diffuses less like a sphere, but more like an ellipsoid) and also indicates healthier or more mature WM. MD indicates the extent to which water molecule diffuses. Higher FA and lower MD indicates greater maturity of WM tracts. In 18-to-22-year-old VLBW adults, IQ increased (1) with higher FA values in several major WM tracts located both centrally and peripherally, as well as (2) with lower MD values in large regions including several subdivisions of the corpus callosum, and subdivisions of the uncinate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus and superior longitudinal fasciculus (Eikenes, Lohaugen, Brubakk, Skranes, & Haberg, 2011). No significant correlations were found in controls. Similarly, Allin et al. (2011) found a positive correlation between FSIQ and PIQ and regional FA. The regions included the

corpus callosum (genu) and the right superior longitudinal fasciculus. PIQ was additionally associated with FA in a cluster including the corpus callosum (body and splenium) and bilateral superior longitudinal fasciculi (Allin et al., 2011). Controls showed no correlation between IQ and regional FA (Allin et al., 2011). In both Eikenes et al. (2011) and Allin et al. (2011), several regions displayed lower FA in preterm group than in controls. Eikenes et al. (2011) additionally observed higher MD in the preterm group in a few regions. Another study found that the variance in IQ observed in preterm born adolescents was mostly accounted for by total WM volume and corpus callosum area, regardless of brain abnormalities reported at birth (Northam, Liegeois, Chong, Wyatt, & Baldeweg, 2011). Such a relationship was not observed in controls (Northam et al., 2011). Overall, the preterm group showed a stronger association compared to controls between IQ and (1) total WM volume or (2) regional WM integrity. Regarding the association between IQ and total WM volume, Northam et al., (2011) suggest that the higher correlation in the preterm individuals could result from the preterm group's altered WM integrity, which might lead to greater sensitivity of intellectual ability to WM volume.

To summarise, preterm individuals showed altered IQ development trajectories. Also, compared to controls, the preterm group had significantly lower IQ which was differentially associated with various brain measures indicating GM and WM volumes and WM integrity.

2.2 Executive function

2.2.1 Executive function in preterm born individuals

In preterm born individuals, EF has been found to be impaired from childhood through adolescence to adulthood. During childhood in particular, preterm born children displayed impairment in planning abilities, motor planning and sequencing and inhibition measured with the Tower of Hanoi task, Finger sequencing task and Tapping Test, respectively, at 5 years of age (Harvey, O'Callaghan, & Mohay, 1999), cognitive flexibility (TMT part B) and attention span (Spatial Span Forward task) at ages 7-9 years (Shum, Neulinger, O'Callaghan, & Mohay, 2008), visuospatial planning and organisation (Block Design task), planning (Tower of London and Rey-Osterrieth Complex Figure tasks) and global EF (Behaviour Rating Inventory of EF questionnaire) at 9 years (Anderson, Doyle, & Grp, 2004) or inhibition (Opposite Worlds and Walk Don't Walk tasks (Test of Everyday Attention for Children)), working memory (Digit Span Backwards and Letter-Number Sequencing tasks (WISC-IV)), verbal Fluency (Semantic Fluency task (NEPSY)), shifting (Creature Counting (Test of Everyday Attention for Children)) between ages 9 and 10 years (Mulder, Pitchford, & Marlow, 2011).

During adolescence, a number of studies have reported EF deficits in preterm born individuals. Burnett, Scratch, et al.'s (2013) review summarised a number of studies in four aspects EF (information processing, attentional control, cognitive flexibility and goal setting).

Preterm adolescents (GA: 31.2 (1.8) weeks) showed slower response speed at age 11 years as measured with the Cognitive Abilities Test (Rose & Feldman, 1996, as cited in

Burnett, Scratch, et al., 2013). Similarly, 14-year-old preterm adolescents also showed significantly slower motor speed in the Motor Screening subtest of the Cambridge Neuropsychological Test Automated Battery (Litt et al., 2012). Also, preterm individuals were reported to have significantly lower processing speed measured by processing speed subtest of Wechsler Intelligence Scales at age 14 (Soria-Pastor et al., 2008) and 18 years (Hallin et al., 2010). In contrast, no group difference in processing speed was found at age 16 years when measured with the Coding subtest of WAIS–R and Mental Control subtest of Wechsler Memory Scale, third edition (WMS-III) (Saavalainen et al., 2007).

Attentional problems have also been observed in preterm individuals. Subnormal performances on attention tests such as Contingency Naming, Verbal Cancellation (Taylor, Klein, Minich, & Hack, 2000) or Test d2 (Weindrich, Jennen-Steinmetz, Laucht, & Schmidt, 2003) were observed in 11-year-old preterm children. At age 14 years, preterm individuals showed impaired performance on the sustained attention subtest (Rapid visual information processing) of the Cambridge Neuropsychological Test Automated Battery (CANTAB), but there was no group difference after removing participants with neurosensory impairment and⁄or IQ <85 (Litt et al., 2012). Seventeen-year-old preterm individuals scored significantly lower on tasks measuring attention span (Spatial Span subtest of CANTAB) (Taylor, Minich, Bangert, Filpek, & Hack, 2004) and selective, shifting and divided attention (‘Elevator with distraction’, ‘Elevator with reversal’ and ‘Telephone search while counting’ subtests of the Test of Everyday Attention, respectively, as well as The Contingency Naming Test additionally measuring shifting attention) (Wilson-Ching et al., 2013), but there was no group difference in sustained attention (measured with The Test of Variables of Attention) (Wilson-Ching et al., 2013). Also, preterm born adolescents at age 16 years scored

significantly lower on inhibition tasks (Color-Word Interference and Tower subtests of Delis-Kaplan EF Scale) (Luu, Ment, Allan, Schneider, & Vohr, 2011).

Cognitive flexibility is another aspect of 'EF' which was found to be impaired in preterm individuals. LBW (< 750 g; mean GA: 26 weeks) individuals scored subnormally at ages 11 (Taylor et al., 2000) and 16 years (Taylor et al., 2004) on the Contingency Naming Test, which assessed speeded processing, shifting attention, and response inhibition (Riddle & Suhr, 2012). TMT (Part B) test results also indicated significantly poorer cognitive flexibility in preterm individuals at ages 14-15 (Nosarti et al., 2008; Rushe et al., 2011, both as cited in Burnett et al., 2013); Kulseng et al., 2007; Narberhaus et al., 2008) and 18 years (Hallin et al., 2010, as cited in Burnett, Scratch, et al., 2013).

In addition, preterm adolescents show deficiency in planning abilities. Preterm adolescents of different cohorts scored significantly lower than controls on Rey-Osterrieth Complex Figure at age 11 years (GA: 25.7 (1.8) weeks; BW < 750g) (Taylor et al., 2000), but not at 14 years (GA < 33 weeks; mean BW: 1299) (Rushe et al., 2001). At age 16 years, LBW individuals (< 1250g; mean GA: 28 weeks) performed equally well as controls on a planning task (Tower subtest of the Delis-Kaplan EF Scale) (Luu et al., 2011).

Taylor, Minich, Klein, & Hack (2004) presented longitudinal findings. They demonstrated that EF measured with Verbal Cancellation Test were significantly poorer in LBW children (< 750g; GA: 26 (2)) at ages 7, 12 and 14 years. Additionally,

improvement in the test performance between ages 7 and 14 years was significantly slower in the preterm group (Taylor et al., 2004).

Only a handful of studies have looked at adult neuropsychological outcomes of preterm birth. Although at least one study showed no attention impairment in preterm adults (Dalziel et al., 2007), others showed that preterm individuals still performed less well compared to their term-born peers in adulthood. The domains in which preterm adults showed deficiency includes divided attention (indicated by the Divided Attention subtests of the Test of Attentional Performance test (Nosarti et al., 2007), as well as CogHealth 3.0.5 which measured simple reaction time, choice reaction time (i.e. binary judgement colour), one-back memory, divided attention and visual paired associate learning (Strang-Karlsson et al., 2010)), conceptual tracking, cognitive flexibility (both measured with TMT (Part B)) (Nosarti et al., 2007), expressive language (measured with Verbal Fluency test), visual scanning, psychomotor speed, and ability to switch between mental sequences (measured with TMT) (Pyhala et al., 2011). Without specifying domains, Strang-Karlsson et al. (2008) reported greater executive dysfunction (indicated by Adult Problem Questionnaire) in preterm born adults. A deficit in inhibition was also observed in early twenties in preterm adults, as indicated by lower score on the Hayling Sentence Completion Test (Nosarti et al., 2007).

In summary, the ex-preterm individuals showed impaired EF in most studies except a few during adolescence and adulthood. Saavalainen et al. (2007) argued that preterm adolescents' normal EF which they observed (1) offers evidence for brain's plasticity and (2) preterm population's catching up with controls in cognitive abilities. Allin et al.

(2008) considered the possibility of "catch-up" by preterm born individuals, but the evidence was inconclusive.

2.2.2 Executive function and brain in preterm born individuals – Structural imaging

Brain imaging studies reported findings which show the relationship between EF and structural brain measures such as CT, GM/WM volumes, FA and brain abnormality (identified through visual inspection). The findings are summarised below for childhood, adolescence and then adulthood.

During childhood, the extent of WM abnormality, which was assessed by visually inspecting the magnetic resonance (MR) images of the brain acquired at term equivalent age, was associated with poorer executive performance (Edgin et al., 2008; Woodward, Clark, Bora, & Inder, 2012; Woodward, Clark, Pritchard, Anderson, & Inder, 2011). For example, Edgin et al. (2008) compared executive performance between controls and preterm children (GA < 33 weeks) at ages 2 and 4 years. Preterm children were subdivided into three WM abnormality groups: no abnormality, mild abnormality and moderate/severe abnormality). At age 2 years, working memory and inhibitory control was measured with a modified version of the Multi-Search Multi-Location test. When the children turned 4 years, a modified version of the Detour Reaching Box (DRB) was used to measure inhibitory control and switching to new rules. The DRB consisted of three phases, where there was one rule for the first phase, another rule during the second phase, and the two rules alternated during the third phase. During the first phase of DRB, preterm children with mild and moderate/severe WM abnormalities needed more trials than controls to master the initial rule. During the last phase (i.e. alternating phase),

preterm children with mild and moderate/severe WM abnormality made significantly more perseverative errors compared to controls as well as preterm children with no WM abnormality. There were significant effects of age and WM abnormalities group on pass rate of the tests. Pass rate of the test was significantly higher at age 4 years than at age 2. Also, controls and the preterm children without WM abnormalities were more likely to pass the tests than the preterm children with mild and moderate/severe WM abnormalities.

At age 4 years, preterm children (mean GA 27.89 weeks; from the same cohort as those studied in Edgin et al. (2008)) achieved significantly lower EF composite scores than controls (Woodward et al., 2011). The executive composite consisted of four tests: Tower of Hanoi (planning ability), Flexible Item Selection Task (concept formation and cognitive flexibility), Visual Search (selective attention and organised search), Shape School (inhibition and cognitive flexibility). When the preterm group was divided into three subgroups (no abnormality, mild abnormality and moderate/severe abnormality) according to the severity of WM abnormality at term equivalent age, more damaged WM was associated with worse performance (Woodward et al., 2011).

Woodward et al. (2012) continued following up the same cohort between ages 4 and 6. EF was measured with the Tower of Hanoi (planning and problem solving), Flexible Item Selection (cognitive flexibility), Visual Search (selective attention) and Shape School task (inhibition and cognitive flexibility) while, at age 6, it was measured with the Tower of Hanoi (planning and problem solving), Visual Search (selective attention), Backward Digit Span (verbal working memory), Backward Corsi Blocks (visuospatial working memory), Detour Reaching Box (inhibition, cognitive flexibility), Conners'

Kiddie-Continuous Performance Test (inhibitory control and sustained attention). As described in Woodward et al. (2011), Woodward et al. (2012) calculated executive composite scores for both ages. At both time points, preterm children (GA ≤32 weeks) with no WM abnormality (measured at term equivalent age) achieved as high executive composite scores as controls did at both time points. On the other hand, preterm children with mild WM abnormality scored significantly lower on an executive composite measure at both time points while they had significantly higher rates of (1) mild delay at age 4 years and of (2) mild and severe delays at 6 years. Mild and severe delays were defined as cognitive scores (e.g. executive composite scores) being 1SD and 2SD, respectively, below control group's mean score. Preterm children with moderate/severe WM abnormality had significantly lower executive composite scores as well as significantly higher mild and severe delays at both ages, compared to controls. These findings suggest that long term EF deficit in preterm children could be attributed to term-age WM abnormality, which, when more severe, leads to greater EF deficit in the long term.

At age 8 years, WM integrity measures such as FA, MD, axial diffusivity and radial diffusivity were compared between control and preterm (GA: 24-30 weeks) groups (Duerden, Card, Lax, Donner, & Taylor, 2013). FA and MD were explained above in "2.1.3" section, and axial and radial diffusivities refer to diffusion of water molecules parallel and perpendicular to, respectively, WM tracts (Counsell et al., 2006). Although a whole-brain analysis did not reveal group difference, a region of interest analysis within the frontostriatal pathways (i.e. areas encompassing external and extreme capsules, basal ganglia, the frontal pole, and the cingulum) showed that the preterm group had significantly lower FA values in left external capsule, superior longitudinal

fasciculus, uncinate fasciculus, and inferior fronto-occipital fasciculus (Duerden et al., 2013). The frontostriatal circuitry is known to mediate EF (Shang, Wu, Gau, & Tseng, 2013) and therefore this region of interest analysis finding is consistent with (Duerden et al., 2013) other finding that the preterm group significantly underperformed in an EF test (Behaviour Rating Inventory of EF). However, there was no significant association between any WM integrity measures and the executive test score. In sum, the link between WM integrity and EF at this age remains unclear.

A CT study at ages 7-10 years demonstrated that preterm children (GA: 24-30 weeks) from the same cohort as those in Duerden et al. (2013) had significantly thinner cortices in seven clusters including right anterior cingulate cortex, supplementary motor area, left isthmus of the cingulate gyrus, right superior temporal sulcus, right anterior insula, right postcentral gyrus and bilateral precuneus (Lax et al., 2013). However, within the preterm group, none of the clusters displayed significant correlations between their average CT and the scores of Behaviour Rating Inventory of EF test, which assesses EF problems in children's everyday life (Lax et al., 2013). The preterm group performed significantly more poorly than controls.

During adolescence, a few studies have demonstrated that better executive performance in preterm born individuals was associated with thinner cortices in the medial regions and with thicker cortices in the lateral temporal areas. LBW adolescents (≤1500g; GA: 24–35 weeks) at age 13-15 years showed association between better selective attention (measured with dichotic listening tasks) and thicker cortices in the superior posterior temporal gyrus, and thinner cortices in the anterior cingulate cortex while term-born peers displayed an opposite pattern (Bless et al., 2013). Also, in a similar group of

preterm adolescents (age 14-15 years) from the same cohort, thinner left entorhinal cortex was associated with better executive performance in tasks measuring visuomotor speed (TMT Part A), problem-solving and cognitive flexibility (Wisconsin Card Sorting Test, Research Edition (Computer Version 3 for Windows)) (Skranes et al., 2012).

Another study conducted during adolescence (14-15 years; preterm group's GA < 33 weeks), which investigated a cohort of individuals born in 1983-1984 who were admitted to the Neonatal Unit of University College London Hospital (UCLH) (i.e., the same cohort I studied in this thesis), demonstrated an association between EF and brain volume in several regions across the brain (Nosarti et al., 2008). GM and WM volumes in the regions where they observed greatest volume difference between controls and preterm individuals explained 29% of the variance in EF (phonemic fluency, semantic fluency and conceptual tracking measured with Controlled Oral Word Association Test, Animals and Objects Trials (Newcombe, 1969, as cited in Nosarti et al., 2008) and TMT Part B, respectively) regardless of group membership. These regions included brainstem, middle and inferior temporal gyri, occipito-frontal fasciculus, fusiform gyrus, parietal lobe, posterior cingulate, precentral and medial frontal gyri and anterior cerebellum (Nosarti et al., 2008). Risks of cognitive impairment (<1SD below control group mean) based on EF and language measures were predicted by the volumes in these regions except the precentral and medial frontal gyri (Nosarti et al., 2008). These results suggest that the same regions which are likely to be vulnerable to the long term consequences of very preterm birth are also centrally implicated in EF processing.

In the same cohort as those in Nosarti et al. (2008), Allin et al. (2005) revealed a relationship between cerebellar volume and executive, visuospatial and language functions in preterm adolescents (GA < 33 weeks, age 14-15 years). Lateral cerebellum and vermis were smaller in the preterm group. There was a positive correlation between lateral cerebellar volume and the task performance in most tests (similarities, block design and object assembly subtests of the WISC-R, with all the subtests of the K-ABC and with Shonnel Reading Age) whereas the mid-cerebellar volume was positively associated with only a few (picture completion subtest of the WISC-R and the reading–understanding subtest of the K-ABC).

Greater cross-sectional area of WM was also linked with preterm individuals' executive performance. For example, in the UCLH cohort, areas of the corpus callosum including genu, isthmus, anterior midbody and posterior midbody and splenium also positively correlated with executive task performance (TMT Part B; Digit Symbol subtest of the WISC-R) in preterm adolescents (GA < 33 weeks; age 14 years) (Narberhaus et al., 2008).

Gender by group interaction on the relationship between GM/WM volumes and EF was also investigated, but the results were non-significant (Scott et al., 2011). The participants were in mid-adolescence (ages 14-15 years; preterm group's GA: 29.1(2.2) weeks (same between genders); UCLH cohort) and the EF tasks were Controlled Oral Word Association Test, Animal Naming and Object Naming Tests and TMT Part B tests, measuring phonological and semantic fluencies and cognitive flexibility, respectively.

In contrast, Rushe et al. (2001) demonstrated that preterm adolescents with whole-brain abnormalities (identified through visual inspection) performed equally well on all executive tasks. Also, both controls and preterm adults (age 19 years; GA < 33 weeks) showed no relationship between EF (semantic and phonological verbal fluency tests and Hayling Sentence Completion Test) and FA values in regions where FA significantly differed between groups in (Allin et al., 2011). Both studies involved the UCLH cohort.

In summary, EF in the preterm born individuals was associated with various structural brain measures, but the associations were sometimes inconsistent.

2.2.3 Executive function and brain in preterm born individuals – Functional imaging

Functional imaging studies on preterm born individual's EF conducted so far looked at infancy, childhood, adolescence and adulthood. However, there are only a few studies, and these are described below.

Doria et al. (2010) looked at resting state networks in preterm infants born between 25.4–35.4 weeks of gestation. They were between 29 and 43 weeks of postmenstrual age, and were subdivided into three age groups (early preterm, preterm, and term-equivalent). A resting state network refers to a set of regions which display correlated activity while a participant lies in the scanner without doing any particular task. It is important to consider resting networks because executive dysfunction can be caused by altered coordination of activity among different functional brain networks (Repovs, Csernansky, & Barch, 2011). A number of networks appear during the resting state, and

some of them resemble functional networks such as executive control, auditory, somatosensory and motor networks (e.g. Doria et al. 2010). Doria et al. (2010) observed a complete executive control network at term-equivalent age, which is before the full acquisition of EF. This seems to show that, from the functional imaging perspective, preterm infants are more or less equipped to acquire EF.

A study in late childhood or early adolescence showed that preterm children recruit the normal regions for executive tasks, but this depends on the task difficulty. Extremely preterm born (GA: 27 (±1.3) weeks) children at age 11 years were scanned (fMRI) while performing combined Stroop n-back tasks which measured working memory and selective attention (Griffiths et al., 2013). The preterm group activated the same areas (cingulate, prefrontal, and parietal cortexes) as controls. However, preterm brains' activation in all the regions was weaker than that in the control group when the cognitive load was increased (colour 1- and 2-back tasks (i.e. remembering previously presented colours)). With easier tasks (word 1- and 2-back tasks (i.e. remembering previously presented words)), the number of regions decreased where preterm group showed weaker activation. In addition, response accuracy was significantly lower, thus corresponding to the fMRI findings.

Whereas Griffiths et al. (2013) showed that more difficult tasks resulted in activation that is weaker in preterm children, but still in the same regions as compared to controls', Nosarti et al. (2009) showed that regions where preterm adults display altered activation change depending on task difficulty. During a letter fluency task, the performance of which showed no group difference, preterm adults (GA < 33 weeks; age 20-21 years) showed differential alterations in brain activation between easy and hard letter trials

(Nosarti et al., 2009). During the easy letter trials, preterm adults showed *decreased* activation in anterior cingulate gyrus, right caudate nucleus and left inferior frontal gyrus than controls. On the other hand, hard letter trials resulted in preterm group's decreased activation in left middle frontal gyrus and *increased* activation in anterior cingulate gyrus. Additionally, preterm adults showed altered BOLD signals in prefrontal and temporal areas compared to controls in the absence of performance difference during completion of tasks involving response inhibition, attention allocation (Lawrence et al., 2009), the learning of visual (Narberhaus et al., 2009) and verbal paired associates (Lawrence et al., 2010). These studies seem to show preterm brain's plasticity of relying on alternative strategies in comparison to controls when performing a variety of cognitive operations. During adolescence (age 16-17 years) as well, Nosarti et al. (2006) observed altered functional neuroanatomy of executive-type tasks in preterm-born individuals, including response inhibition and attention allocation (using a go-no-go task), in the absence of performance differences in the preterm (GA < 33 weeks) compared to a control group. Between-group differences in BOLD signal were noted in fronto-striatal networks. Their interpretation was (1) that an alternative network was recruited when the original network was dysfunctional and (2) that this enabled normal functioning (Nosarti et al., 2006).

In sum, the preterm brain demonstrates a typical executive control network in infancy (as appearing in resting state network studies). However, the engagement of these typical regions seems to be suboptimal (e.g., weaker activation) in childhood, resulting in poorer performance on executive-type tasks. By adolescence and early adulthood performance on relatively easy tasks does not seem to be impaired, but its neuroanatomical substrates remain altered, reflecting possible evidence of compensation and the use of alternative strategies for task completion.

2.3 Memory

2.3.1 Memory function in preterm born individuals

Memory functions in preterm individuals have been investigated from infancy to adulthood. A number of studies have reported subnormal memory in preterm born individuals compared to controls at different ages, although some reported non-significant group difference especially during adulthood.

During infancy, several studies have shown preterm individuals to have impaired memory. In Woodward, Edgin, Thompson and Inder (2005), 2-year-old preterm (GA ≤ 32 weeks and birthweight < 1500g) infants showed significantly poorer encoding ability during performance of an object working memory task (multisearch multilocation). The task required children to watch the experimenter hide sweets in one of three locations inside a wooden box and then retrieve them. In the first phase (training phase), the children learned how to retrieve a sweet from a chosen location. In the second phase (pre-switch phase), children retrieved sweets from a particular location which remained the same across all trials. The second phase was passed when children successfully retrieved the sweets three times consecutively. The third phase (post-switch phase) was the same as the second phase except that sweets are hidden in another location which also remained unchanged across trials. Woodward et al. (2005) reported that preterm children were significantly more likely to repeat the pre-switch phase as well as to fail to pass to the post-switch phase.

Findings from early childhood are somewhat inconsistent. A study conducted at age 3-4 years revealed that preterm children's (GA < 30 weeks or birthweight < 1250 g) had impaired spatial short term memory as measured with the Memory for location subtest of the Stanford-Binet intelligence scale (Caravale et al., 2005). However, at age 4 years, there was no significance difference between ELBW participants (GA ≤ 33 weeks; birthweight < 1000g) and late preterm (GA: 34-36 weeks) or term individuals in Delayed location recall task of modified Hopkins Board test (Baron, Erickson, Ahronovich, Litman, & Brandt, 2010). Similarly, Kilbride et al. (2004) demonstrated no sigificant difference between 5-year-old ELBW children (birth weight: 450-800g) and controls in task performance of short term memory subtest in Stanford-Binet IQ test. Reasons for such contrast are unclear, but it could be due to differences in sample composition. More studies are required to clarify this issue.

In later childhood, findings are more consistent. Seven-to-nine-year-old preterm children (GA 30.32±3.3 (range 24–39) weeks) displayed significantly shorter spatial memory span (task based on Corsi block task (Milner, 1971, as cited in Luciana, Lindeke, Georgieff, Mills, & Nelson, 2007) and made significantly more errors in spatial working memory tasks (self-ordered searching task (Petrides and Milner 1982, as cited in Luciana et al., 2007) (Luciana et al., 2007). Similarly, at age 9 years, verbal working memory indicated by the Digit Span test was significantly poorer in ELBW participants (GA < 28 weeks or birthweight < 1000g) (Anderson et al., 2004). Consistently, Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever and Oosterlaan's (2009) meta-analysis also showed lower working memory performance (measured with Digit Span test) reported by six different studies covering ages between 7 and 15 years.

Deficient spatial working memory was also observed in childhood (Baron et al., 2010; Luciana et al., 2007).

Poorer memory skills in preterm individuals continued to be observed during adolescence in the majority of the studies, but a non-significant group difference was reported in at least one study (e.g. Saavalainen et al., 2007). Compared to controls, 16-year-old preterm adolescents (age; birth weight <1250 g; GA: 28 (2)) showed significantly poorer performance on the California Verbal Learning Test (CVLT) Children's Version (verbal memory) and the Rey-Osterrieth Complex Figure Test (visuospatial memory) (Luu et al., 2011). Also, preterm adolescents (age 14-20 years; GA: 26.6 (2.0); birthweight: 883 (161) g) showed impaired visual memory as indicated by significantly lower scores in immediate visual memory and delayed visual memory subtests of the Rey Visual Design Learning Task (Molloy et al., 2013). This significant difference persisted for only delayed visual memory after removing participants with impairments in visual acuity, visual perception, visual–motor integration, and/or intellectual or neurosensory impairments. Deficient spatial working memory compared to controls was another finding reported at age 11 (Cambridge Neuropsychological Test Automated Battery) when the variance of spatial working memory was predicted by GA in the preterm group (Curtis, Lindeke, Georgieff, & Nelson, 2002) as well as at 15 years (Litt et al., 2012). However, Saavalainen et al. (2007) presented mixed findings. Whereas preterm born 16-year-old performed significantly worse than controls on the Spatial Span Backward subtest of the WMS-III, no group difference was found on other working memory tests such as the Digit Span Forward/Backward, Spatial Span Forward and Letter-Number Sequencing (WMS-III) and Arithmetic tests (Wechsler Adult Intelligence Scale-Revised) (Saavalainen et al., 2007).

Studies involving young adults generally reported a non-significant group difference between preterm individuals and controls in memory task performance. At 19 years of age, preterm individuals performed as well as controls on a short-term memory task (Digit Span) (Tideman, 2000) whereas Allin et al. (2011) reported significantly lower performance of preterm group in the CVLT which assessed verbal memory and will be described in detail in Chapter 6 (section "6.1.4.3.2"). These results suggest that different aspects of memory functioning following very preterm birth may show differential long-term vulnerabilities. Subnormal memory performance in preterm individuals was observed again at age 25 years (Pyhala et al., 2011). After adjusting for parental education, current head circumference, and head circumference SD score at birth, preterm adults achieved significantly lower scores on subtests (immediate and delayed recalls) of the Rey-Osterrieth Complex Figure Test (ROCFT) (measuring visual memory) whereas no group difference was observed on the Stroop Test (measuring working memory) (Pyhala et al., 2011). Group differences in the delayed recall subtest of the ROCFT were not significant after further adjusting for IQ (Pyhala et al., 2011). Consistently, preterm participants (GA: 32.3–35.0 weeks) performed equally well to controls in a working memory test (Benton Visual Retention) at age 31 years (Dalziel et al. 2007).

2.3.2 Memory processing and functional brain alterations in preterm born individuals

There have been various studies between infancy and adulthood testing different aspects of memory function. Functional imaging studies used electroencephalography (EEG), magnetoencephalography (MEG) and fMRI to investigate the relationship between memory and neuronal activity in the preterm brain. Some are described below.

A few studies conducted at early ages looked at brainwaves as measured with EEG and MEG. At term equivalent age, brain activities indicated sign of recognition memory in controls, but not in preterm infants (Therien, Worwa, Mattia, & DeRegnier, 2007). The study measured event-related potentials with EEG while preterm infants (GA < 32 weeks) listened to a voice which was either their mothers' or a strangers'. Additionally, Doesburg et al. (2011) observed that, while children (age 7-8 years) successfully performed (i.e. unsuccessful trials were not analysed) visual short-term memory task, the control and preterm groups displayed a distinctive pattern of brainwave synchronisation (measured with MEG; synchronisation refers to brainwaves appearing coherently among different regions). The measured frequencies of brainwaves were theta (4–7 Hz), alpha (8–14 Hz), beta (15–30 Hz) and gamma-band (30–60 Hz) synchronisation, and the group difference in synchronisation was mostly observed in the alpha band centred at 10Hz. Whereas controls showed long-range synchronisations in alpha band, the preterm group showed desynchronisation in this band. These results reflect (1) that preterm children has altered functional connectivity while carrying out a visual short term memory retention task and (2) that the alpha brainwaves could be important in altered functional connectivity in the preterm group (Doesburg et al., 2011).

On the other hand, fMRI studies showed spatial difference in activity patterns between preterm individuals and controls. For example, while no group difference in N-back task performance (i.e. accuracy or reaction times) was observed between controls and preterm children (age 7-9 years; GA < 32 weeks), the preterm group showed decreased brain activity in the left precuneus and right hippocampal regions compared to controls when the 1-back condition (i.e. remembering stimulus from previous trial) was

contrasted with the 0-back (i.e. responding to a particular stimuli, therefore requiring no working memory) condition (Taylor, Donner, & Pang, 2012). In addition, controls showed frontal activation in the dorsal lateral prefrontal cortex, anterior cingulate cortex and middle frontal cortex, whereas the preterm group showed no significant activation in frontal regions (Taylor et al., 2012). Stimuli for the N-back task were abstract drawings. Another fMRI study by (Griffiths et al., 2013), which has already been described in section "1.2.1.2.5" above, also demonstrated that working memory–selective attention tasks (combined Stroop n-back) activated cingulate, prefrontal, and parietal cortices in 11-year-old preterm (GA 27 (±1.3) weeks) and term-born children, but activation was significantly weaker in preterm children (Griffiths et al., 2013). In addition, these regions showing weaker activation in preterm children became smaller when tasks required lower cognitive demands (Griffiths et al., 2013).

Group differences in fMRI activation pattern were observed again at age 12-16 years (Gimenez et al., 2005). The learning condition (learning 16 novel face-name pairs), when contrasted against the control task (examination of two repeated face–name pairs), activated the right fusiform gyrus and the left inferior occipital gyrus in both groups. However, the preterm group (GA ≤ 34 weeks) showed stronger activation in right hippocampus when compared against the control group. Task performance was significantly worse in the preterm individuals. However, another study observed no significant group difference (preterm group GA: 27-35 weeks) in hippocampal activity during either encoding or retrieval phases of 'delayed match to sample' and 'delayed nonmatch to sample' tasks measuring explicit memory (Curtis, Zhuang, Townsend, Hu, & Nelson, 2006). During these tasks, participants (mean age: 13.8 years) were first presented (encoding phase; 3 seconds) with a visual stimulus (patterns in squares), and

after a delay phase (15 seconds), the initially presented stimulus was presented again together with a different one (retrieval phase; 3 seconds). During the retrieval phase, the delayed match to sample task required participants to select the initially presented stimulus whereas the other one needed to be chosen in the delayed nonmatch to sample task. On the other hand, Curtis et al. (2006) also reported that preterm individuals (GA: 27-35 weeks) showed significantly greater activation in the right caudate nucleus and weaker activation in the left caudate nucleus during both encoding and retrieval phases of the spatial span task, respectively, in the absence of group difference in task performance. The spatial span tasks began with presentation of four squares, each of which changed colours one by one, and participants were required to remember and retrieve the orders of the colour change. These two studies seem to suggest that activities in limbic structures are particularly important for preterm individuals.

During adulthood, group differences in fMRI activation during visual (Narberhaus et al., 2009) or verbal (Kalpakidou et al., 2012; Lawrence et al., 2010; Salvan et al., 2013) paired associates learning task were observed in more widespread regions. The four studies described here used the UCLH cohort. In these studies, the tasks were designed so that preterm participants would perform similarly to controls, in order to avoid BOLD differences associated with performance rather than group membership (e.g. Nosarti et al., 2006). At age 20 years, preterm individuals (GA ≤ 33 weeks) displayed, in the encoding condition (mean signal across four blocks) of a visual paired associates learning task, greater activation in the left caudate nucleus, the right cuneus and in the left superior parietal lobule, as well as weaker activation in the right inferior frontal gyrus (Narberhaus et al., 2009). On the other hand, the recognition condition of the same task (mean signal across four blocks) induced greater activation in the preterm

brain's right posterior cerebellum, and bilaterally in anterior cingulate gyrus (Narberhaus et al., 2009).

Twenty-year-old preterm individuals (GA <33 weeks) showed greater activation compared to controls in left parahippocampal and precentral gyri during encoding condition and left precentral gyrus during recall condition of a verbal paired associates learning task (Lawrence et al., 2010). This task was analysed in the same way as the visual version of the task described above, measuring the mean signal across four blocks. Volume analysis additionally revealed decreased GM volume in the left and right hippocampi as well as increased GM in the left parahippocampal gyrus in preterm adults (Lawrence et al., 2010). In the preterm group only, a positive association was found between functional activation in left parahippocampus during the encoding condition of the fMRI task (preterm > control) and GM volume in the same area (Lawrence et al., 2010). This association was mediated by GA.

Another study at age 20 years also showed that, as participants learned the same set of verbal paired associates (repeated four times), the patterns of regional activation differed between controls and preterm adults (preterm GA < 33 weeks; 20 years) (Salvan et al., 2013). During the encoding condition, differential activation patterns were observed in the right anterior cingulate, superior frontal gyrus and part of the caudate nucleus where the preterm group showed greater activation in later blocks of trials, possibly reflecting more cognitive effort (Salvan et al., 2013). During the recall condition, the preterm group displayed a progressive decrease in activation in parts of the left posterior parahippocampal gyrus, posterior hippocampus and thalamus (pulvinar). Salvan et al. (2013) further investigated functional results in relation to

possible WM alterations. They identified WM tracts passing through right anterior cingulate/caudate and left hippocampal/thalamic clusters (where fMRI activation significantly differed as just described), and carried out voxel-wise FA comparison within those tracts. The tracts that went through the anterior cingulate/caudate region were the anterior part of the corpus callosum, tracts of the internal capsule, anterior thalamic radiations, frontostriatal tracts and the fronto temporal section of the inferior fronto-occipital fasciculus. Also, the left hippocampal/thalamic areas were connected with the hippocampal fornix, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus and the splenium of the corpus callosum. The voxel-wise FA comparison within those tracts revealed that, whereas the tracts penetrating through anterior cingulate/caudate regions showed no significant FA difference between groups, the tracts stemming from left hippocampal/thalamic regions showed significantly lower FA than controls in left hippocampal fornix, splenium of the corpus callosum, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus.

Kalpakidou et al. (2012) also used the same verbal paired associates learning tasks in controls and preterm adults (GA < 33 weeks) at age 20-25 years, and investigated the effects of neonatal brain injury, as assessed by cerebral ultrasound, on adult functional neuroanatomy. Results of this study reported a linear pattern of activation according to neonatal risk. Preterm born young adults exhibited less activation than controls in the right middle frontal gyrus during encoding and in the right posterior cingulate gyrus during recall, with the preterm subsample who sustained periventricular haemorrhage and ventricular dilatation showing decreased activation than the preterm subsample who sustained uncomplicated periventricular haemorrhage, who in turn exhibited decreased activation compared to the preterm subsample with normal neonatal ultrasound. Controls showed the greatest regional activation compared to all 3 preterm subgroups.

The results of Kalpakidou et al. (2012) and Lawrence et al. (2010) studies, although using the same fMRI task, are difficult to compare as Lawrence et al. (2010) studied only preterm born individuals with low neonatal risk.

2.3.3 Memory function and structural brain alterations in preterm born individuals

Preterm birth is often accompanied by hypoxic ischaemic damage (Martin, Wang, Koroglu, Di Fiore, & Kc, 2011) which is known to lead to memory deficiency as well as brain alterations in several areas (Caine & Watson, 2000). In this section, findings of the relationship between memory and brain structures in preterm individuals are presented.

Woodward et al. (2005) reported the importance of both cerebrospinal fluid and WM in preterm infants' (GA ≤ 32 weeks and birthweight < 1500g) object working memory (multisearch multilocation task described above in section "2.3.1"). There was a linear negative association between cerebrospinal fluid volume measured at term equivalent age (40 weeks gestation) and task performance at age 2 years (i.e. bigger cerebrospinal fluid was associated with worse performance). In addition, when the preterm infants were divided into different groups (i.e. no injury, mild injury and moderate/severe injury) according to the level of WM injury at term equivalent age (40 weeks gestation), those with the greatest injury had the lowest success rate in task performance.

WM was shown to play a significant role in preterm individuals' memory function during adolescence (age 14 years) as well (Narberhaus et al., 2008). Everyday memory (measured with the Rivermead Behavioural Memory Test) was positively correlated

with the size of genu and isthmus, which are parts of corpus callosum, in the preterm group (Narberhaus et al., 2008). Additionally, in young preterm adults (age 19 years; GA < 33 weeks), memory score (a composite score made up of scores on the CVLT and WMS (immediate and delayed picture recall)) was significantly and positively associated with FA values in genu, body and splenium (corpus callosum), bilateral superior longitudinal fasciculi, and left superior corona radiata (Allin et al., 2011). These regions are where the preterm group had lower FA values compared with controls.

Among other structures, the hippocampus and adjacent structures were also reported to be important in the preterm adolescents' memory. For example, preterm born adolescents (median age 14 years; GA ≤30 weeks) showed a positive association between everyday memory (Rivermead Behavioural Memory Test) performance, which was significantly worse in preterm individuals, and hippocampal size (i.e. smaller hippocampus indicated worse memory) (Isaacs et al., 2000). Also, worse immediate memory span for non-verbal material (Knox cube test) was associated with thinner left entorhinal cortices in 14-to-15-year-old LBW adolescents (≤1500g; GA: 29.1 (2.7) weeks) (Skranes et al., 2012).

Among the preterm infants (age 2 years; GA < 30 weeks or birthweight < 1250g), those with working memory deficit (as indicated by failing to alternate during delayed alternation task) had significantly smaller hippocampal volumes compared to the preterm children with normal working memory scores, even after controlling for total brain volume and relevant perinatal, social and developmental factors (Beauchamp et al., 2008), thus confirming the importance of the hippocampus. However, other structural

volumetric studies indicate that it may be more than alterations of the hippocampus itself which are responsible for preterm individuals' memory deficits. Omizzolo et al. (2013) studied preterm children (age 7 years; GA < 30 weeks or birthweight < 1250g) and found that they performed significantly more poorly than controls on tasks measuring immediate visual memory (Block Recall subtest of Working Memory Test Battery for Children test; Dot locations subset of the Children's Memory Scale) and verbal working memory (Backward Digit Recall subtests of Working Memory Test Battery for Children test) and delayed visual memory (Dot locations subset of the Children's Memory Scale). Hippocampal volume was also significantly smaller in the preterm group. However, hippocampal volume did not significantly correlate with the task scores (Omizzolo et al., 2013). Omizzolo et al. (2013) interpreted this as, within preterm individuals, (1) the hippocampus being not the only structure responsible for memory and (2) other regions being possibly recruited to compensate for increased task difficulty (Just & Varma, 2007; Lawrence et al., 2010, both as cited in Omizzolo et al., 2013). This, again, leads to the "differential wiring of brains" view.

On the other hand, the importance of subcortical structures in memory function has also been reported. Omizzolo et al. (2014) showed the same results as those in Omizzolo et al. (2013) in terms of task performance in similar samples of controls and preterm children (GA < 30 weeks and/or birthweight < 1250 g). Worse memory performance was generally associated with the extent of brain injuries (i.e. abnormalities in WM, cortical GM, deep GM (basal ganglia and thalamus) and cerebellum) observed at term. The best predictor of memory performance was the presence of abnormalities in deep GM. The memory measure best predicted by brain abnormality was the total number of words recalled across trials 1-5 in CVLT - Children's Version (measuring verbal learning) (Omizzolo et al., 2014).

In sum, various brain structures have been associated with preterm individuals' normal or subnormal performance (i.e. lower than controls' performance rather than below clinical cut-off score labelled as 'impaired') although the involvement of the hippocampus has been most often observed.

2.4 Psychiatric outcome

2.4.1 Psychiatric outcome in preterm born individuals

Preterm born individuals have been generally reported to experience more psychiatric symptoms during childhood (Anderson, Doyle, & Victorian Infant Collaborative Study, 2003; Hille et al., 2001; Johnson & Marlow, 2011; Rogers, Lenze, & Luby, 2013; Treyvaud et al., 2013), adolescence (Botting et al., 1997; Burnett et al., 2011; Conrad, Richman, Lindgren, & Nopoulos; Indredavik et al., 2004; Johnson et al., 2010b; Loe, Lee, Luna, & Feldman, 2011; Saigal, Pinelli, Hoult, Kim, & Boyle, 2003; Somhovd, Hansen, Brok, Esbjorn, & Greisen, 2012) and adulthood (Boyle et al., 2011; Nosarti et al., 2012; Walshe et al., 2008). Such adverse psychiatric outcomes have been demonstrated to be more likely to appear when preterm birth is accompanied by low socioeconomic status (Lindstrom, Lindblad, & Hjern, 2009).

Nosarti (2013) discussed the possible causal directions between psychiatric problems and preterm birth. One view is that mothers with psychiatric problems are at higher risk

of giving preterm birth (Paarlberg et al., 1999). A contrasting view, though, suggests that preterm birth is one of various psychiatric risk factors (Carpenter, 1987).

However, other studies have reported non-significant differences in psychiatric problems in preterm born adolescents (Burnett, Davey, et al., 2013; Indredavik et al., 2004; Sullivan, Msall, & Miller, 2012) and adults compared to controls (Dalziel et al., 2007). The non-significant findings have been interpreted as preterm participants 'not fully paying attention to their mind and behaviour' or being uncomfortable disclosing such problems (Sullivan et al., 2012).

In preterm born individuals, greater prematurity has also been related with other issues which could result in social problems. These issues include increased tendencies to have mental retardation (Moster, Lie, & Markestad, 2008), history of having been hospitalised due to a psychiatric disorder (Lindstrom et al., 2009), purchase of at least one ADHD medication (Lindstrom, Lindblad, & Hjern, 2011) and hyperkinetic disorder (Linnet et al., 2006).

In addition, Strang-Karlsson et al. (2008) showed that, among VLBW adults, the small-for-GA group with higher GA (= 31.2 weeks) had significantly greater emotional instability than the appropriate-for-GA with lower GA (= 28.2 weeks) and term-born controls. The small-for-GA was defined as 2 SD below the mean according to Finnish birth weight standards (Pihkala et al., 1989, as cited in Strang-Karlsson et al. 2008). On the other hand, appropriate-for-GA group and control groups had similar outcomes (Strang-Karlsson et al., 2008). These results show the importance of intrauterine growth

rather than the extent of prematurity itself in emotional health (Strang-Karlsson et al., 2008).

Taken together, a number of studies reported more psychiatric issues in preterm born individuals than in controls, but non-significant group difference was also reported. It is unclear whether (1) maternal psychiatric problems lead to preterm birth and psychiatric problems in the preterm born or (2) preterm birth results in psychiatric issues. One study also showed that subnormal intrauterine growth (represented by birth weight) rather than low GA itself could be important in preterm individuals' emotional instability (Strang-Karlsson et al., 2008). Overall, rather than preterm birth directly leading to psychiatric problems, factors associated with preterm birth could be more important. Further research is required to clarify this issue.

2.4.2 Psychiatric outcome and its functional and structural brain correlates in preterm born individuals – review by Nosarti (2013)

Nosarti (2013) reviewed studies on psychiatric disorders and behavioural problems and their functional and structural brain correlates in preterm born individuals with a focus on adolescence. Part of the review is summarised in this section.

Nosarti (2013) concentrated on the neurodevelopmental hypothesis (Murray, Lappin, & Di Forti, 2008), which proposes that brain damage at an early age, whether caused by genetic or environmental factors or both, interacts with the developing brain and that

such an interaction could result in higher likelihood of having psychopathology in adolescence and adulthood (Murray et al., 2008).

Nosarti (2013) pointed out that preterm born individuals have increased risk of attention deficit hyperactivity disorder (reviewed in Johnson & Marlow, 2011, as cited in Nosarti, 2013) which is accompanied by poor performance in go-no-go task (Garavan et al., 2002, as cited in Nosarti, 2013) and altered brain activity during the stop task (Rubia et al., 2005, as cited in Nosarti, 2013) - both go-no-go and stop tasks assessed response inhibition. As described in section "1.2.1.2.5", Nosarti et al. (2006) reported that the preterm group's brain activation was altered on the go-no-go task.

Brain volume studies have revealed a link between smaller left caudate nucleus and hyperactivity scores (from Rutter Parents' Scale) indicating attention deficit-type of problems in preterm born male adolescents (Nosarti et al., 2005, as cited in Nosarti, 2013). A consistent view with these results is that the basal ganglia has a role in the pathogenesis of ADHD (Frodl & Skokauskas, 2012, as cited in Nosarti, 2013). Contrasting findings, though, showed no group difference in caudate volume, but reduced bilateral hippocampal volumes in preterm adolescents with attention deficit (measured with Connor's Hyperactivity scale) (Abernethy, Palaniappan, & Cooke, 2002). Nosarti (2013) suggested that the inconsistent findings could be due to different methodologies (e.g. different region of interest used in the analyses).

Attention deficits in preterm individuals were also shown to be associated with microstructural WM disorganisation in the internal capsule and the posterior corpus

callosum at age 11 years (Nagy et al., 2003, as cited in Nosarti, 2013) and in periventricular regions at age 15 years (Skranes et al., 2007, as cited in Nosarti, 2013). At age 15, WM deficits were additionally linked with overall mental health functioning scores (Children's Global Assessment Scale (CGAS)) (Skranes et al., 2007, as cited in Nosarti, 2013) and high inattention scores were associated with more severe WM alterations in external capsule and superior and middle fascicles. These findings are consistent with the report that structural connectivity is associated with inattention and impulsivity in adult attention deficit hyperactivity disorder (Konrad et al., 2010).

Other studies have investigated the impact of periventricular damage sustained during the neonatal period. When Nosarti et al. (2011, as cited in Nosarti, 2013) grouped preterm born adolescents into three groups (normal, periventricular haemorrhage, and periventricular haemorrhage with ventricular dilatation), they observed more generalised behavioural problems in the most damaged group compared to the other two. This finding was still statistically significant after adjusting for GA or IQ. Also, thalamus, prefrontal cortex and cerebellum, which were structurally altered in preterm adolescents having periventricular haemorrhage with ventricular dilatation (Nosarti et al., 2008, as cited in Nosarti, 2013), were also found to be altered in psychiatric disorders with typical onset during adolescence (James et al., 2004, as cited in Nosarti, 2013).

In preterm children with periventricular leukomalacia, a condition characterised by WM cell death leading to enlarged lateral ventricles, CT in frontal area was positively associated with internalising (withdrawal, somatic complaints, anxiety/depression) and externalising scores (delinquency and aggressive behaviour) as measured by CBCL

(Zubiaurre-Elorza et al., 2012, as cited in Nosarti, 2013). A relevant finding from another study is the correlation between internalising scores and CT in the fusiform gyrus (Kaiser et al., 2010, as cited in Nosarti, 2013), a brain area considered a core 'neural signature' of autism showing structural deficits in both autistic individuals and their unaffected siblings (Kaiser et al., 2010, as cited in Nosarti, 2013).

While most studies have reported cross-sectional findings, a longitudinal study revealed an association between preterm individuals' cerebellar volume decrease (by 3%; control group showed no significant change) between 14 and 19 years (Parker et al., 2008, as cited in Nosarti, 2013). The cerebellar volume decrease was associated with worse self-reported mental health (measured with General Health Questionnaire), particularly in the following domains: concentration, feeling useful, confidence, decision-making capacity and feeling of worthlessness (Parker et al., 2008, as cited in Nosarti, 2013).

Social difficulties, which were observed in preterm born individuals as indicated by subnormal scholastic adjustment (Sykes et al., 1997, as cited in Nosarti, 2013), socialisation skills and social competence (Schmidt et al., 2008, as cited in Nosarti, 2013), was also investigated in relation with brain metrics. For example, social difficulties (measured with Social Adjustment score) were significantly associated with left caudate volume in preterm born adolescents (Nosarti et al., 2005, as cited in Nosarti, 2013). A consistent finding is that the caudate nucleus is related with not only pathophysiology of ADHD, but also reciprocal social and communicative impairment in conditions such as autism spectrum disorder (Qiu et al., 2010, as cited in Nosarti, 2013). Also, in another study (Skranes et al., 2007, as cited in Nosarti, 2013), preterm adolescents who scored high on an autism spectrum screening questionnaire displayed

WM microstructural deficits in the external capsule and in the superior fasciculus. WM deficits in these two regions and in the internal capsule and occipital regions were found to best distinguish autistic children from controls, possibly because they are involved in connecting regions related with social cognition (Ingalhalikar et al., 2011, as cited in Nosarti, 2013).

Preterm birth was also found to result in increased vulnerability to stress. For example, young adults born with ELBW (< 1000g) displayed more internalising behavioural problems than controls (Schmidt et al., 2010, as cited in Nosarti, 2013). The adults born with ELBW also displayed stronger frontal lobe brain activity (measured with EEG) in the right hemisphere compared to the left (Schmidt et al., 2010, as cited in Nosarti, 2013). Such asymmetry was found to be associated with handling of negative emotions (e.g., distress and sorrow) (Coan & Allen, 2004, as cited in Nosarti, 2013), and Schmidt et al. (2010, as cited in Nosarti, 2013) suggested that it could be related with predisposing ELBW individuals to experience difficulties in stress regulation. An association between stress vulnerability and LBW or impaired fetal growth was also suggested in (Nilsson et al., 2001, as cited in Schmidt, Miskovic, Boyle, & Saigal, 2010).

It is unknown how brain alterations leads to psychopathology, but Nosarti (2013) suggests that it could be enhanced by dysregulation of neurotransmitters involved in psychiatric disorders. Some hypotheses propose that early brain injuries result in altered prefrontal–hippocampal development, which is often reported following very preterm birth, and this leads to increased striatal dopamine release (Howes & Kapur, 2009, as cited in Nosarti, 2013). Findings which are consistent with this view have been reported

as follows. Animal models suggest that neonatal damage to the hippocampus leads to altered brain development, and this results in the lesioned animals having stronger mesolimbic dopamine response to both stressful and pharmacologic stimuli compared with healthy animals (Lipska et al., 1993, as cited in Nosarti, 2013). Excitotoxic lesions to the medial prefrontal cortex also leads to greater dopamine-mediated behavioural responses in rats (Flores et al., 1996, as cited in Nosarti, 2013). Adverse effects of specific lesions manifest only after a certain level of maturity is reached, as demonstrated in animal studies (e.g., Lipska, 2004, as cited in Nosarti, 2013). Social vulnerability could also be a possible cause of dopamine dysregulation, and lies on the causal pathway to psychiatric disorder (Selten & Cantor-Graae, 2005, as cited in Nosarti, 2013), or the other way round (dopamine dysregulation causing social vulnerability) (Nosarti, 2013).

Genetic factors could also affect psychopathology in preterm born individuals (Nosarti, 2013). At age 19 years, preterm adults were more likely to have anxiety and depression than controls, and this risk increased when they had a first-degree relative with a history of psychiatric disorder (Walshe et al., 2008, as cited in Nosarti, 2013). However, for genetic variants to cause psychopathology, a particular biological risk could be required. For example, hippocampal volume decrease due to genetic liability in schizophrenia patients was greater when accompanied by neonatal hypoxia (Cannon et al., 2002, as cited in Nosarti, 2013). Also, gene effects on brain development could vary at different ages, as demonstrated by Lenroot and Giedd (2008, as cited in Nosarti, 2013). At an early age, genetic influences on the brain seem to be stronger in basic sensorimotor functions (Lenroot & Giedd, 2008, as cited in Nosarti, 2013). In contrast, at later ages, these regions seem to be under stronger influence of the environment than genes (Lenroot & Giedd, 2008, as cited in Nosarti, 2013). Gene effects appear to become

stronger at later ages for high order cognitive functions, such as language (Lenroot & Giedd, 2008, as cited in Nosarti, 2013).

Chapter 3: Literature review - Neurological outcome in adolescence/adulthood in term-born and preterm-born individuals

The development of various brain imaging methods have made it possible to examine brains of living participants. The present chapter briefly describes the imaging methods, and further describes previous studies which provided structural measures within both control and preterm groups.

3.1 Neuroimaging methods

As described in the previous section, cognitive/psychiatric impairments are manifestations of alterations to the brain. Such alterations can be investigated with functional (e.g. regional activation of the brain during task performance) and structural (e.g. volume of the brain associated with level of task performance) neuroimaging. There are different means of these investigations, of which some of the common ones include positron emission tomography (PET), computed tomography, EEG and MEG and magnetic resonance imaging (MRI). Among these, MRI is one of the most commonly used methods.

3.1.1 Magnetic resonance imaging

MRI is used to examine both functional and structural aspects of the brain. fMRI provides a temporal resolution of a few seconds (i.e. signal change is detected a few seconds after brain activity changes) and a spatial resolution of a few millimetres. Structural MRI provides no information regarding the link between brain activation and structure, but noticeably better spatial resolution compared to fMRI, enabling more thorough investigation of brain structures.

3.1.2 Modalities of structural magnetic resonance imaging analysis

Structural MRI allows various types of structural analysis of the brain, depending on methods of scanning, image processing and analyses.

In brief, there are two main types of MR images used to examine brain structure: T1 and T2 weighted. For example, in T1 weighted images, fat appears white or bright, and water or cerebrospinal fluid appears dark. In contrast, fat looks dark, and blood, edema, and cerebrospinal fluid appear bright on T2 weighted images (Mettler, 2005, as cited in El-Dib, Massaro, Bulas, & Aly, 2010). Structural studies of the brain usually use T1 images. On the other hand, T2 images are useful for clinical diagnosis. Therefore, most brain imaging studies discussed in this study used T1 images.

Once structural images are acquired, they are first segmented (broken down into their major constituent parts using appropriate image analysis methods) and then analysed. Depending on the segmentation method, different types of analyses are possible (i.e. different measures of brain structure can be investigated). The most common measure

of the brain used in analyses is the volume. For this, the brain is first segmented into GM and WM and then their volumes are calculated separately. For the GM, thickness and surface area can be looked at as well, which together comprise volume (i.e. GM volume = (GM thickness) x (GM surface area). Images are segmented in different ways (i.e. different algorithms are used) between CT or surface area analyses and volume analyses. Also, there are various software packages specifically designed for different types of segmentation and analyses. Some commonly used ones include Voxel-Based Morphometry toolbox (http://dbm.neuro.uni-jena.de/vbm/) (image segmentation for cortical volume analysis (i.e. for segmentation only, and not for analysis)) working on Statistical Parametric Mapping software (http://www.fil.ion.ucl.ac.uk/spm/) (cortical volume analysis), FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) (image segmentation and cortical surface area/thickness analyses), CIVET pipeline (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET) (image segmentation for CT analysis) and SurfStat (http://www.math.mcgill.ca/keith/surfstat/) (CT analysis).

Another useful and widespread method of structural is scanning is diffusion MRI (also known as diffusion weighted MRI and diffusion tensor imaging (DTI)). This technique measures how water molecules diffuse along the WM fibres. Diffusion MRI produces measures such as MD or FA, axial and radial diffusivities. As already explained in a section above ("2.1.3"), MD indicates the extent to which water molecule diffuses. Lower MD indicates narrower space inside axons, reflecting better cellular health or maturity. Higher factional anisotropy indicates greater directionality (i.e. water diffuses less like a sphere, but more like an ellipsoid) and also indicates healthier or more mature WM. FA's directionality also allows visualisation of the WM tracts (e.g. Catani, Jones, & ffytche, 2005). Some studies also measure, axial diffusivity and radial diffusivity,

which measure the extent to which water diffuses along and perpendicular to, respectively, WM fibres.

3.1.3 Cortical thickness

In this study, I have analysed the thickness of GM, which is usually referred to as "CT" and can be defined as the distance, at a given point, between the inner and outer boundaries of the cortex (the boundaries between GM and WM / GM and cerebrospinal fluid respectively).

Depending on cortical regions, CT ranges between 1.5 and 4.5mm (Parent & Carpenter, 1995, as cited in Narr et al., 2007), and reflects cytoarchitectural characteristics of the neuropil including the density and arrangement of neurons, neuroglia, and nerve fibers (Narr et al., 2007). CT, although shown to relate to other local measures of GM (Narr et al. 2005, as cited in Narr et al., 2007), may have stronger links with cognition and/or intellectual ability than volumetric or intensity-based GM concentration measures (Narr et al., 2007).

3.1.3.1 Significance of cortical thickness in development

The following observations suggest that CT is a useful proxy measure of neurodevelopment. First, cognitive functions are closely related with CT. For example, cognitive development is correlated with non-linear changes in CT in normative samples (Sowell et al., 2004). Subnormal or supernormal CT in preterm-born

individuals is also related to altered cognitive functions (Martinussen et al., 2005). Second, the correlation strength of CT between two regions depended on the anatomical distance between them (He, Chen, & Evans, 2007) which might suggest an anatomical connection. For example, CT correlations exponentially decreased when the anatomical distance exceeded 35mm (He et al., 2007). Short-range connections (< 75mm) were observed mostly in the posterior cortex whereas long-range connections (> 75mm) were mainly observed in the frontal cortex (He et al., 2007). Considering these findings, it would be useful to monitor, along the trajectory of development, how CT covariance changes and how this is associated with cognitive functions in normative samples, and subsequently compare these developmental changes with those observed in clinical samples.

3.1.3.2 Cortical thickness development in normative (term-born) individuals

The developmental trajectory of CT in normative samples has been investigated in more depth in younger rather than older subjects, in both cross-sectional and longitudinal studies. First, cross-sectional studies reported CT decreases between childhood and early adulthood. O'Donnell, Noseworthy, Levine, & Dennis (2005) looked at striate, frontopolar and dorsolateral regions, and observed significant linear CT decrease in the latter two areas. Tamnes et al. (2010) examined the whole brain and reported significant CT decrease in most regions. Also, the extent of change differed among the regions (Tamnes et al., 2010). The greatest decrease was observed in the posterior regions, especially in the parietal lobe (Tamnes et al., 2010). Occipital and frontal lobes showed smaller CT decrease while temporal lobe showed the smallest CT decrease as well as increase in entorhinal cortex and temporal pole (Tamnes et al., 2010). The decrease was

generally linear, but quadratic decrease (initial rapid decrease and slowing down later) was also observed in most regions (Tamnes et al., 2010). On the other hand, longitudinal studies have reported both CT decrease and increase. Shaw et al. (2008) showed that the trajectory of CT change varied according to layers and cortical regions (Shaw et al., 2008). As shown in Table 3-1, a cortex with more complex laminar architecture, which also has more layers (Kaas, 1987; Puelles, 2001; Allman et al., 2002; Striedter, 2005, all as cited in Shaw et al., 2008), shows more complicated growth trajectories. In addition, Figure 3-1 (Shaw et al., 2008) shows different growth trajectories according to cortical regions. A cubic trajectory of CT change is seen in most of the lateral frontal, lateral temporal, parietal and occipital isocortex - increase during childhood, decrease during adulthood followed by stabilisation. A quadratic growth pattern, which lacks the stabilisation period in early adulthood, appears in much of the insula and anterior cingulate cortex. A linear trajectory is displayed in posterior orbitofrontal and frontal operculum, portions of the piriform cortex, the medial temporal cortex, subgenual cingulate areas, and medial occipitotemporal cortex. Consistently, Sowell et al.'s (2004) longitudinal study of 45 children (aged 5 and 11) revealed differential patterns of cortical thickening (Wernicke’s and Broca’s areas in the left hemisphere) and more widespread thinning (right frontal and bilateral parietal and occipital association cortices) in different brain regions.

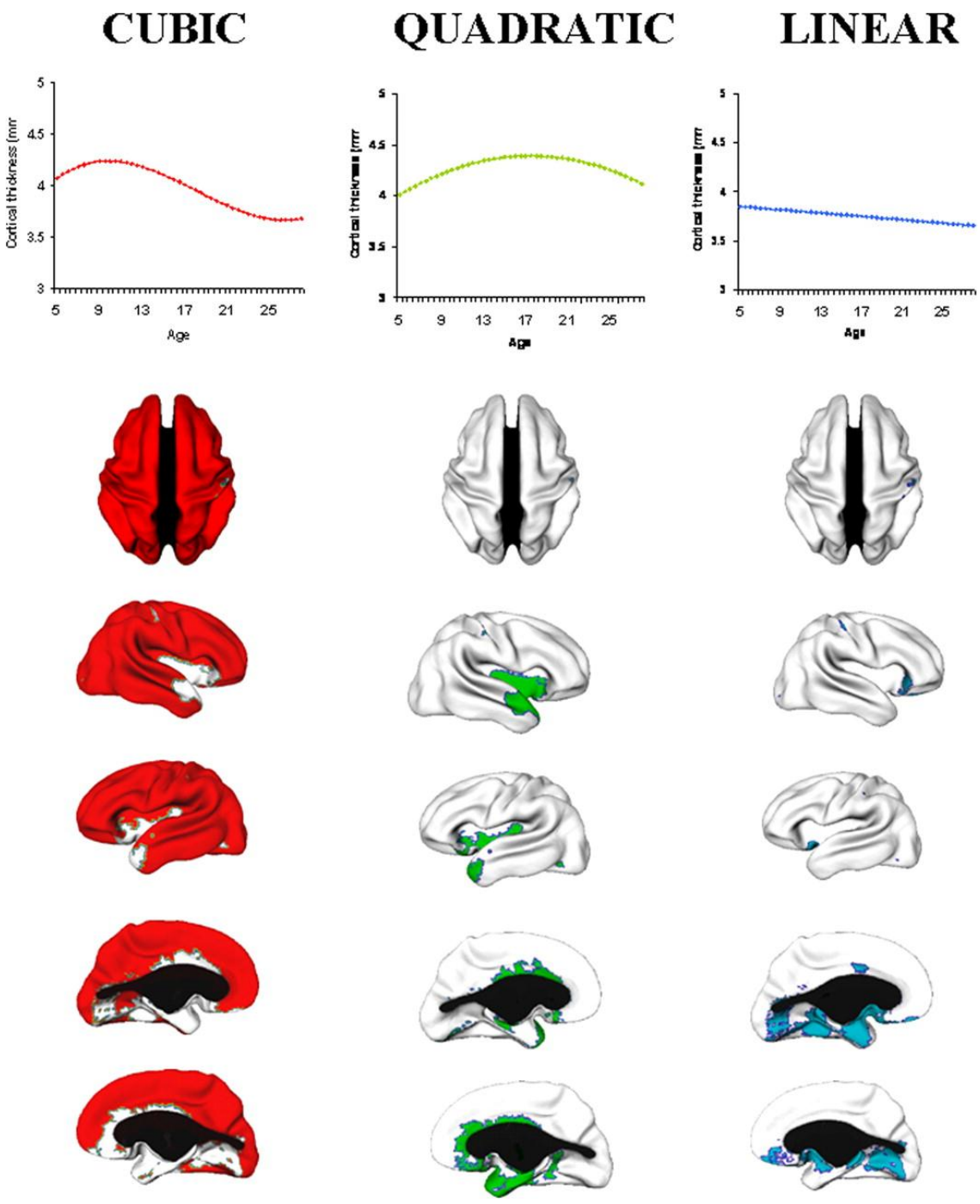
Table 3-1

Trajectories of cortical development according to layers (reconstructed based on Shaw et al. (2008)).

	Number of layers	Growth trajectory	Complexity of laminar structure
Allocortex	3	Mostly linear	Least complex
Transition cortex	Intermediate	Quadratic + linear	Intermediate
Isocortex	4-6	Cubic	Most complex

Figure 3-1

Trajectories of cortical development according to cortical regions (Adopted: Figure 1 in Shaw et al. (2008)).



Whereas younger healthy subjects (mean age: 22.8, range: 18-31) showed both pronounced thinning and thickening, healthy subjects between early (mean age: 48.6, range: 41-57) and late adulthood (mean age: 76.6, range: 60-93) showed cortical thickening in only a few regions which were mainly the anterior cingulate and medial orbitofrontal/subcallosal cortex (Salat et al., 2004). However, the same cross-sectional study demonstrated cortical thinning in many regions including primary sensory, primary somatosensory and motor and association cortices (Salat et al., 2004). The thinning was most significant in inferior prefrontal, precentral and supramarginal regions, but least significant in temporal lobe (Salat et al., 2004).

These results show that most brain regions show quick increase of CT in early childhood followed by decrease until early adulthood. Overall, CT in most regions, especially those involved in basic functions such as motor and somatosensory areas, seems to show a progressive decrease.

3.1.3.3 Cortical thickness alterations in preterm individuals

While normative age-related CT changes have been investigated across the whole life span, CT differences between preterm individuals and controls have been mostly investigated during adolescence. As summarised in Table 3-2, compared to controls, preterm individuals tend to have more widespread regions of thinner rather than thicker cortices. Furthermore, the regions which are found to be altered in preterm groups largely overlap with the brain areas displaying a widespread and gradual cortical thinning during adolescence in normative samples (Figure 3-1 (Shaw et al., 2008)). Such regions include parietal (pre- and post-central gyrus, the supra-marginal part of the parietal inferior gyrus (Martinussen et al., 2005) and posterior inferior parietal cortices

(Nagy, Lagercrantz, & Hutton, 2011)), temporal (intermedius primus Jensen sulcus, occipito-temporal medial gyrus (Martinussen et al., 2005)), superior (Frye, Malmberg, Swank, Smith, & Landry, 2010) and middle temporal cortices (Frye et al., 2010; Martinussen et al., 2005; Nagy et al., 2011) and inferior frontal cortices (Frye et al., 2010).

Table 3-2

Details of preterm-born subjects included in cortical thickness comparison with normal population.

Authors	Details of preterm-born subjects			Findings (compared to controls)	
	Age (years)	GA (weeks)	birth weight (g)	Thinner cortex	Thicker cortex
Lax et al. (2013)	7-10	<32	Not specified	Right anterior cingulate cortex, supplementary motor area, left isthmus of the cingulate gyrus, right superior temporal sulcus, right anterior insula, right postcentral gyrus and bilateral precuneus	
Martinussen et al. (2005)	15	29.1 ± 2.7	1195 ± 239	Parietal (pre- and post-central gyri and the supra-marginal part of the parietal inferior gyrus) and temporal (temporal middle gyrus, intermedius primus Jensen sulcus, occipito-temporal medial gyrus, parahippocampal part) cortices	Medial region (pericallosal sulcus) and in the frontal (frontal superior gyrus, orbital gyrus and rectus gyrus), temporal (circular insula superior sulcus) and occipital regions (occipital superior gyrus)
Frye et al. (2010)	16	≤ 36	≤ 1600	Superior and middle temporal cortices and inferior frontal cortices	Anterior cingulate cortex
Nagy et al. (2011)	14.90 (12.38-17.7)	28.54	≤ 1486	Bilateral middle temporal and posterior inferior parietal cortices	Small areas in the right anterior inferior temporal gyrus and left ventrolateral prefrontal cortex
Bjuland et al. (2013)	18–21	29.3 ± 2.5)	1221 ± 231	Left frontal and parietal lobes, and bilateral temporal lobes	Bilateral medial inferior and anterior parts of the frontal lobes, and occipital poles

3.1.3.4 Cortical thickness alterations in preterm individuals – influencing factors

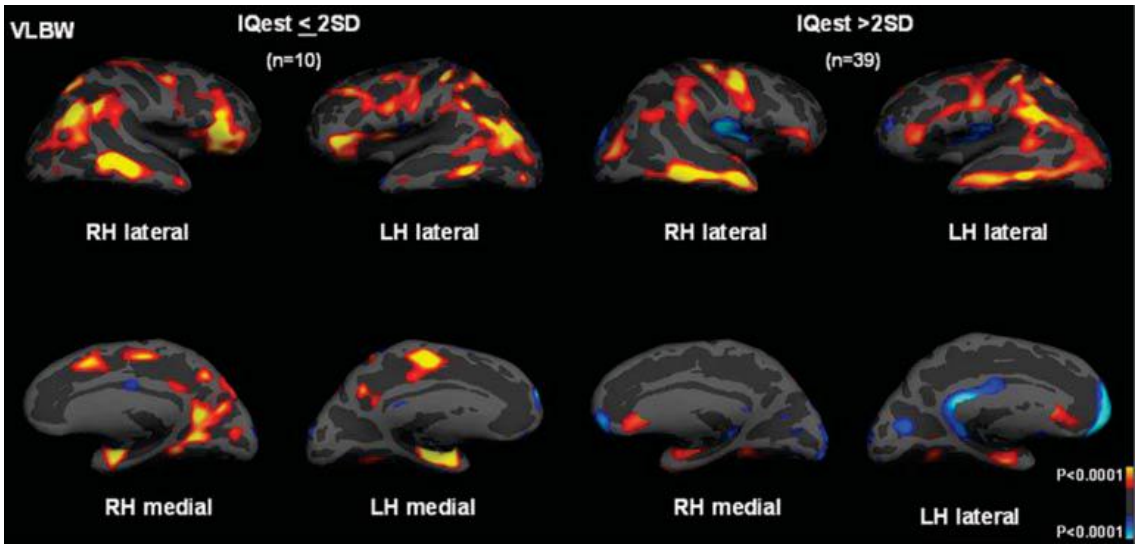
Such differences in CT in preterm-born adolescents may be affected by several factors, such as birth weight (BW), gestational age (GA) (Martinussen et al., 2005; Nagy et al., 2011), head circumference at birth (Martinussen et al., 2005) or environmental factors (Frye et al., 2010). For example, Nagy et al. (2011) divided their preterm-born adolescents into subgroups according to BW (low (≤ 1000g) and high (> 1000g)) and GA (low (≤ 28 weeks) and high (> 28 weeks)). Then, they found that, in the regions where the preterm group had thinner (middle temporal areas and posterior inferior parietal regions, bilaterally) or thicker (right anterior inferior temporal gyrus and left ventrolateral prefrontal cortex) cortices than controls, not many changes were observed when including only the preterm individuals with low BW or GA. In contrast, for the preterm individuals with high BW or GA, altered thickness was observed in different regions (i.e. right dorsolateral prefrontal cortex was thinner in the preterm group, and no region was significantly thicker in the preterm group). These results suggest that greater immaturity at birth, whether it regards length (GA) or extent (birth weight) of intrauterine growth, could result in more severe structural alteration of the brain. Consistently, Martinussen et al. (2005) showed that the regions of thinner cortices became more widespread with lower GA, BW or head circumference at birth. Environmental factors such as parenting style were studied by (Frye et al., 2010). Their results revealed that, among preterm individuals, those with inconsistently responsive mothers showed greater whole brain thickness compared to the others with consistently responsive or unresponsive mothers. They suggested that mothers' inconsistent responsiveness required more cognitive processes and therefore were associated with CT increase.

The difference in CT (cross-sectional) or CT changes (longitudinal) can be interpreted in different ways. First, it could show delayed development (Allin, Walshe, & Nosarti, 2010; Nosarti et al., 2008). That is, the preterm-born population shows slow development for a while, but it eventually catches up with the term-born population by a certain age. Second, it might indicate permanent developmental alterations. These contradictory possibilities need to be tested through longitudinal research expanding into late adulthood.

Another point to consider is that CT is closely associated with functional outcome as already described in previous sections ("2.1.3" (IQ), "2.2.2" (EF) and "2.3.3" (memory)). In preterm-born adolescents, functional deficits are often associated with thinner cortices (See Figure 3-2 and Table 3-3). Consistently, Frye et al. (2010) argued that the brain regions for which preterm-born adolescents have thinner cortices subserve cognitive functions that are often deficient in preterm-born children and adolescents. Such problems include EF (Anderson et al., 2004; Aylward, 2002; Bayless & Stevenson, 2007, all as cited in Frye et al., 2010), reasoning skills (Smith et al., 2000, as cited in Frye et al., 2010), and language deficits (Sansavini et al., 2006, 2007; Stolt et al., 2007, all as cited in Frye et al., 2010).

Figure 3-2

Cortical thickness alterations in the VLBW (GA: 29.1 ± 2.7 weeks; BW: 1195g ± 239g; age 15 years) subgroups compared to controls. VLBWgroup was divided into subgroups with low ("IQest ≤ 2SD") and normal ("IQest > 2SD") IQest, where low IQ was defined as being 2SD below the control group mean. VLBW individuals had significantly smaller CT in yellow regions and greater CT in blue regions. This figure has been adopted from Martinussen et al. (2005).



Abbreviations: BW = birth weight; CT = cortical thickness; IQest = estimated intelligence quotient; SD = standard deviation; VLBW = very low birth weight;

Table 3-3

Preterm-born individuals' functions related with thinner or thicker cortex (within preterm group, not compared against controls).

	Authors	Subjects	Thinner cortex associated with better function		Thicker cortex associated with better function	
			Regions	Associated functions	Regions	Associated functions
Preterm	Bless et al. (2013)*	BW ≤ 1500g; GA: 24–35 weeks; age 13-15 years	Anterior cingulate cortex	Selective attention	Superior posterior temporal gyrus	Selective attention
	Skranes et al. (2012)	BW ≤ 1500 g; age 14-15 years			Entorhinal cortex	IQ Attention Immediate memory problem-solving and cognitive flexibility
	Lohaugen et al. (2009a)	BW < 1500g; age 15 years			Entorhinal cortex	Low IQ and reduced EF
	Lohaugen et al. (2009b)	BW ≤ 1500g; age 15 years			Left parahippocampal and right motor cortical areas	Motor impairment
					Bilateral parahippocampal areas	Visuo-motor perceptual problems
					Left occipital area	Low IQ

*Control group showed correlations between cortical thickness and functional outcome in the opposite directions in these regions.

Abbreviations: BW = birth weight; EF = executive function; GA = gestational age; IQ = intelligence quotient

In normative samples, dynamic changes in CT are associated with functional outcomes during development. Shaw et al. (2008) pointed out that not only cognitive and sensory abilities sharpen but also corresponding cortices thicken during childhood, and this continues in adolescence during which cortical thinning occurs. Sowell et al. (2004) also speculated that cortical thickening in Broca's and Wernicke's areas during childhood is linked with language learning. In addition, Salat et al. (2004) proposed that thinning of prefrontal cortex observed between early and late adulthood is related with declining EF.

Attempts have been made to explain the mechanisms of cortical thickening and thinning in the normal population. Cortical thickening during childhood, which is a critical period for cognitive development, may represent experience-driven shaping of cortical columns, dendritic spines and axons (Chklovskii et al., 2004; Mataga et al., 2004; Hensch, 2005; Sur and Rubenstein, 2005, all as cited in Shaw et al., 2008). On the other hand, cortical thinning during adolescence could result from use-induced selective removal of synapses (Huttenlocher and Dabholkar, 1997, as cited in Shaw et al., 2008) that could improve neural circuits, including those supporting cognitive functions (Hensch, 2004; Knudsen, 2004; both as cited in Shaw et al., 2008). However, findings from histology-based research suggest that cortical thinning is unlikely to be caused by neuronal death because post-mortem studies revealed a comparable number of neurons in older and younger subjects (for reviews, see Dani, 1997; Morrison and Hof, 1997, both as cited in Salat et al., 2004) and these findings are supported by studies using non-human primates (Peters et al., 1998, as cited in Salat et al., 2004). Instead, cellular shrinkage and reduction in dendritic arborisation have been put forward as representing more probable causes for cortical thinning (Morrison and Hof, 1997, as cited in Salat et al., 2004). An alternative view is that cortical thinning could represent increased

proliferation of myelin into the periphery of the cortical neuropil (Sowell et al., 2004). MR signal which used to represent GM would gradually appear as WM signal along the progression of the proliferation (Sowell et al., 2004). This would be reflected in the presence of cortical thinning and brain growth at the same location (Sowell et al., 2004).

Mechanisms underlying increased or decreased CT in preterm-born subjects as compared to controls have also been hypothesised, but they remain largely unclear. Thicker cortices could result from disrupted apoptosis caused by hypoxia immediately following birth (Martinussen et al., 2005) whereas thinner cortices in preterm-born subjects could be a direct consequence of cortical neuronal damage (Martinussen et al., 2005) or aberrant cortical maturation (Lohaugen, Martinussen, Evensen, et al., 2009). Alternatively, it could be caused by WM damage (Lohaugen, Martinussen, Evensen, et al., 2009; Martinussen et al., 2005) which could in turn affect connectivity and thereby subcortical GM (Volpe, 2009) and cortical development (Lohaugen, Martinussen, Evensen, et al., 2009).

Overall, further longitudinal research on CT in preterm samples is important for at least three reasons. First, as just mentioned, the mechanisms responsible for the CT differences between preterm and control individuals are generally little understood. Second, there have been not enough longitudinal studies tracking CT changes in preterm individuals. The studies conducted up to date investigating CT in preterm born samples are mostly cross-sectional in design. Third, cortical volume (CV) alone, which many studies on preterm birth have investigated, does not represent the whole aspect of cortical structure. This is because CV consists of two distinct determinants which are CT and cortical surface area (Raznahan et al., 2011) and can change in opposite

directions (Raznahan et al., 2011). Additionally, CV is more strongly related with cortical surface area than CT (Winkler et al., 2010), indicating that the CT studies will add more uniquely than cortical surface area to the existing literature. Considering these issues, I believe that my PhD project, which is a part of a longitudinal project initiated in 1979, will make a significant contribution to improving the understanding of CT as well as CV development in preterm-born populations by investigating longitudinal CT changes from mid- (age 15) to late adolescence (age 19) in individuals who were born very preterm and controls.

3.2 Present thesis

The present thesis mainly examined the impact of preterm birth on CT in longitudinal and cross-sectional analyses in mid- and late adolescence (at age 15 (Time 1) and 19 years (Time 2)), and the longitudinal CT changes were further analysed in relation with cognitive outcome at Time 2. The focus has specifically been on ages 15 and 19 years because this is a period of considerable development at the level of the brain, cognition and behaviour.

Also, the reasons for selecting CT are as follows. First, the brains of preterm individuals have been most often studied in terms of cortical volume (Beauchamp et al., 2008; Brunnemann et al., 2013; Gadin et al., 2012; Healy et al., 2012; Kesler et al., 2004; Kesler et al., 2008; Keunen et al., 2012; Lind et al., 2011; Ment et al., 2009; Nosarti et al., 2002; Nosarti, Allin, Frangou, Rifkin, & Murray, 2005; Omizzolo et al., 2013; B. S. Peterson et al., 2003; B. S. Peterson et al., 2000; Soria-Pastor et al., 2009; Srinivasan et al., 2007; Towusewi & Pallotta; Van Kooij et al.; Zubiaurre-Elorza et al., 2011) rather

than CT (Frye et al., 2010; Lohaugen, Martinussen, Evensen, et al., 2009; Lohaugen, Martinussen, Haraldseth, et al., 2009; Martinussen et al., 2005; Nagy, Lagercrantz, Forssberg, & Hutton, 2009; Nagy et al., 2011; Skranes et al., 2012; Zubiaurre-Elorza et al., 2012). Second, analysing CT or surface area could yield more informative and fine-tuned findings than volumetric analysis because CT and surface area are components of volume. Third, cortical volume is associated to a greater extent with cortical surface area than thickness (Ecker et al., 2013; Koolschijn & Crone, 2013) and therefore the contribution of CT research to the existing volumetric literature is likely to yield information which has not yet been systematically investigated.

The studies conducted as part of this PhD are presented in chapters 4, 5 and 6. These include cross-sectional (chapter 4) and longitudinal analyses (chapter 5) using a univariate approach as well as longitudinal analysis using a multivariate approach (chapter 6). Each chapter explains the methods of analyses, and reports and discusses the results. The last chapter provides general conclusions and some considerations for future directions (chapter 7).

Descriptions of chapters 4, 5 and 6 are given in the following three paragraphs, together with experimental hypotheses.

Chapter 4 will describe and discuss the assessment of cross-sectional impact of preterm birth on CT at Time 1 and Time 2. There were two hypotheses. One was that the cortex of preterm-born adolescents at Time 1 would be thinner compared to controls in large areas of the brain specifically in frontal, temporal and parietal regions (Martinussen et

al., 2005; Nagy et al., 2011), suggesting developmental delay. The other hypothesis was that, at Time 2, the areas where preterm-born individuals display thicker cortices would decrease compared to those observed in Time 1 (Bjuland et al., 2013; Martinussen et al., 2005), suggesting a developmental 'catch up'.

Chapter 5 will describe and discuss the assessment of longitudinal CT changes within each group in CT from Time 1 to Time 2, as well as between-group difference in the CT change. One hypothesis was that both groups would display significant CT decreases in most brain areas, but that cortical alterations would still be present in medial temporal areas in the preterm sample (Shaw et al., 2008; Tamnes et al., 2010). I further hypothesised that there would be a significant between-group difference in CT changes between Time 1 and Time 2, especially in parietal, temporal and frontal cortices, which would show an altered trajectory of cortical development in preterm individuals during the transition between adolescence and early adulthood (Frye et al., 2010; Martinussen et al., 2005; Nagy et al., 2011)

In Chapter 6, I compared cognitive scores (EF, memory and IQ acquired at Time 2) between groups and analysed CT. For the CT analysis, regional CT patterns at Time 1 that best distinguished between the groups were first identified using a multivariate analysis method – the method is called support vector machine (SVM) which will be described in Chapter 6. I referred to this as "patterns" to indicate the difference in this CT comparison method from that used in Chapters 4 and 5. In Chapter 4 and 5, CT was directly compared between groups at each cortical point. On the other hand, in Chapter 6, the relations were considered between each cortical point and all the others, in addition to the direct comparison. Based on the CT "pattern", I assessed the extent to

which Time 1's group-distinguishing CT patterns would predict group membership at Time 2 – I hypothesised that the prediction accuracy would be high. The rationale for the hypothesis is as follows. I expect that developmental 'catch-up' in CT will occur, not to the full extent. If the catch-up happens to the full extent, preterm and control brains would show no difference and therefore prediction will be completely inaccurate. However, it appears that catch-up will be only partial because considerable group difference in CT will likely remain at early adulthood (Bjuland et al., 2013), resulting in high prediction accuracy.

Additionally, from Chapter 6's CT analyses, I identified the regions displaying top group distinguishability at Time 1, and examined the association between (1) CT changes in these regions and (2) cognitive scores at Time 2 which were significantly different between groups. The hypothesis was that greater thinning would be associated with higher cognitive scores in both groups.

Chapter 4: Study 1 - Extensive cortical thickness alterations in preterm adolescents diminish by early adulthood

This chapter describes a cross-sectional analysis using a univariate approach. This consisted of comparing cortical thickness (CT) at each vertex using (1) vertex-wise t-statistic and (2) correction for multiple comparisons based on random field theory (RFT). It is "univariate" in that each vertex is considered spatially independent, as described in (Ecker et al., 2010). It is important to define this, as in Chapter 6 I will describe a multivariate approach, which considers correlations among regions. The multivariate approach used in Chapter 6 employed support vector machine (SVM) which examined each vertex's contribution, relative to those of the other vertices, to the group difference of each whole brain. The SVM analysis comprised two steps: (1) developing an algorithm which best discriminated the Time 1 brains between groups (i.e. control and preterm) and (2) using the algorithm to predict the group membership of Time 2 brains.

This chapter begins with the description of the methods regarding the study population, scanning protocols, image processing and statistical analyses. This will be followed by the Results section, showing the findings from comparing neonatal and socio-

demographic data and cross-sectional CT analysis. Lastly, the cross-sectional cortical thickness (CT) findings will be discussed.

4.1 Methods

4.1.1 Study population

I studied two cohorts of participants born before 33 weeks of gestation and admitted consecutively to the Neonatal Unit of University College London Hospital (UCLH) (Nosarti et al 2008). The first cohort drew on all individuals born in 1979–82 who were enrolled for long-term follow-up (Nosarti et al., 2002, Nosarti et al., 2004). The second cohort included a selected group of individuals born in 1983–84 (Allin et al 2007). This selection was necessitated by an expansion in capacity of UCLH in 1983, which prevented inclusion of the entire consecutive series due to limited research resources. The selection criteria were: all individuals born at 28 or less weeks of gestation, as well as a random sample of one in four of those born from 29 to 33 weeks of gestation.

A sample of 47 individuals who were delivered at term (38-42 weeks of gestation) at UCLH in 1979-80 acted as controls. At Time 1, 21 received a structural MRI scan. Additionally, 106 full-term individuals were recruited by advertisements in the press. At Time 2, 50 controls were assessed; 34 controls were recruited from the subjects who took part in the assessment at Time 1, and therefore received an MRI scan twice (at Time 1 and Time 2), while the other 16 controls were individuals who had not taken part in previous assessments and were recruited by advertisement in the local press.

All study participants were English native speakers. Inclusion criteria were no history of neurological impairment, such as severe head injury, stroke, epilepsy or multiple sclerosis; severe eyesight, hearing and/or motor impairment; metal implants or a fitted pacemaker; operations to the head or the spine; claustrophobia; and pregnancy for female participants. Each participant was screened on the telephone before any prior arrangement, in order to reconfirm they met the inclusion criteria described above.

Additionally, all participants were excluded where their brain images had poor quality, based on the criteria described in "Quality control" section below. Then, participants were divided into two groups according to the age at which they were scanned: A) mean age 15 years (Time 1) and B) mean age 20 years (Time 2).

As a result, 248 (88 controls and 160 preterm individuals) and 109 participants (42 controls and 67 preterm individuals) were included in the main analysis for Time 1 and Time 2, respectively. An additional set of analyses were also conducted, including only the participants scanned at both time points (n = 72; (21 controls and 51 preterm individuals)). The second set will not be discussed in detail because it is a secondary analysis, carried out in order to describe the cohorts included in the SVM analysis (Chapter 6). The SVM analysis required a measure of CT change between Time 1 and Time 2 and therefore could accommodate only those participants scanned twice.

Ethical approval for the study was granted by the Institute of Psychiatry Ethics Committee. All participants provided written informed consent to undergo assessments, including MRI.

Prior to entering the MRI scanner, participants were told that they could leave the scanner at any time and without giving a reason if they felt any discomfort. During the whole duration of the scanning session a researcher was in the control room, and was able to communicate with the participants. Likewise, participants were able to communicate with the researcher via a microphone. Participants were informed that if the neuro-radiographers found anything of concern in their scans they would be informed of this via their GPs.

Travel expenses were reimbursed and refreshments were provided to all participants. Information about participants was confidential and numerical codes were used to identify them on computer files.

4.1.2 Magnetic Resonance Imaging

4.1.2.1 Scanning - Time 1

Magnetic resonance imaging (MRI) was performed on two sites on 344 participants. For the 1979–82 cohort and controls a 1.5 Tesla GE Signa Horizon machine (General Electric Medical Systems, Milwaukee, WI, USA) was used at the Institute of Neurology, London (n = 182). The 1983–84 cohort and controls were scanned using a 1.5 Tesla GE Signa N/Vi system at the Maudsley Hospital, London (n = 162). At both sites, three-

dimensional T1-weighted magnetic resonance (MR) images were acquired in coronal plane, with the spoiled gradient recalled (SPGR) pulse sequence (flip angle 35°, field of view 240mm, echo time 5ms, repetition time 35ms). Each image contained 124 slices (slice thickness: 1.5mm / slice gap: 0mm) with a matrix size of 256 x 256 voxels (voxel size: 0.93 mm x 0.93 mm). All images were acquired in radiological convention (left of image = participant's right).

4.1.2.2 Scanning - Time 2

All participants (n = 146) were scanned at the Maudsley Hospital with the same scanning protocol used at Time 1, as described in the preceding section.

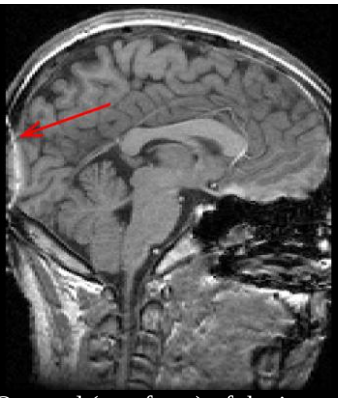
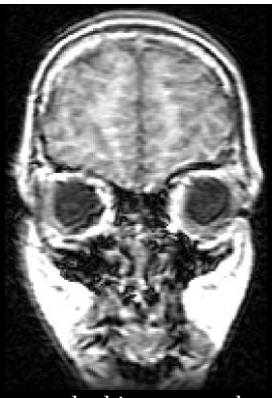
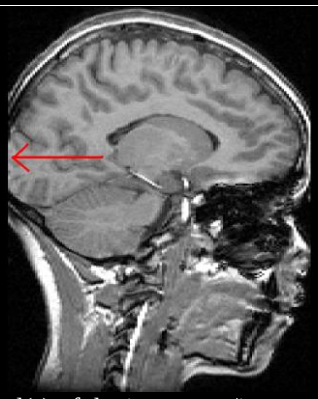
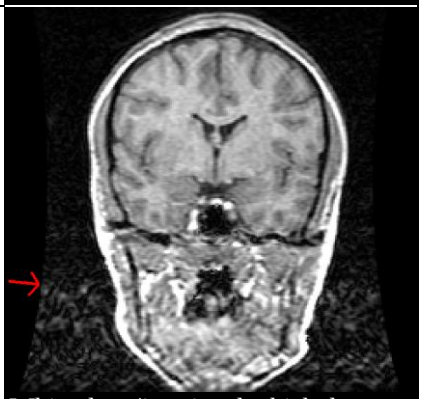
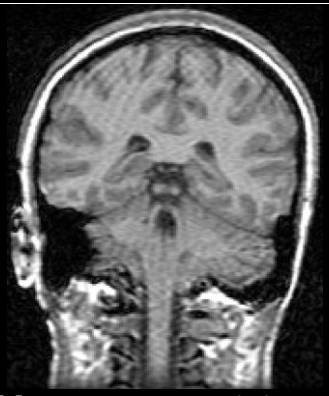
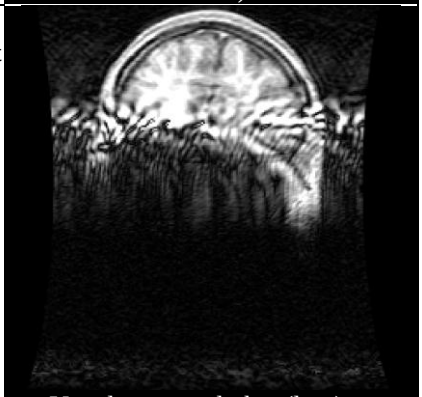
4.1.2.3 Quality control

Quality control was carried out as described in (Simmons et al., 2011; Simmons et al., 2009) to ensure adequate quality of the T1-weighted volume images. Each raw image was visually inspected for the artefacts described in Table 4-1. For each type of artefact, a supervisor (Dr Andy Simmons) selected a reference image, based on his judgement regarding whether the image processing software (CIVET pipeline) would be able to withstand the artefacts. Each reference image served as a threshold. That is, any image which looked as bad as or worse than the reference images were excluded from preprocessing.

The included images were preprocessed, and the above-described procedure was repeated for the preprocessed images (i.e. images of cortical surfaces) to decide whether to include or exclude them in the analyses.

Table 4-1

Types of artefacts based on which some images were excluded.

Artefact	Description	Artefact	Description
Aliasing (also called wrap-around)	 One end (e.g. front) of the image intrudes into the other end (e.g. back). For example, the tip of the nose pokes into the back of the head.	**Poor grey/white matter contrast**	 Grey and white matter shows subnormal difference in signal intensities. This could pose challenge in tissue classification.
Clipping	 End(s) of the image are/is cut off.	**Noise**	 White dots (i.e. signal which does not represent data) appear all-over or over part of the images. One common cause for this is metal (e.g. dental braces).
Motion artefact	 Wavy patterns appear in image. Classification of grey and white matter tissues depend on the signal intensity (i.e. brightness of the voxel), and therefore the fluctuating signal intensities represented by the wavy pattern could result in inaccurate tissue classification.	**Signal loss/amplification**	 Voxels appear darker (loss) or brighter (amplification). One common cause for this is metal (e.g. dental braces).

4.1.3 Image processing

4.1.3.1 Format conversion

All images were converted from University of North Carolina (UNC) format into medical imaging NetCDF (MINC) format. This was carried out either (1) from UNC to MINC or (2) from Analyze to UNC to MINC.

The Analyze→ UNC → MINC conversion was applied for cases where the original UNC images were unavailable. There were 92 such images, which were all acquired at the Institute of Neurology at Time 1.

The Analyze-to-UNC and UNC-to-MINC conversions were done using "analyze2unc" and "unc2mnc" scripts, respectively. Analyze-to-MINC scripts ("rawtominc", "ana2mnc" and "nii2mnc") were also available, but I have not used them. That was because I was unable to ensure that their conversion parameters (e.g. left-right flip or non-flip) were the same as "unc2mnc".

4.1.3.2 Cortical surface extraction

The cortical surfaces were extracted from the T1-weighted MR images using the CIVET pipeline (version 1.1.9) (Ad-Dab'bagh et al., 2006) according to the following steps:

1) T1-weighted MR images were linearly registered to montreal neurological institute (MNI)-Talairach stereotaxic space using the ICBM152 template as the registration target (Mazziotta, Toga, Evans, Fox, & Lancaster, 1995) - ICBM stands for International Consortium for Brain Mapping. Registration refers to stretching or shrinking images to make them fit a template. In "Linear" registration, the extent of

stretches and shrinks are consistent in all voxels. In non-linear registration, the extent of stretches and shrinks can differ between voxels.

2) Images were corrected for signal intensity non-uniformity (Sled, Zijdenbos, & Evans, 1998). This makes brightness even across all parts of the image in case part of the image appears brighter or darker than the rest of the image (e.g. top part of the image is brighter than the bottom).

3) A brain mask was calculated (Smith, 2002). This identified the voxels which were part of the brain, as opposed to skull or air.

4) Images were segmented into grey matter (GM), white matter (WM), cerebrospinal fluid and background (Zijdenbos, Forghani, & Evans, 1998).

5) Partial volumes in each voxel were estimated (Tohka, Zijdenbos, & Evans, 2004). Partial volume refers to the likely proportion of tissue classes in a voxel. For example, a partial volume could indicate that a voxel consists of 60% GM, 30% WM and 10% cerebrospinal fluid. Each voxel was first labelled as the most predominant tissue type. The intensity distribution of each tissue class across neighbouring voxels was used to calculate the parameter for the partial volume estimation. This parameter was used to correctly classify the voxels which were likely to be affected by a partial volume effect.

6) A *non-linear* transformation was calculated from the images in stereotaxic space to the ICBM152 template, and major structures were identified (Collins, Holmes, Peters, & Evans, 1995).

7) Cortices were extracted by first identifying the "white surface" (i.e. border between grey and WMs) and then expanding the surface until reaching the "grey surface" (i.e. border between GM and cerebrospinal fluid). Each "surface" is a triangular mesh composed of 81,924 vertices (i.e. cortical points) with the first half being in the left

hemisphere and second half in the right. Each vertex on the grey surface had a corresponding vertex on the white surface, and the distance between each pair was defined as the CT at a given vertex (Kim et al., 2005).

8) CT was smoothed using a 20mm full width at half maximum (FWHM) kernel (Chung & Taylor, 2004). Smoothing refers to averaging each vertex's signal with its neighbouring vertices' signals. This blurs the image (i.e. decreases the resolution of the image), but it also increases signal-to-noise ratio.

*The number of independent observations, which is originally the number of vertices, decreases after smoothing. This is because each vertex's "smoothed" signal relies on neighbouring vertices' signals, resulting in spatial correlation. Also, it is not simple to calculate the number of independent observations in smoothed images (Brett, Penny, & Kiebel, 2004). Therefore, for the analysis of smoothed images, the usual method of correction for multiple comparisons (e.g. Bonferroni correction), which takes into account the number of all vertices can be too stringent. This can be resolved by correcting for multiple comparisons using RFT, which will be discussed in the following section.

9) Finally, the cortical surfaces of all brains were non-linearly registered to the ICBM 152 surface template to achieve correspondence of vertices across participants (Robbins, 2003). That is, this allowed for the same vertex (e.g. vertex number 5000) from different participants to represent the same cortical region.

This process yielded, for each image, CT data represented in two text files. One was a TXT (".txt") file containing CT (in mm) for each vertex (total: 81,924 vertices). The other was an OBJ (".obj") file containing spatial info (i.e. coordinates and how vertices were related with one another to form the cortical surfaces) for all vertices. The shape of

the surface, for example, was configured by the OBJ file. During the analysis, the TXT files were used for statistical analyses (e.g. vertex-wise t-test), while the OBJ files were used for defining clusters (e.g. location).

4.1.4 Statistical analyses

4.1.4.1 Neonatal and socio-demographic data

Univariate analysis of variance (ANOVA) was used to compare age, gestational age (GA) at birth and birth weight in grams. For comparing the distributions of gender and socioeconomic status, chi-squared tests were carried out.

4.1.4.2 Cortical thickness data

A previous study with the same dataset did not detect a significant effect of MRI acquisition site (i.e. Institute of Neurology and Institute of Psychiatry) on data analyses (Nosarti et al., 2008), therefore all scans available were included in the current analysis. I analysed all available brain images using the SurfStat toolbox (http://www.stat.uchicago.edu/faculty/InMemoriam/worsley/research/surfstat/) under MATLAB (version R2012b).

The statistics included (1) defining statistical models, (2) vertex-by-vertex t-statistic and (3) correction for multiple comparisons. The correction for multiple comparisons were carried out based on RFT (Worsley, Andermann, Koulis, MacDonald, & Evans, 1999) which can be described as follows. First, the smoothness (spatial correlation) of the statistical map is calculated. This yields resolution elements (more commonly referred

to as “resels”), which are a block of values (voxels, in case of the present study) and are the same size as the FWHM (smoothing kernel). Resels are a similar concept to independent observations and are determined by the extent of smoothness and number of vertices in the image. The number of resels can then be used with an Euler characteristic (EC) value to calculate the “height threshold” (i.e. statistical value above which any value is unlikely to have emerged by chance). EC determines the number of clusters that can be formed above a given threshold, and this will in turn yield the required height threshold. For detailed information, see Brett et al. (2004).

The statistical models are explained below.

4.1.4.2.1 Cross-sectional analysis

Univariate/general linear/fixed effects models (Y = 1 + Age + Group + Gender) were fit.

In all analyses, gender (which is known to be associated with different CT (Lv et al., 2010)), age and white noise were used as nuisance variables. As shown above, the model does not show white noise. This is because SurfStat controlled for it implicitly in fixed-effects models.

4.2 Results

4.2.1 Neonatal and socio-demographic data

As shown in Table 4-2, the two groups did not differ statistically in gender and socio-economic status, but they differed in age at assessment, birth weight and gestational age at birth at both time points, with preterm-born participants being slightly older than controls. Level of education at Time 2 showed non-significantly different distributions between groups at either time point when all participants were included, but the difference was significant when including only the participants who were scanned at both time points. Distribution of ethnicity was also significantly different between groups among all participants who were assessed at Time 1 as well as among those who were scanned at both Time 1 and Time 2. It should be noted that ethnicity record at Time 1 was not available for a considerable number of controls.

The preterm-born participants who were assessed only at Time 1 did not differ from those assessed at both time points in gestational age ($F_{(159)} = 13.66$, $p = 0.10$) and birth weight ($F_{(159)} = 1.78$, $p = 0.19$).

Table 4-2

Participants' neonatal and socio-demographic details.

		All scanned at Time 1			All scanned at Time 2				Scanned at both time points		
		Control	Preterm	Statistics	Control	Preterm	Statistics		Control	Preterm	Statistics
Number of participants		88	160		42	67			21	51	
Age (Mean/SD)		15.0/0.7	15.2/0.5	**$F_{(247)}$ = 7.74, p = 0.0058**	19.3/1.2	20.2/1.2	**$F_{(108)}$ = 13.45, p = 0.0004**	*Time 1*	15.0 (0.7)	15.4 (0.5)	**$F_{(71)}$=9.61, p = 0.0028**
								Time 2	19.2 (0.7)	20.1 (1.0)	**$F_{(71)}$ = 14.44, p = 0.0003**
Male ratio (%)		55.7	51.9	$X^2_{(1)}$ = 0.33, p = 0.5654	52.4	44. 8	$X^2_{(1)}$ = 0.60, p = 0.4392		47.6	45.1	$X^2_{(1)}$ = 0.04, p = 0.8453
Gestational age at birth (Mean/SD)		40.2/1.3	29.1/2.3	**$F_{(223)}$ = 1364.51, p < 0.000001**	40.2/1.6	28.8/2.2	**$F_{(100)}$ = 705.94, p < 0.000001**		40.1 (1.7)	28.7 (2.3)	**$F_{(71)}$ =428.68, p < 0.000001**
Birth weight in grams (Mean/SD)		3377/428	1285/369	**$F_{(216)}$ = 1240.18, p < 0.000001**	3318/391	1214/372	**$F_{(98)}$ = 671.54, p < 0.000001**		3287 (362)	1228 (388)	**$F_{(69)}$ = 403.20, p < 0.000001**
Socio-economic status (Number (%))	I-II	35 (39.8%)	59 (36.9%)	$X^2_{(4)}$ = 1.08, p = 0.8970	22 (52.4%)	26 (38.8%)	$X^2_{(4)}$ = 5.87, p = 0.2089	*Time 1*			$X^2_{(4)}$ = 2.74, p = 0.6019
	III	24 (27.3%)	52 (32.5%)		12 (28.6%)	30 (44.8%)					
	IV-V	14 (15.9%)	27 (16.9%)		7 (16.7%)	9 (13.4%)		*Time 2*			$X^2_{(3)}$ = 1.17, p = 0.7603
	Unclassified	8 (9.1%)	12 (7.5%)		0 (0.0%)	2 (3.0%)					
	Missing	7 (8.0%)	10 (6.3%)		1 (2.4%)	0 (0.0%)					
Education at Time 2 (Number (%))	A-level	Not applicable			37 (88.1%)	63 (94.0%)	$X^2_{(2)}$ = 3.91, p = 0.1419		18 (85.7%)	50 (98.0%)	**$X^2_{(2)}$ = 7.94, p = 0.0189**
	BTEC/NVQ	Not applicable			0 (0.0%)	1 (1.5%)			0 (0.0%)	1 (2.0%)	
	Receiving higher education	Not applicable			5 (11.9%)	2 (3.0%)			3 (14.3%)	0 (0.0%)	
	Missing	Not applicable			0 (0.0%)	1 (1.5%)			0 (0.0%)	0 (0.0%)	
Ethnicity (Number (%))	White	43 (48.9%)	116 (72.5%)	**$X^2_{(9)}$ = 18.11, p = 0.0339**	27 (64.3%)	52 (77.6%)	$X^2_{(6)}$ = 9.02, p = 0.1725		10 (47.6%)	40 (78.4%)	**$X^2_{(5)}$ = 12.34, p = 0.0304**
	Black-Caribbean	6 (6.8%)	10 (6.3%)		6 (14.3%)	5 (7.5%)			5 (23.8%)	3 (5.9%)	
	Black-African	2 (2.3%)	4 (2.5%)		1 (2.4%)	2 (3.0%)			1 (4.8%)	1 (2.0%)	
	Black-Other	6 (6.8%)	2 (1.3%)		4 (9.5%)	1 (1.5%)			3 (14.3%)	1 (2.0%)	
	Indian	0 (0.0%)	10 (6.3%)		0 (0.0%)	3 (4.5%)			0 (0.0%)	3 (5.9%)	
	Pakistani	0 (0.0%)	1 (0.6%)		0 (0.0%)	0 (0.0%)					
	None of these	3 (3.4%)	5 (3.1%)		3 (7.1%)	4 (6.0%)			2 (9.5%)	3 (5.9%)	
	Mixed Black African white	0 (0.0%)	3 (1.9%)		1 (2.4%)	0 (0.0%)			0 (0.0%)	0 (0.0%)	
	Mixed Black Caribbean White	0 (0.0%)	1 (0.6%)		0 (0.0%)	0 (0.0%)			0 (0.0%)	0 (0.0%)	
	Mixed White Pakistani	1 (1.1%)	0 (0.0%)		0 (0.0%)	0 (0.0%)			0 (0.0%)	0 (0.0%)	
	Missing	27 (30.7%)	8 (5.0%)		0 (0.0%)	0 (0.0%)			0 (0.0%)	0 (0.0%)	

SD = standard deviation

4.2.2 Cortical thickness data

4.2.2.1 Cross-sectional analysis

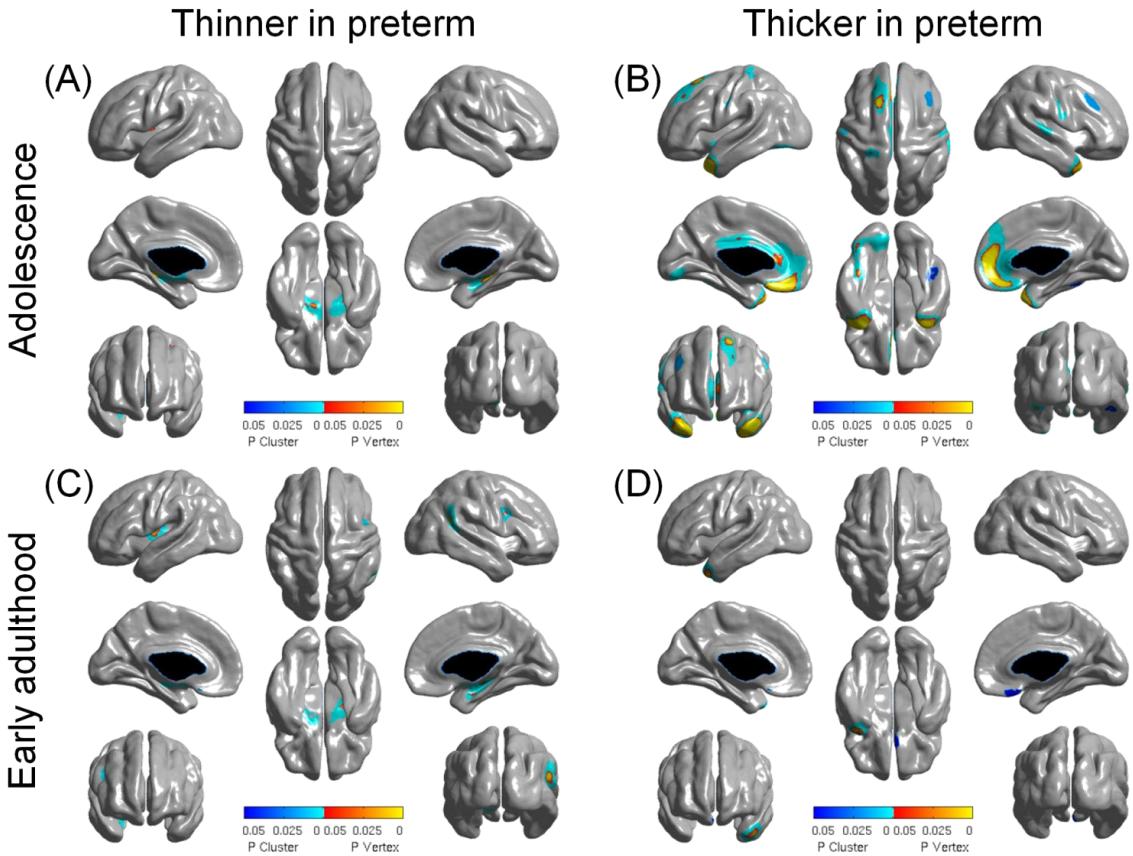
Analysing all participants, at Time 1, the preterm group had significantly reduced CT compared to controls in bilateral parahippocampal regions and left insula (Figure 4-1A). On the other hand, CT was significantly greater in the preterm group in lateral occipitotemporal gyri in both hemispheres at Time 1 (Figure 4-1B). In the left hemisphere, this cluster extended to inferior occipital and lingual gyri. Other regions with significantly greater CT included bilateral temporal poles and ventromedial frontal regions (extending to left cingulate gyrus and right dorsal frontal regions), left superior frontal gyrus, right middle frontal gyrus, lateral parts of bilateral central sulci, left postcentral gyrus, left insula and right superior temporal gyrus. By Time 2, only CT in left temporal pole and right gyrus rectus were significantly greater in the preterm group compared to controls (Figure 4-1D). Also, the preterm group still displayed significantly reduced CT in bilateral parahippocampal regions and left insula at Time 2, with the addition of areas centred in right temporoparietal junction and the posterior part of the inferior frontal sulcus (Figure 4-1C). Effect sizes of group difference are shown in Table A-1 in Appendix.

Use of only 72 participants who were scanned at both Time 1 and Time 2 generally resulted in smaller clusters (Figure A-1 in Appendix). At Time 1, the preterm group displayed no regions where they had significantly thinner cortex than controls. Greater CT in the preterm group compared to controls was observed only in the left temporal pole. At Time 2, the cortex was thinner in preterm individuals in bilateral medial

temporal and right inferior parietal region. Increased CT in the preterm group was seen in the left temporal and occipitotemporal poles.

Figure 4-1

Cross-sectional differences in CT. Age and gender were controlled for. Blue-turquoise regions represent clusters (cluster $p < 0.05$) and red-yellow regions represent cluster peaks (vertex $p < 0.05$).



4.3 Discussion

As mentioned in section "4.1.1", there are two sets of analyses with one using all participants and the other involving only 72 participants (scanned at both time points). Here I will discuss mainly the first set of analyses. This is because the second set of analyses was carried out to characterise those subjects used in the SVM analysis (Chapter 6) which included only the participants scanned twice.

4.3.1 Cross-sectional analysis

4.3.1.1 Regions displaying thicker cortex in the preterm group compared to controls

In the present study, when including all participants available at each time point, the most extensive group differences were found in terms of greater CT in the preterm group compared to controls in adolescence (i.e. clusters are biggest in Figure 4-1B compared to Figure 4-1A, C and D). The most prominent alterations in the preterm group was found in bilateral temporal poles and ventromedial frontal regions (extending to left cingulate gyrus and right dorsal frontal regions) as well as left occipitotemporal gyri (extending to inferior occipital and lingual gyri) (Figure 4-1B). By age 20 years, the number of areas showing greater CT in the preterm group compared to controls substantially decreased, with CT remaining significantly greater in the preterm group only in left temporal pole and right gyrus rectus (Figure 4-1D). On the other hand, Martinussen et al. (2005) observed, at age 15 years, thicker cortex in preterm group (GA

29.1 ± 2.7 weeks) compared to controls mostly in bilateral insula, left posterior cingulate area and medial aspects of bilateral frontal and occipital poles, with the left frontopolar cluster being especially big. At ages 18-21 years, the bilateral frontal and occipital poles remained thicker in preterm individuals (GA 29.3 ± 2.5 weeks) compared to controls (Bjuland et al., 2013), especially, the medial frontopolar clusters expanded noticeably, covering almost all of the ventral areas.

Overall, the common observations between the present study and Martinussen et al. (2005) was that the areas which were thicker in the preterm group than controls were more visible from a medial perspective than a lateral one at adolescence. However, at early adulthood, such tendency became more prominent only in Bjuland et al. (2013) and not in the present study. Furthermore, Bjuland et al. (2013) observed noticeable increase of cluster sizes whereas the present study reports massively reduced cluster sizes. I suggest that this difference between the present study and Martinussen et al. (2005) and Bjuland et al. (2013) could reflect differences in the study cohorts, such as sample size as well as analysis methods. In the present study when examining only those 72 participants who were scanned at both time points, the magnitude of between-group differences decreased although the regions where cortical differences were observed were very similar (Compare Figure 4-1 and Figure A-1). Furthermore, the Norwegian studies selected their participants on the basis of their birth weight (≤1500 g), while the participants studied here were selected according to gestational age.

4.3.1.2 Regions displaying thinner cortex in the preterm group compared to controls

Generally, in the present study, regions where CT was smaller in the preterm group than controls (1) were few at adolescence and (2) slightly more numerous at adulthood. In contrast, the Norwegian studies reported (1) widespread regions showing CT reduction in preterm adolescents (Martinussen et al., 2005) and (2) decrease of the regions at adulthood, especially in the right hemisphere (Bjuland et al., 2013). These are described in more detail in the following paragraph.

At adolescence, Martinussen et al. (2005) reported CT reduction in their preterm sample in much more extensive areas (than those reported in the present study), mostly in the lateral aspect of the brain (bilateral inferior temporal regions, occipital and inferior parietal regions, and posterior and inferior frontal areas) and also a few medial regions mainly around bilateral parahippocampal and anterior cingulated areas. The present study reports reduced CT in preterm adolescents in bilateral parahippocampal regions, but no other region has been observed except a tiny cluster in left insula, all of which remained thinner at early adulthood. Preterm adults in the present study additionally displayed smaller CT in in right posterior inferior frontal sulcus, which were also observed in (Bjuland et al., 2013). In addition, I observed thinner cortex in preterm adults than in controls in right temporoparietal junction while Bjuland et al. (2013) reported such finding in the temporoparietal junction of the opposite hemisphere. Overall, the clusters reported in Bjuland et al. (2013) were widespread mainly in the left hemisphere, whereas the present study reported relatively small clusters bilaterally in both hemispheres. As in the previous section, I suggest that this difference could be due to methodological differences.

One common observation at adolescence between the present study and Martinussen et al. (2005) is thinner cortex in the preterm group in the bilateral parahippocampal areas. It is noteworthy that bilateral hippocampal alterations were observed not only at Time 1, but also Time 2, in the present study. Therefore, it is possible that thinner cortex in bilateral parahippocampal areas is not representative of a developmental delay, but a permanent structural deficit; these medial temporal lobe areas mature early, and are unlikely to show rapid development at later stages in life, as reported in Gogtay et al. (2004)'s longitudinal study using healthy participants between ages 4 and 21 years. On the other hand, risk factors associated with very preterm birth such as neonatal hypoxic/ischemic damage have been shown to lead to reduced GM density focally in bilateral hippocampus and putamen but not in its adjacent structures (Gadian et al., 2000), such as the parahippocampal area. Such a finding was reported from children aged 12-16 years who experienced neonatal hypoxic-ischemic episodes (Gadian et al., 2000). However, the parahippocampal cortex is highly interconnected with the hippocampus (Libby, Ekstrom, Ragland, & Ranganath, 2012) and hippocampal volume changes together with thinner parahippocampal cortex are observed in healthy samples (Walhovd et al., 2014). I speculate here that developmental alterations affecting the volume of the hippocampus may affect the development of the parahippocampal cortex (Walhovd et al., 2014). However, as changes in CT in parahippocampal regions continue beyond adolescence (Tamnes et al., 2010), it remains to be ascertained whether CT alterations in this areas represent a developmental delay or a permanent structural deficit in the preterm sample.

4.3.1.3 Overview

Volumetric differences associated with preterm birth were previously reported in several of the regions in which CT alterations were observed in the current study. For instance, at adolescence smaller GM and WM volumes were observed in a similar preterm group to the one I studied in insula, as well as greater GM and WM volumes in occipitotemporal gyri, medial frontal regions and cingulate gyrus (Nosarti et al., 2008). Taken together, these results suggest that specific brain areas may be preferentially vulnerable to structural alterations following very preterm birth. Region-specific associations between CT and cortical volume or surface area in this sample will be investigated in future studies, as the relationship between different types of brain metrics may contribute to an increased understanding of markers of developmental vulnerability (Benetti et al., 2013). Examples of identified relationships between different brain measures are (1) the significant and positive correlation between CT and cortical density in all brain regions except temporal poles and medial frontal regions (measured in healthy controls and first episode schizophrenia patients in their mid-twenties (mean age)) (Narr et al., 2005), (2) high correlation between cortical volume and surface area as opposed to the low correlation between cortical volume and CT (measured in participants aged 48.6±13.2 years) (Winkler et al., 2010) and (3) differential regional heritabilities among CT, surface area and volume (e.g. CT had highest heritabilities in postcentral and posterior cingulate gyri whereas cortical surface area and volume had highest heritabilities in precuneus and cuneus, respectively) (Winkler et al., 2010).

In terms of possible functional correlates associated with the cortical alterations observed in my study, a common characteristic of prefrontal and temporal regions, where the greatest cortical maturational delays were observed in the preterm group, is that they belong to heteromodal areas of the cerebral cortex. These are made up by

reciprocally interconnected regions responsible for integrating sensory information into high-order cognitive processes, via in-depth associative elaboration (Mesulam, 1998). Cortical maturational delays (i.e. delayed thinning) in heteromodal cortices may be partly responsible for the cognitive deficits observed in preterm-born samples (Bless et al., 2013; Heinonen et al., 2013; Nosarti et al., 2007), as cortical thinning may reflect selective removal of synapses that may contribute to the establishment of neural circuits supporting cognitive processes (Hensch, 2004; Shaw et al., 2007). Similarly, cortical maturational delays in insula, which has been described as critical for emotional awareness (Gu, Hof, Friston, & Fan, 2013) may contribute to the understanding of poor social competence described in preterm adolescents (Healy et al., 2013).

In addition to their central involvement in high-order cognitive functions, alterations in fronto-temporal networks have been associated with an increased vulnerability to develop psychiatric problems in a variety of clinical and sub-clinical samples, including schizophrenia, individuals at risk of psychosis (Benetti et al., 2009; Borgwardt et al., 2007) and ADHD (Shaw et al., 2007). Reduction in GM in temporal cortices has further been associated with early-life psychosocial adversities in individuals without a current psychiatric diagnosis (Walsh et al., 2014). As the altered patterns of cortical development following preterm birth observed here implicate similar brain cortices to those described in psychiatric disorders known to be more prevalent in preterm samples than controls (Johnson & Wolke, 2013; Nosarti et al., 2012), I speculate that an increased risk of developing psychiatric disorder following preterm birth may be underpinned by region-specific altered cortical development. Support to the intermediate phenotype hypothesis has been provided by other studies including one by Shaw and colleagues (2011) which observed neurodevelopmental changes in CT

resembling those found in ADHD in typically developing youth exhibiting hyperactive/impulsive signs (Shaw et al., 2011).

It is also important to consider how the degree of prematurity could affect CT development. This was well demonstrated in the Norwegian cohort at both adolescence (Martinussen et al., 2005) and adulthood (Bjuland et al., 2013). When preterm individuals were divided into low (GA ≤ 28 weeks) and high GA (> 28 weeks) subgroups or into low (birth weight < 1250g) and high birth weight (≥ 1250g) subgroups, the group difference in CT between controls and preterm individuals was mostly maintained in the low GA or low birth weight group. In contrast, the group difference greatly diminished in high GA or high birth weight group, with the diminution being greater at early adulthood than at adolescence. The greater diminution of CT alteration in preterm group at early adulthood could indicate that the effect of prematurity on CT becomes more prominent in early adulthood than in adolescence. Therefore, whether the observed structural alterations indicate a developmental delay or permanent deficit could depend on the extent of prematurity; they could indicate (1) a developmental delay in the less premature subgroup and (2) a permanent deficit in more premature individuals.

Based on this assumption, I suggest that the decrement of regions where the preterm group showed thicker cortices between Time 1 and Time 2 could reflect developmental catch-up of the less premature subgroup (and not of the more premature individuals) via accelerated cortical thinning. So, I emphasise that future studies more thoroughly

examine how GA mediates the impact of preterm birth on cognitive and brain development.

The following chapter will describe a longitudinal analysis intended for a more thorough investigation of CT development between Time 1 and Time 2 within-, as well as between-group.

Chapter 5: Study 2 - Cortical thickness decreases more prominently in the preterm group between adolescence and adulthood.

In this chapter, I will describe within and between group longitudinal analyses using a univariate approach.

As in the last chapter, this chapter consists of Methods, Results and Discussion sections.

5.1 Methods

5.1.1 Study population

Details are provided in section “4.1.1”.

5.1.2 Magnetic Resonance Imaging

Scanning protocols and quality control procedure are described in subsections of section "2.1.2".

5.1.3 Image processing

Details of image format conversion (from UNC format to MINC format) and cortical surface extraction are given in subsections of section "4.1.3".

5.1.4 Statistical analyses

5.1.4.1 Neonatal and socio-demographic data

This is described in section "4.1.4.1"

5.1.4.2 Cortical thickness data

See section "4.1.4.2" for details.

5.1.4.2.1 Longitudinal analysis

As mentioned earlier, one set of analyses involved all participants whereas a second set included only those scanned at both time points. For the first set, a significant issue was that some participants were scanned at only one time point. However, this problem was tackled by using a mixed effects model, which can deal with missing data in longitudinal analyses (or repeated measures analyses) (Lindstrom & Bates, 1988) and handle irregular intervals between measurements (Pinheiro & Bates, 2000, as cited in Shaw et al., 2006).

Univariate/general linear/mixed effects models were used. For the within-group longitudinal analysis, the model was defined as Y = 1 + Time + Gender + Subject + I. Time-by-group interaction (i.e. group difference in longitudinal changes) was modelled as Y = 1 + Time + Group + (Time*Group) + Gender + Subject + I.

In all analyses, white noise (I) and gender were used as nuisance variables. Subject was included as a random-effect variable to take into account the within-subject correlation which (1) is inherent in repeated measures (Bland & Altman, 1995) and (2) increases Type I error rate (i.e. make the effect appear stronger than it actually is) (Muller & Barton, 1989). If the variance of Subject is 0, Subject becomes non-existent (i.e. the same as not being included in the model); if the variance of Subject is infinite, Subject becomes a fixed effect variable like other variables. The model is called a mixed effects model because it includes both random effect variable (Subject) and fixed effect variables (all the others).

5.2 Results

5.2.1 Neonatal and socio-demographic data

Results are given in Table 4-2 in section "4.2.1".

5.2.2 Cortical thickness data

5.2.2.1 Within-group longitudinal cortical thickness changes

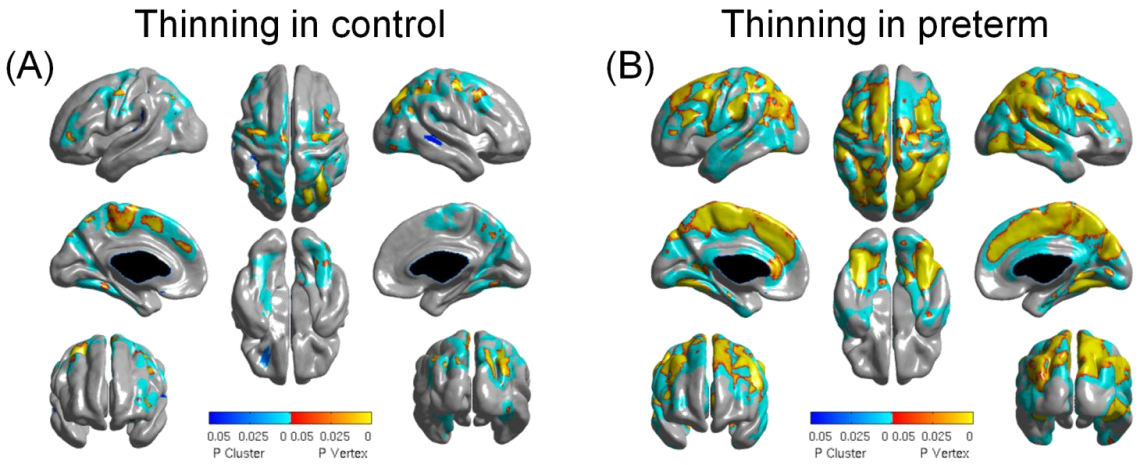
In both sets of analyses including all or only the 72 participants scanned twice, both control and preterm groups displayed no significant CT increases, but only significant decreases.

Results of the analyses including all participants showed that CT significantly decreased in both groups from Time 1 to Time 2, after controlling for gender. In controls, CT decrease was observed predominantly in posterior frontal regions, parietal areas and ventral aspects of temporal lobes extending into occipital lobes bilaterally, as well as left medial frontal cortex (Figure 5-1 (A)). In the preterm group, a more pronounced decrease occurred in similar, but much more widespread regions (Figure 5-1 (B)).

Similar regions showed significant CT decrease when analysing only 72 participants scanned at both time points (Figure A-2 in Appendix), with the size of the clusters and extent of decrease being smaller compared to the results of the analyses including all participants.

Figure 5-1

Within-group longitudinal changes in CT. Gender was controlled for. Blue-turquoise regions represent clusters (cluster $p < 0.05$) and red-yellow regions represent cluster peaks (vertex $p < 0.05$).



5.2.2.2 Between-group comparison of longitudinal cortical thickness changes

Results of group-by-time interaction analysis, with gender effect removed, were non-significant. That is, CT change from Time 1 to Time 2 did not significantly differ between controls and preterm born individuals. This was true both when all participants were included and when only those scanned twice were included.

5.3 Discussion

As mentioned in section "4.1.1", there are two sets of analyses with one using all participants and the other involving only 72 participants (scanned at both time points). Here I will discuss just the first set of analyses because the second set of analyses was carried out only to characterise those participants used in the SVM analysis (Chapter 6) which included only the participants scanned twice.

5.3.1 Longitudinal analysis

Overall, CT did not significantly increase, but only significantly decreased between Time 1 and Time 2 in both groups, reflecting maturational events observed in normative samples (O'Donnell et al., 2005; Shaw et al., 2008; Tamnes et al., 2010). Within the age range of the present study, as described in Chapter 3 (section "3.1.3.2"), Tamnes et al.'s (2010) cross-sectional study reported linear and quadratic (initial rapid decrease which slows down later) CT decreases in most brain regions, whilst (Shaw et al., 2008)'s longitudinal study observed slow linear decrease as well as rapid cubic decrease (following increase which peaks at around age 10 years) (Figure 3-1). (O'Donnell et al.,

2005)'s region of interest (ROI) study also observed linear CT decrease with age specifically in the frontopolar and dorsolateral areas.

The results of my study show that CT decrease was more extensive and widespread in preterm individuals than controls. Consistent with the idea of maturational delay in the preterm group, CT in a number of regions, especially frontal and temporal areas, was greater in preterm-born individuals at Time 1 (Figure 2B) and this difference diminished by Time 2 (Figure 2D). These findings could indicate that the patterns of CT alterations following very preterm birth reflected developmental delay at Time 1 and that by Time 2 preterm born individuals caught up with controls, therefore displaying fewer CT differences. These results are consistent with previous findings from region of interest studies in the same subject sample, which found decreased surface area of the corpus callosum in preterm-born individuals compared to controls at mid-adolescence (Nosarti et al., 2004), but it did not statistically differ between the groups at early adulthood (Allin et al., 2007). Also, Parker et al. (2008) observed significant cerebellar volume decrease in the preterm group only. These two studies are described in the following two paragraphs.

Corpus callosum surface area was calculated on the mid-sagittal slice, using Analyze™ software (Allin et al., 2007; Nosarti et al., 2004). Nosarti et al.'s (2004) cross-sectional study demonstrated that, at age 15 years, total corpus callosum area was significantly smaller (7.5%) in the preterm adolescents (GA < 33 weeks) than controls, after adjusting for total WM volume. When the corpus callosum was divided into four subsections (anterior, mid-anterior, mid-posterior and posterior), the absolute size of the callosal subregions was significantly smaller in the preterm group in mid-posterior and

posterior quarters by 11.6% and 14.7%, respectively, compared to controls. Additionally, the preterm individuals were divided into three subgroups according to the neonatal ultrasound classification: those with periventricular haemorrhage and ventricular dilatation (PVH+DIL), others with periventricular haemorrhage without complications (PVH) and, and lastly those without PVH (i.e. normal ones) (NO-PVH). Within the preterm group, the PVH+DIL subgroup displayed significantly smaller corpus callosum area than the PVH or NO-PVH subgroup. Specifically, the PVH+DIL subgroup had (1) 14.7% and 16.9% decreased total corpus callosum area compared to the PVH and the NO-PVH subgroups, respectively, (2) 32.8% reduced mid-posterior quarter than the NO-PVH subgroup, and (3) 19.9% and 23.4% smaller posterior quarter than the PVH and NO-PVH subgroups, respectively. This group difference diminished at age 19 years, as revealed by a longitudinal study (Allin et al., 2007). Allin et al. (2007) confirmed again that the total corpus callosum area was significantly smaller (by 13.7%) in the preterm group than in the term group at age 15 years. However, the group difference became non-significant (5.3% smaller in preterm group) at 19 years of age. Also, the preterm group displayed statistically significant increase in total corpus callosum area (13.4%) and areas of all four subsections (6.7%, 15.4%, 21.9% and 9.5% in anterior, midanterior, midposterior and posterior quarters, respectively) from ages 15 to 19 years. In contrast, the control group showed statistically non-significant increase in total corpus callosum area (3.3%) and areas of all subsections (2.4%, 3.6% and 2.1% in anterior, midanterior and posterior quarters, respectively) except the midposterior quarter (8.2%) where the increase was significant. There was no significant interaction between time point and group, regarding corpus callosum size (i.e. increase of corpus callosum size was not significantly different between groups). Overall, Nosarti et al. (2004) and Allin et al.'s (2007) findings showed diminishing group difference in corpus

callosum size between adolescence and early adulthood, thus suggesting that the preterm individuals made a developmental ‘catch-up’ with controls during this period.

Also, although cerebellar volume, as acquired with Cavalieri method using `MEASURE' software (Johns Hopkins University, Baltimore, USA, as cited in Parker et al., 2008), was not significantly different between controls and preterm individuals either at age 15 or 19 years, significant interaction was observed between time point and group (Parker et al., 2008). That is, cerebellar volume significantly shrunk (by 3.11%) in the preterm group between the time points whereas no significant changes were observed in controls (Parker et al., 2008). These findings appear to indicate developmental ‘catch-up’ as well because slight decrease in cerebellar volume during this period has been observed in normative populations (Tiemeier et al., 2010; Wierenga et al., 2014).

In summary, the greater within-group CT decrease in the preterm individuals (regarding which, the difference was prominent as inspected visually although statistically non-significant), diminution of cross-sectional differences between Time 1 and Time 2 as well as previous studies involving the same cohort together suggest that preterm group made a CT-developmental catch-up with controls between adolescence and early adulthood.

5.3.1.1 Mechanisms of cortical thinning

Results of this study suggest that CT decreased in both groups from adolescence to early adulthood, showing no significant increase in CT in any region. This is consistent with previous reports of CT decrease during adolescence in most brain regions.

The mechanisms underlying CT decrease are unclear, but several hypotheses have been proposed. Gogtay et al. (2004) speculated that reduction of cortical density, which is highly correlated with CT (Narr et al., 2005), could be due to cell shrinkage (Morrison & Hof, 1997, as cited in Gogtay et al., 2004) or synaptic pruning (Crews, He, & Hodge, 2007, as cited in Gogtay et al., 2004). Axons and synapses are produced in excess in early puberty, followed by speedy pruning in later adolescence (Giedd et al., 1999; Andersen et al., 2000; Andersen and Teicher, 2004, all as cited in Crews et al., 2007). For example, synapse loss occurs in prefrontal cortex of humans and non-human primates during adolescence (Huttenlocher, 1984; Zecevic et al., 1989, both as cited in Crews et al., 2007). The hippocampus has also been reported to lose branches within dendritic arbors during adolescent maturation (Swann et al., 1999, as cited in Crews et al., 2007). In addition, both dendritic pruning and synaptic losses have been observed in medial amygdala (Zehr et al., 2006, as cited in Crews et al., 2007), nucleus accumbens (Teicher et al., 1995; Tarazi et al., 1998b, both as cited in Crews et al., 2007) and hypothalamus (Choi and Kellogg, 1992; Choi et al., 1997, both as cited in Crews et al., 2007) in adolescence.

Cortical thinning could also be caused by changes in the number of neuropils. In rhesus monkeys, CT was found to be significantly and positively correlated with the number of neuropils (Bourgeois, Goldman-Rakic, & Rakic, 1994). A neuropil was defined as cortical tissue after excluding the blood vessels, cell bodies, myelinated axons, and large

dendritic trunks. Therefore, the neuropils included small dendrites and spines and fine glial processes, unmyelinated axons, and axon terminals (Bourgeois and Rakic, 1993, as cited in Bourgeois et al., 1994). CT as well as the percentage of neuropils in the cortical tissue was measured in monkeys aged between GA 47 days to 20 years. CT showed significant and positive correlation with neuropil percentage across twenty-three monkeys (this correlation was not included in Bourgeois et al. (1994), but I calculated it using Table 2 in their paper).

In addition, cortical myelination, which has been reported to occur or continue in late period (e.g. second decade of life (cingulate) or first and second decades of life (subiculum and presubiculum) (Benes, 1989)), could result in cortical thinning during adolescence. This view, however, has received both supportive and contradictory evidence. In support of this view, cortices with heavier myelination were found to be thinner (except in primary motor area), whereas more lightly myelinated cortex was reported to be thicker (except in frontal pole which was lightly myelinated and thin) (Triarhou, 2007a, as cited Glasser & Van Essen, 2011), as revealed histologically.

However, an important issue to consider is whether cortical myelination could cause miscalculation of CT in MR images. The concern arises because cortical surface running through the partial-volume voxels (i.e. voxels which contain different tissues (e.g. GM and WM together) can be difficult to define. Confirming this concern, CT was found to be underestimated in heavily myelinated and thin areas (mainly in parts of postcentral gyrus and early visual cortex) while CT in lightly myelinated areas (frontal and cingulate regions) are at risk of overestimation (Glasser & Van Essen, 2011).

As opposed to Glasser and Van Essen (2011), Wu et al. (2014) concluded that CT underestimation is not attributable to increased myelination of superficial WM. Superficial WM refers to WM just under the cortex and includes a mixture of short association fibers such as intracortical axons directly connected to GM, subcortical association fibers (U-fibers) which run through the cortical sulci to link adjacent gyri, and some termination fibers from the deep fiber pathways (Parent and Carpenter, 1996; Oishi et al., 2008, both as cited in Phillips et al., 2013). According to Wu et al. (2014), if greater myelination in the GM-WM border is serious enough to alter the signals in those voxels and therefore leads to underestimation of CT, such myelination should also cause changes in superficial WM which can be measured by diffusion tensor imaging (DTI) methods. Based on these assumptions, they suggested that the great similarity between the development of superficial WM and CT would indicate that the observed cortical thinning can be attributed to increased myelination of superficial WM (i.e. observed cortical thinning is not real, but an underestimation of CT caused by myelination in superficial WM). They examined the MR images of participants aged 10-18 years and measured the development of CT (from T1 structural images) and superficial WM (using DTI measures). The DTI measures included fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity, indicating myelination, axon packing density, and/or axonal coherence (Beaulieu, 2002; Song et al., 2002, 2003, 2005, all as cited in Wu et al., 2014). After visually comparing the maps of CT development and superficial WM development across the ages, they reported a lack of overlap between the two maps, except in the orbitofrontal cortex and posterior cingulate area, thus concluding that the observed cortical thinning was not caused by increased myelination in superior WM. They argued that cortical thinning observed in the orbitofrontal cortex could not be attributed to changes in myelination. That is because radial diffusivity showed no changes (i.e. myelination level remained the same),

although fractional anisotropy and axial diffusivity increased (i.e. axonal coherence or density improved).

All in all, cell shrinkage or synaptic pruning seems to be the most probable cause of cortical thinning during adolescence. On the other hand, a clear association between increased cortical myelination and cortical thinning has not been conclusively documented.

5.3.1.2 Methodological issue

Mass-univariate statistical methods apply correction for multiple comparisons to its statistical output (e.g. in Chapter 4 and the present chapter, RFT-based correction has been applied to vertex-wise t-test output). Ecker et al. (2010) argued that such correction could be too stringent to detect subtle effects – in other words, it increases Type II error (i.e. false negatives (finding no effect when there is one)) rate. According to this view, the RFT-based correction may have caused failure to detect statistically significant group differences in CT changes in the current dataset. Also, univariate methods (e.g. vertex-wise t-test) are unable to detect subtle effects which (1) are spatially distributed across the brain (Orru, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012) because they examine differences at each vertex, and (2) may be better suited at being investigated using multivariate approaches, such as SVM (Ecker et al., 2010). Regions identified by SVM could reflect either (1) great group difference (e.g. in CT) in a specific region, or (2) this specific region being strongly inter-correlated with other network components (Ecker et al., 2010). Even though RFT considers spatial distribution of effects by taking into account spatial correlation of signals, it is spatially

limited to adjacent vertices and also fails to consider the network across regions further apart. For this reason, I conducted SVM analysis to investigate longitudinal CT changes in relation to cognitive outcome at early adulthood, as described in the following chapter.

Chapter 6: Study 3 - Patterns of cortical thickness change during the second half of adolescence are associated with cognitive outcome at early adulthood.

In the previous chapter, I showed that random field theory (RFT)-based univariate measure may not have been sensitive enough to detect spatially distributed and subtle differences in cortical thickness (CT). Provided that this assumption is correct, such insensitivity could have led to non-significant findings in the between-group comparisons of longitudinal CT changes. Therefore, in this chapter, I have carried out an analysis using support vector machine (SVM) which is known to be able to identify such subtle differences scattered in different parts of the brain. The analysis has been carried out in two phases. In the first phase, an algorithm has been developed which best distinguished the brains between groups at Time 1. The next phase has involved prediction of group membership at Time 2 using the algorithm.

Additionally, I chose the regions with best group distinguishability at Time 1 which has been identified in the first phase of SVM analysis. Then I assessed the association between (1) CT changes in these regions and (2) cognitive scores at Time 2 which were significantly different between groups.

This chapter consists of Methods, Results and Discussion sections.

6.1 Methods

6.1.1 Study population

Among the 248 and 109 participants from Time 1 and 2, respectively, included in Chapter 4 and 5's univariate analysis, this chapter's SVM (multivariate) analysis included only the 72 participants (21 controls and 51 preterm individuals) who were scanned at both time points. Further details were given in Chapter 4, although the study population will be described here briefly.

Participants were selected from two cohorts (one born in 1979–82 and the other born in 1983–84) of participants born before 33 weeks of gestation and admitted consecutively to the Neonatal Unit of University College London Hospital (UCLH) (Nosarti et al 2008). Then, a subset of these cohorts was chosen according to a set of selection criteria and scanned for structural brain images. Details are provided in Chapter 4 (section "4.1.1").

After that, the participants with problematic images were further excluded. This left 248 and 109 participants, who were included in this chapter's neuropsychological outcome

analysis (i.e. comparing between groups the neuropsychological scores of Time 2) only. Detailed exclusion criteria are provided in Chapter 4 (section "4.1.2.3").

Among these participants, only those scanned at both time points (21 controls and 51 preterm participants) were included in all analyses: (1) neuropsychological outcome analysis, (2) SVM analysis of CT and (3) association between neuropsychological scores from Time 2 and CT changes between Time 1 and Time 2 in the clusters identified in the SVM analysis. The third analysis required a measure of CT change between Time 1 and Time 2 and therefore could accommodate only those participants scanned twice.

6.1.2 Magnetic Resonance Imaging

At Time 1, magnetic resonance imaging (MRI) was performed at two sites: Institute of Neurology and Maudsley Hospital, both located in London. At time 2, scanning occurred only at Maudsley Hospital. Details are given in Chapter 4 (section "4.1.2.1").

Also, as described in the previous section, "quality control" was carried out to exclude participants with poor image quality from analyses.

6.1.3 Cortical surface extraction

The cortical surfaces were extracted from the T1-weighted magnetic resonance (MR) images using the CIVET pipeline (version 1.1.9) (Ad-Dab'bagh et al., 2006). This yielded, for each image, CT data represented in two text files: ".txt" file with CT in millimetres and ".obj" with spatial info (e.g. shape of the cortical surface).

Details for this section is given in Chapter 4 (section “4.1.3.2”).

6.1.4 Neuropsychological assessment

All study participants were assessed at Time 2 with the following well-validated measures: Wechsler Abbreviated Scale of Intelligence (WASI) for intelligence, Controlled Oral Word Association Test (COWAT) and Hayling Sentence Completion Test (HSCT) for executive function, and California Verbal Learning Test (CVLT) and Wechsler Memory Scale-Revised (WMS-R) for memory.

6.1.4.1 Intelligence

6.1.4.1.1 Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI (Wechsler, 1999), which is (1) shorter than the full and extended version, WAIS-III and (2) considered to provide an estimate of WAIS-III summary scores (as explained in Axelrod (2002)), provides estimates of verbal (VIQ), performance (PIQ) and full-scale intelligence quotient (FSIQ) scores. The WASI contains 4 subtests, which are Vocabulary, Similarities, Block Design, and Matrix Reasoning. The VIQ score is formed by adding Vocabulary and Similarities subtests together, PIQ from Matrix Reasoning and Block Design, and FSIQ from (1) Vocabulary and Matrix Reasoning or (2) all four subtests. For this study, I used FSIQ.

Each subtest examines the following (as described in http://www.pearsonclinical.com/psychology/products/100000593/wechsler-abbreviated-scale-of-intelligence-wasi.html?Pid=015-8981-502#tab-details)

- Vocabulary: fund of knowledge (knowledge acquired through life experiences (Gonzalez, Moll, & Amanti, 2013)), word knowledge and verbal concept formation
- Similarities: verbal reasoning and concept formation
- Matrix Reasoning: visual information processing and abstract reasoning abilities
- Block Design: ability to analyse and synthesise abstract visual stimuli, nonverbal concept formation, visual perception and organisation, simultaneous processing, visual-motor coordination, learning, and the ability to separate figure and ground in visual stimuli

WASI was found to have high construct validity (Hays, Reas, & Shaw, 2002). This was demonstrated by (1) higher correlation among scores of similar subtests (e.g. Vocabulary subtest was correlated most strongly with Similarities subtest), indicating high convergent validity, and (2) difference between verbal and non-verbal subtests, indicating and discriminant validity. Convergent and discriminant validities together form construct validity (Trochim, 2006). Also, WASI has high reliability, as explained in (Saklofske, Caravan, & Schwartz, 2000). The reliability for FSIQ derived from all four subtests are 0.96 and 0.98 for children and adults, respectively.

6.1.4.2 Executive function

Two tasks were used which are described in the following paragraphs.

6.1.4.2.1 Controlled Oral Word Association Test (COWAT)

The COWAT measured phonemic fluency (Benton & Hamsher, 1976) which, together with semantic fluency, forms a category of verbal fluency. Verbal fluency involves

retrieving information from memory, and the retrieval requires selective attention, mental set shifting, internal response generation, and self-monitoring (Patterson, 2011). During COWAT tasks, participants were asked to verbally name as many words as possible starting with the letters F, A and S, separately. For each letter, participants were given 1 minute. Total number of words produced in the "F", "A", and "S" trials were used as the score. Task performance on the COWAT was found to increase from ages 5 to 17 years (Martins, Vieira, Loureiro, & Santos, 2007) or from 9 to 24 years (Porter, Collins, Muetzel, Lim, & Luciana, 2011), as revealed cross-sectionally.

Such an increase could be relevant to cortical thinning observed over this period. Porter et al. (2011) demonstrated that, after controlling for the effects of age (9-24 years), gender and VIQ, CT was negatively associated with COWAT total score in the following regions of both hemispheres: areas encompassing the posterior and anterior parts in the left hemisphere language network (Costafreda et al., 2006, Indefrey and Levelt, 2000 and Vigneau et al., 2006, all as cited in Porter et al., 2011), bilateral prefrontal regions implicated in online performance monitoring (e.g. anterior cingulate and lateral prefrontal cortices (D'Esposito et al., 1999, MacDonald et al., 2000 and Miller and Cohen, 2001, all as cited in Porter et al., 2011), and bilateral medial parietal regions linked with greater effort and concentration while finding words (e.g. precuneus (Dräger et al., 2004, as cited in Porter et al., 2011). These regions were found to display CT decrease in cubic or linear trajectories between 3.5 to 33 years (Shaw et al., 2008), which could explain the COWAT score increase during adolescence.

6.1.4.2.2 Hayling Sentence Completion Test (HSCT)

The HSCT measures response initiation and inhibition (Burgess & Shallice, 1997). Participants are presented with sentences, each of which has the last word missing. Participants are required to add the last word as quickly as possible so that the sentence makes sense (initiation condition; e.g. "He mailed the letter without a … (participant says) stamp.") or no sense (inhibition condition; e.g. "The captain wanted to stay with the sinking … (participant says) banana.") (these examples have been taken from Bielak, Mansueti, Strauss, & Dixon (2006)). In the inhibition condition, participants are required to inhibit producing a meaningful word. Performance on the HSCT has been found to be sensitive to frontal lobe lesions. For example, frontal-damaged patients required longer time for the initiation condition and produced more meaningful words in the inhibition condition, compared to patients with lesions in other brain areas (Paul W. Burgess & Shallice, 1996). Additionally, frontal-damaged patients show less sign of using strategies in the inhibition condition compared to the control group (Burgess & Shallice, 1996). The strategies observed in the control group were to name objects they could see in the room or to create a semantic category and name its members (Burgess & Shallice, 1996).

Global executive function ('Global EF') score was calculated as the sum of Z scores of the COWAT and HSCT measures. The tests were carried out verbally and therefore were not limited by writing ability (e.g. manual motor coordination). This was important because preterm individuals have been shown to display more motor problems as early as during infancy (Soares, Cunha, & Tudella, 2014) and early childhood (Van Hus, Potharst, Jeukens-Visser, Kok, & Van Wassenaer-Leemhuis, 2014) and as late as age 23 years (Husby, Skranes, Olsen, Brubakk, & Evensen, 2013). For

preterm participants, the Z scores were obtained using means and standard deviations (SD) from controls, which by default were set to 0 and 1, respectively.

6.1.4.3 Memory

Two tasks were used, which are described in the following paragraphs.

6.1.4.3.1 Wechsler Memory Scale-Revised (WMS-R)

The WMS-R assesses memory functions in several domains (e.g. verbal, visual). For this study, the Visual Reproduction subtests were used, i.e. immediate and delayed recall of non-verbal material (Wechsler, 1987). The verbal subtests were not used because they would overlap with the CVLT scores when calculating the Global memory score.

6.1.4.3.2 California Verbal Learning Test (CVLT)

The CVLT (Dellis, Kramer, Kaplan, & Ober, 1987) examined verbal memory through the following procedure described in (Numan, Sweet, & Ranganath, 2000). The first phase consists of learning trials. "List A" contains 16 shopping items: four categories (fruits, spices, tools, and clothing), each containing four items. List A is presented five times and, after each presentation, participants perform immediate free recall (i.e. attempt to specify as many words in List A as possible). The second phase includes an interference trial. During this phase, participants perform one trial of immediate free recall after being presented once with the "List B". List B contains 16 new shopping items, of which eight derives from two of the List A categories (fruits, spices) and the other eight from two new categories (fish, utensils). Then, free recall and category-cued recall is examined for List A items. This is followed by a 20-minute delay, during which participants perform nonverbal tasks. Then, a third phase initiates which tests free recall, cued recall, and recognition memory of List A.

The CVLT adds to the WMS-R a thorough evaluation of the strategies, processes, and errors which participants display while learning verbal material (Delis, Cullum, Butters, Cairns, & Prifitera, 1988). While WMS-R examines how much information is remembered on several different tasks, the CVLT offers a multifactorial examination of how an examinee learns, or fails to learn, word lists (Delis et al., 1988).

'Global memory' score was calculated as the sum of Z scores of the CVLT and WMS-R measures. For preterm participants, the Z scores were obtained using means and SDs from controls, which by default were set to 0 and 1.

6.1.5 Statistical analyses

6.1.5.1 Support vector machine analysis

As mentioned at the end of the previous chapter, univariate data analyses failed to detect between group differences in longitudinal cortical changes. Furthermore, univariate methods have been criticised as not being optimal for the detection of subtle effects which could be spatially distributed in the brain (Orru et al., 2012). There is another important limitation to those methods. That is, univariate methods focus on differences at group level and therefore may possess insufficient statistical power to identify each individual's extent of difference (Orru et al., 2012). Such group-based inference limits clinical applications of the findings (e.g. structural and functional deficits of the brain in several disorders such as mild cognitive impairment, probable dementia of Alzheimer type, major depression, bipolar disorder, schizophrenia and generalised anxiety disorder

(Arnone et al., 2011, Davatzikos and Resnick, 2002, Ellison-Wright and Bullmore, 2010, Etkin and Wager, 2007, Smieskova et al., 2010 and Zakzanis et al., 2003, as cited in Orru et al., 2012)) because clinical decisions should be made on each individual rather than group (Orru et al., 2012). This problem similarly applies to research into brain alterations following very preterm birth. A univariate approach can identify structural brain alterations in a very preterm group, but only multivariate methods can be useful in identifying the significance of such alterations at the individual level (i.e. individual risk).

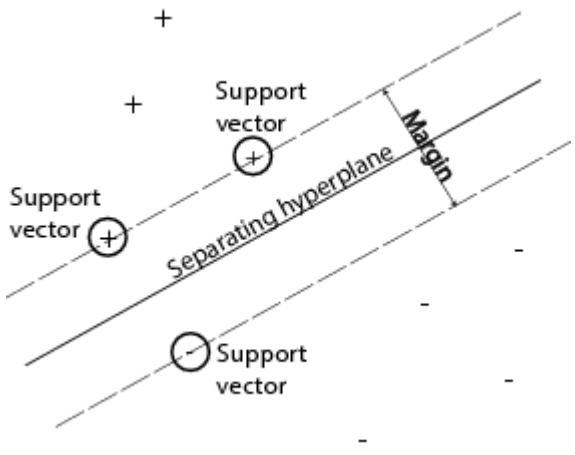
One alternative approach to neuroimaging data analysis is supervised machine learning, an approach that originally comes from research into artificial intelligence, and aims at developing algorithms and techniques for automatically extracting information from the data (Hastie et al., 2001, as cited in Orru et al., 2012). Supervised machine learning is advantageous to the traditional univariate methods in that it tackles both problems mentioned above: (1) individual inferences and (2) detection of spatially distributed and subtle effects in the brain (Orru et al., 2012). Regarding the second point, Ecker et al. (2010) further explained that, conventional mass-univariate methods such as voxel-based morphometry (VBM) considers each voxel is spatially independent from one another whereas a multivariate technique like SVM takes into account inter-regional correlations. So, as explained in the previous chapter, individual regions could show great group difference (or "high discriminative power") because either (1) there is a great group difference in that area, or (2) this region is strongly inter-correlated with other network components (Ecker et al., 2010).

Support vector machine (SVM) (Vapnik, 1995) is a type of supervised machine learning and multivariate method (Gaonkar & Davatzikos, 2013; Orru et al., 2012). It is multivariate because it assumes all dimensions (i.e. vertices) are considered to influence one another and therefore considers the relative weight of each dimension in distinguishing each datum (i.e. each whole brain) into groups. That is, when a vertex is identified to be important in group discrimination, its importance has been determined in relation with that of all the other vertices. Such consideration of each vertex's relationship with the whole brain is different from the vertex-wise univariate measure used in Chapters 4 and 5, which, at best, took only each vertex's neighbouring vertices together using RFT. The random-field-theory-based univariate statistics calculates smoothness (or spatial correlation (Brett et al., 2004)) of the statistical map. All vertices within any given region as big as the smoothness (e.g. 20mm) are considered a unit called a "resel" (= resolution element). In each resel, all vertices are considered to be correlated with each other. Overall, the difference is clear between the multivariate (SVM) and univariate (i.e. group comparisons based on vertex-wise t-test and RFT-based correction) measures.

SVM can be used when the data has two classes (i.e. groups). An SVM analysis is comprised of two phases: training and testing. During training, an SVM algorithm is trained to recognise patterns in group-labelled data. This involves identifying a hyperplane which maximally distinguishes data points (i.e. brains) between groups, based on all 81,924 dimensions (= total number of vertices in the brain) comprising each data point – see Figure 6-1 for a similar example. In the testing phase, the SVM algorithm classifies a new set of data into groups defined in the training phase. For the testing phase, the accuracy for the blind-prediction is calculated.

Figure 6-1

An example of support vector machine identifying a hyperplane which maximally separates two groups. Each symbol (+ or -) can be considered as the brain scan of each participant, and therefore consists of as many dimensions as, for example, the number of vertices (i.e. 81,924 in the present study). Each group's brain scan closest to the separating hyperplane is called a support vector. When lines are drawn (1) parallel to the hyperplane and (2) through the support vectors, the distance between these lines is called a margin. Figure has been adopted from http://www.mathworks.co.uk/help/stats/support-vector-machines-svm.html.



One important thing to note about the training phase is that data can be represented as kernels (which were used in the present study) instead of feature vectors. A feature vector is like a coordinate representing a data point (i.e. brain) defined by its dimensions (e.g. participant A's brain = [Vertex 1's thickness, Vertex 2's thickness, … , Vertex 81,924's thickness]. On the other hand, a kernel is a matrix of pairwise similarities between data points. Using a kernel is computationally more efficient as it represents the number of data points (n = 144 {= (21 controls + 51 preterm individuals) x 2 time points}) rather than the number of dimensions (n = 11,797,056 (= 144 x 81,924). Kernels can be linear or non-linear, but linear kernels are usually used when data can be linearly separated (Orru et al., 2012) (such as the data for the present study). Figure 6-1 shows an example of linear separation – in a non-linear separation, the separating hyperplane will not be straight. Non-linear kernels can be used if linear separation of the data is not possible, but it can be less accurate than using linear kernels. This section was summarised from Orru et al. (2012).

A testing phase should not include any data included in the training phase as this would bias the accuracy (i.e. falsely increase the accuracy). To avoid such bias, two different sets of data can be used: one for training and the other for testing. However, this will double the amount of data to be collected. An alternative method is cross-validation. This involves having multiple trials of training and testing, where at each trial, different subsets of data are assigned to training and testing groups. Then, accuracies are averaged across all trials (Lemm et al., 2011, as cited in Orru et al., 2012)). One such method which is often used is the leave-one-out cross validation, which involves (1) training SVM using all brains but one (thus, the name leave-"one"-out) in each group (i.e. leaving 2 brains per trial) and (2) classifying the excluded pair in the testing phase

(Hastie et al., 2001, as cited in Orru et al., 2012). This is repeated many times (e.g. 1,000) and the average classification accuracy is calculated.

A number of studies have demonstrated that SVM can successfully distinguish between groups for both clinical and non-clinical purposes. For example, healthy individuals' brain activities could be identified, with high accuracies, to be associated with lying or telling the truth (Davatzikos et al., 2005). In Davatzikos et al. (2005), participants were given cards (5 of clubs or 7 of spades). Then, while the participants were in an functional MRI (fMRI) scanner, they were presented with a card and required to admit or deny having it. A tester specified, before the scanning, one card to admit the possession of, and another for denial. One card to admit and another to deny the possession of were specified before the participants were scanned. As assessed by leave-one-out cross validation, brain activities of "lie" trials were correctly classified 90% of the time. For the "truth" trials, the classification was correct 85.8% of the time. Examples of successful clinical applications of SVM are as follows. Using structural MR images, healthy controls were effectively distinguished from patients of Alzheimer's disease (Kloppel, Stonnington, et al., 2008), pre-symptomatic gene carriers of Huntington's disease (Kloppel, Draganski, et al., 2008) or participants at-risk mental state for psychosis (Koutsouleris et al., 2009), with classification accuracies of 81.1-96.4%, 82.2% and 82%, respectively (for more examples, see Table 6-1).

Table 6-1

"Studies investigating the diagnostic potential of neuroimaging data and SVM.". This table has been adopted from Orru et al. (2012) in which full records of the references are provided.

Author	Comparison	Sample size	Technique	Accuracy (%)
Arimura et al. (2008)	PDAT vs. HC	PDAT = 29; HC = 25	Structural MRI	82.7
Davatzikos et al. (2008)	MCI vs. HC	MCI = 15; HC = 15	Structural MRI	90
Duchesne et al. (2008)	PDAT vs. HC	PDAT = 75; HC = 75	Structural MRI	92
Fan et al. (2008a)	MCI vs. HC	MCI = 15; HC = 15	Structural MRI & PET	100
Ferrarini et al. (2008)	PDAT vs. HC	PDAT = 58; HC = 28	Structural MRI	84
Klöppel et al. (2008a)	PDAT vs. HC	PDAT = 20; HC = 20	Structural MRI	95
	PDAT vs. FTLD	PDAT = 18; FTLD = 19	Structural MRI	89.2
Vemuri et al. (2008)	PDAT vs. HC	PDAT = 190; HC = 190	Structural MRI & genetic data	89.3
Gerardin et al. (2009)	PDAT vs. HC	PDAT = 23; HC = 23	Structural MRI	94
	MCI vs. HC	MCI = 23; HC = 25	Structural MRI	83
Magnin et al. (2009)	PDAT vs. HC	PDAT = 16; HC = 22	Structural MRI	94.5
Haller et al. (2010)	HC vs. MCI	HC = 35; MCI = 67	Structural MRI, DTI FA	91.4
Nho et al. (2010)	PDAT vs. HC	PDAT = 182; HC = 226	Structural MRI	90.5
Oliveira et al. (2010)	PDAT vs. HC	PDAT = 14; HC = 20	Structural MRI	88.2
Plant et al. (2010)	PDAT vs. HC	PDAT = 32; HC = 18	Structural MRI (GM + WM)	90
	MCI vs. HC	MCI = 24; HC = 18	Structural MRI (GM + WM)	97.62
Salas-Gonzalez et al. (2010)	PDAT + MCI vs. HC	PDAT + MCI = 167; MCI = 52	PET	86
	PDAT vs. HC	PDAT = 53; HC = 52	PET	95
	MCI vs. HC	MCI = 114; HC = 53	PET	88
Abdulkadir et al. (2011)	PDAT vs. HC	PDAT = 95; HC = 95	Structural MRI (GM)	84.5
Chen et al. (2011)	PDAT vs. HC	PDAT = 21; HC = 20	Resting-state functional MRI	87
	MCI vs. HC	MCI = 15; HC = 20	Resting-state functional MRI	95
Chincarini et al. (2011)	PDAT vs. HC	PDAT = 144; HC = 189	Structural MRI	Sens. = 89; Spec. = 94
Cui et al. (2011a)	MCI vs. HC	MCI = 79; HC = 204	Structural MRI & DTI	71.09
Dukart et al. (2011)	PDAT vs. FTLD vs. HC	PDAT = 21; FTLD = 14; HC = 13	Structural MRI (GM) & PET	91.7
Graña et al. (2011)	PDAT vs. HC	PDAT = 20; HC = 25	DTI FA	100
		PDAT = 20; HC = 25	DTI MD	98
Hinrichs et al. (2011)	PDAT vs. HC	PDAT = 48; HC = 66	Structural MRI & PET & CSF (tau, amygdaloid-beta 142, p-tau 181P, t-tau, APOE genotype) & NMs	88.2
Zhang et al. (2011a)	PDAT vs. HC	PDAT = 45; HC = 50	Structural MRI & PET & CSF(Aβ42, t-tau and p-tau)	92
	MCI vs. HC	MCI = 91; HC = 50	Structural MRI & PET & CSF(Aβ42, t-tau and p-tau)	80
Zhang et al. (2011b)	PDAT vs. HC	PDAT = 51; HC = 52	Structural MRI & PET & CSF(Aβ42, t-tau and p-tau)	93.2
	MCI vs. HC	MCI = 99; HC = 52	Structural MRI & PET & CSF(Aβ42, t-tau and p-tau)	76.4
Fu et al. (2008)	MD vs. HC	MD = 19; HC = 19	Functional MRI	86
Marquand et al. (2008)	MD vs. HC	MD = 20; HC = 20	Functional MRI	67.5
Costafreda et al. (2009a)	MD vs. HC	MD = 37; HC = 37	Structural MRI	67.6
Hahn et al. (2010)	MD vs. HC	MD = 30; HC = 30	Functional MRI	83
Nouretdinov et al. (2010)	MD vs. HC	MD = 19; HC = 19	Structural and fMRI	76.3
Gong et al. (2011)	RDD vs. HC	RDD = 23; HC = 23	Structural MRI (GM)	67.39
	NDD vs. HC	NDD = 23; HC = 23	Structural MRI (GM)	76.09
	RDD vs. HC	RDD = 23; HC = 23	Structural MRI (WM)	58.70
	NDD vs. HC	NDD = 23; HC = 23	Structural MRI (WM)	84.65
Koutsouleris et al. (2009)	HC vs. ARMS	HC = 17; ARMS-T = 15; ARMS-NT = 18	Structural MRI	82
Davatzikos et al. (2005)	SCH vs. HC	SCH = 69; HC = 79	Structural MRI	81.1
Shen et al. (2010)	SCH vs. HC	SCH = 32	Functional MRI	84.37
Yang et al. (2010)	SCH vs. HC	SCH = 20; HC = 20	Combined fMRI and genetic data	83
Costafreda et al. (2011b)	SCH vs. HC	SCH = 32; HC = 40	Functional MRI	92
	BD vs. HC	BD = 32; HC = 40	Functional MRI	79
Sun et al. (2009)	PS vs. HC	PS = 36; HC = 36	Structural MRI	86.1
Ingalhalikar et al. (2010)	SCH vs. HC	SCH = 27; HC = 37	DTI	90.62
	ASD vs. HC	ASD = 25; HC = 23	DTI	89.58
Ecker et al. (2010a)	HC vs. ASD	HC = 22; ASD = 22	Structural MRI (GM)	81
		HC = 22; ASD = 22	Structural MRI (WM)	68
		HC = 22; ASD = 22	Structural MRI (GM + WM)	77
Ecker et al. (2010b)	HC vs. ASD	HC = 20; ASD = 20	Structural MRI	85
Duchesne et al. (2009)	IPD vs. PPS	IPD = 16; PPS = 16	Structural MRI	90.6
Focke et al. (2011)	IPD vs. PSP	IPD = 21; PSP = 10	Structural MRI (GM)	87.1
		IPD = 21; PSP = 10	Structural MRI (WM)	96.77
	IPD vs. MSA	IPD = 21; MSA = 11	Structural MRI (GM)	71.87
		IPD = 21; MSA = 11	Structural MRI (WM)	n.s.
	IPD vs. HC	IPD = 21; HC = 22	Structural MRI (GM or WM)	n.s.

ASD, autistic spectrum disorders; BD, bipolar disorder; FTLD, frontotemporal lobar degeneration; HC, healthy controls; MCI, mild cognitive impairment; MD, major depression; NDD, non-refractory depressive disorder; PDAT, probable dementia of Alzheimer'stype; PS, psychosis; RDD, refractory depressive disorder; SCH, schizophrenia; IPD, Idiopathic Parkinson's Disease; PPS, Parkinson Plus Syndromes; PSP, Progressive Supranuclear Palsy; MSA, Multiple Systems Atrophy; NMs, Neuropsychological Measures; n.s., non-significant result.

6.1.5.2 Support vector machine analysis – method

SVM analysis was used to study spatially discriminating features between the two groups at Time 2 based on spatially distributed differences in CT at Time 1. For this analysis, only images for participants who were scanned at both time points were used. Analysis was comprised of two phases as mentioned above: i) the training phase, where a classifier was trained using group-labelled data (CT at Time 1 in 21 controls and 51 preterm individuals); ii) the testing phase, where unseen data (CT at Time 2 in the same subjects used in the training phase) were introduced to be classified. A linear kernel was used to represent the data, reduce computational cost and improve classification accuracy. The goal of using the longitudinal data set for both phases of classification (CT at Time 1 for training and CT at Time 2 for testing, both from the same participants) was to identify those areas in which spatially discriminating features between the two groups at Time 1 could be used to predict group membership at Time 2. The classification accuracy of the classifier was calculated using leave-one-out cross validation method across 1000 permutations. Results (Figure 6-2) show brain areas in which patterns of CT best distinguished between the two groups. By "best", I mean 5% of vertices (4009 vertices) with the highest SVM weights. I will refer to these regions as 'top 5%'.

However, use of same participants at both time points could have made this study prone to inaccurate statistics caused by within-subject correlation (Bland & Altman, 1995). That is, as mentioned in the previous chapter, within-subject correlation could make the effect appear stronger than it actually is (i.e. Type I error rate could increase). To address this issue, an additional analysis was performed, as described below.

6.1.5.2.1 Checking effect of within-subject correlation

To assess the extent of overfitting due to within-subject correlation, I trained and tested an additional SVM classifier using participants in either training or testing phase only (i.e. no participant was included in both training and testing phases). The training phase used CT from randomly selected 42 controls and 42 preterm individuals scanned at Time 1, and the testing phase involved CT from newly and randomly selected 42 controls and 42 preterm-born individuals scanned at Time 2 - 42 participants were chosen because this was the maximum number of participants in either group who were scanned at only one time point. Mean classification accuracy was calculated as described above, using leave-one-out cross validation through 1000 permutations and taking the mean classification accuracy across permutations. Then, the mean classification accuracy was compared with that of the original SVM elaborated in the previous section. Additionally, the 'top 5%' regions for this additional SVM at each permutation were selected, as in the original SVM. Finally the extent of the overlap of the 'top 5%' regions identified by the two SVMs (i.e. the one in this section and that from the previous section) at each permutation was calculated, which was then averaged across all permutations.

6.1.5.3 Longitudinal changes in cortical thickness and neuropsychological and behavioural outcome

For all participants included in the SVM analysis (i.e. 72 participants who were scanned at both time points), CT change was calculated by performing a vertex-wise subtraction of CT measured at Time 1 from CT measured at Time 2.

Subsequently, an inclusive mask of 1% of the brain with the highest SVM weights was created ('top 1%', 803 vertices), in order to confine the structure-function analyses to those areas displaying the most pronounced between-group differences in patterns of spatially discriminating features. Within the 'top 1%' areas, vertex-by-vertex correlations were performed, in control and preterm participants separately, between CT change and Global EF at Time 2 that differed statistically between the groups (see "Scanned at both time points" column in Table 6-2). FSIQ was significantly associated with global EF scores ($r=0.47$, $p<0.0001$), hence it was not independently investigated in the subsequent analyses. In the Results section I report clusters containing ≥ 20 vertices in which CT change significantly correlated with the chosen outcome measure.

6.2 Results

Neonatal and socio-demographic data are described in Chapter 4 (Table 4-2).

6.2.1 Neuropsychological outcome

Controls performed significantly better than preterm-born individuals in all neuropsychological subtests except the recall subtests of the CVLT (Table 6-2). The global EF and global memory scores were also significantly higher in controls.

When only those participants who were scanned at both time points were compared, controls scored significantly higher than preterm individuals in IQ and COWAT, as well as in global EF.

Table 6-2

Neuropsychological and behavioural outcome in preterm-born individuals and controls.

	All scanned at Time 2			Scanned at both time points		
	Mean (SD)		ANOVA	Mean (SD)		ANOVA
	Control (n = 42)	Preterm (n = 67)		Control (n = 21)	Preterm (n = 51)	
Full scale IQ						
WASI	105.5 (13.9)	96.4 (13.9)	**$F_{(108)}$ = 11.05 (p = 0.0012)**	104.2 (14.3)	96.7 (14.5)	**$F_{(71)}$ = 4.00 (p = 0.0495)**
Global memory [a]		*-2.6 (5.1)*	***$F_{(108)}$ = 8.31 (p = .0048)***		*-1.9 (5.4)*	*F(71) = 2.13 (p = 0.1491)*
CVLT (Recall (list A))	56.3 (8.8)	53.5 (9.8)	$F_{(108)}$ = 2.25 (p = 0.1369)	54.9 (9.0)	54.7 (10.1)	$F_{(71)}$ = 0.01 (p = 0.0925)
CVLT (Recall (list B))	6.5 (1.9)	6.2 (2.1)	$F_{(108)}$ = 0.77 (p = 0.3815)	6.4 (2.2)	6.3 (2.2)	$F_{(71)}$ = 0.02 (p = 0.8768)
CVLT (Recognition hits)	15.2 (0.8)	14.7 (1.6)	**$F_{(108)}$ = 4.01 (p = 0.0476)**	15.4 (0.7)	14.9 (1.5)	$F_{(71)}$ = 2.10 (p = 0.1515)
WMS (Immediate visual memory)	11.4 (2.1)	9.8 (3.3)	**$F_{(108)}$ = 7.38 (p = 0.0077)**	11.0 (2.2)	9.8 (3.3)	$F_{(71)}$ = 2.38 (p = 0.1274)
WMS (Delayed visual memory)	10.6 (2.9)	8.5 (3.4)	**$F_{(108)}$ = 10.57 (p = 0.0015)**	10.1 (2.9)	8.5 (3.4)	$F_{(71)}$ = 3.48 (p = 0.0662)
Global executive function [a]		*-0.9 (1.8)*	***$F_{(108)}$ = 6.95 (p = 0.0096)***		*-1.0 (2.0)*	***$F_{(71)}$ = 4.15 (p = 0.0455)***
HSCT (Scaled)	5.9 (1.5)	5.1 (2.0)	**$F_{(108)}$ = 4.90 (p = 0.0290)**	5.7 (1.6)	4.9 (2.1)	$F_{(71)}$ = 2.05 (p = 0.1569)
COWAT	40.5 (10.6)	36.2 (9.7)	**$F_{(108)}$ = 4.67 (p = 0.0330)**	40.9 (9.3)	35.8 (9.8)	**$F_{(71)}$ = 4.10 (p = 0.0468)**

COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; HSCT = Hayling Sentence Completion Test; SD = standard deviation; WASI = Wechsler Abbreviated Scale of Intelligence; WMS = Wechsler Memory Scale

[a] Global scores are the sum of domain-specific Z scores; for preterm participants these were obtained using means and SDs from controls, which by default were set to 0 and 1.

6.2.2 Cortical thickness

6.2.2.1 Longitudinal prediction of cortical thickness alterations using support vector machine

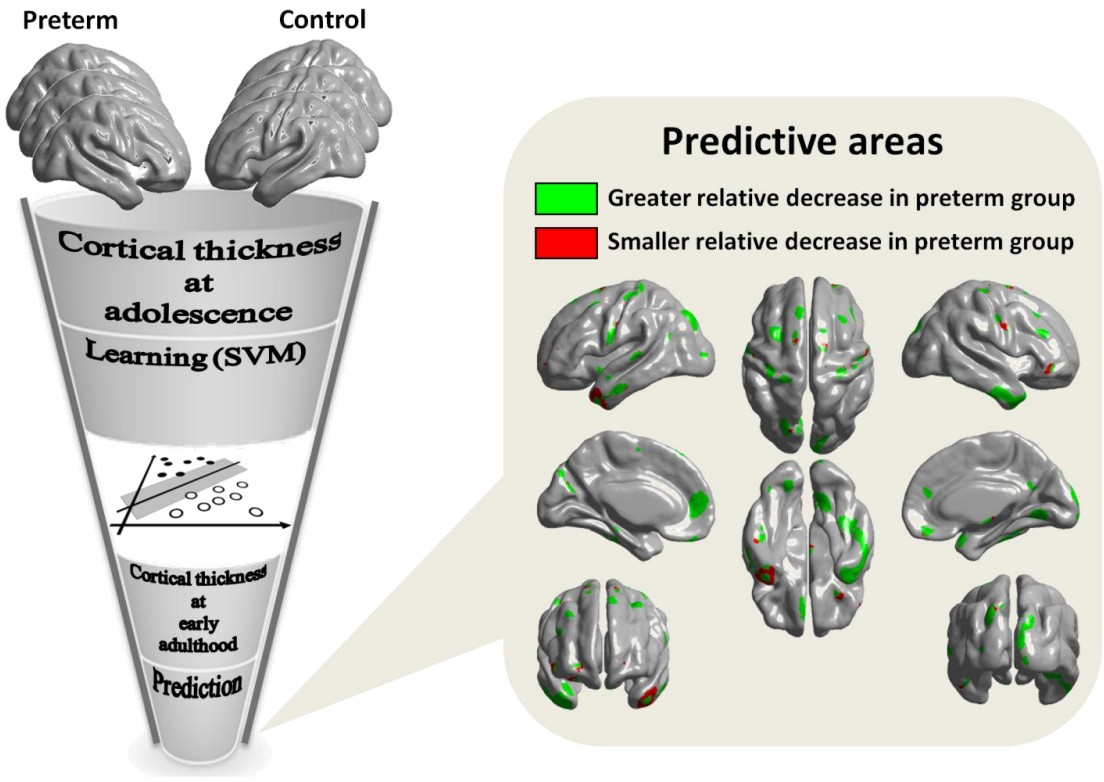
Spatial pattern of CT at Time 1 predicted group membership at Time 2 with 86.5% mean classification accuracy. The 'top 5%' regions (i.e., 5% of the brain with the highest SVM weights) which spatially discriminated between the groups included predominantly bilateral temporal poles and anterior inferior temporal gyri, bilateral superior parietal lobes, right occipitotemporal and lingual gyri as well as bilateral medial frontal areas (Figure 6-2). In most of these areas, preterm individuals displayed greater relative decrease (GRD; greater decrease or smaller increase) in CT than controls, except mainly around left temporal pole where both greater and smaller relative decreases were observed in the preterm group. I termed it greater/smaller relative "decrease" considering that the observed CT change was predominantly a decrease in both groups and that there was no significant CT increase.

As described in section "6.1.5.2.1", to assess the extent of potential overfitting due to within-subject correlation which accompanies longitudinal measures, an additional SVM was constructed involving different sets of participants who were included in either the training or testing phase only. This additional SVM showed a mean classification accuracy of 86.3% (SD = 3.6%) across 1000 permutations. There was no significant difference in classification accuracy between the original SVM (using training data at Time 1 and testing data from the same participants at Time 2) and this additional SVM (using training and testing data from different sets of participants)

(confidence level: 95%). There was an average 95.3% (SD = 8.9%) overlap of the ‘top 5%’ regions between this additional SVM and the original SVM across all permutations.

Figure 6-2

Prediction of regional CT alterations at Time 2 based on SVM weight vectors acquired from group classification at Time 1.



*SVM = support vector machine

*The map on the right shows 5% of the brain with the highest SVM weights (i.e. best discriminability between groups). “Greater relative decrease” in preterm group refers to greater decrease or smaller increase of CT from Time 1 to Time 2 in preterm group compared to controls.

6.2.2.2 Correlation between longitudinal cortical thickness change and global executive function at early adulthood

Results of the vertex-by-vertex correlations carried out in each group between CT change in the 'top 1%' regions and global EF scores at Time 2 identified three significant clusters (≥ 20 vertices).

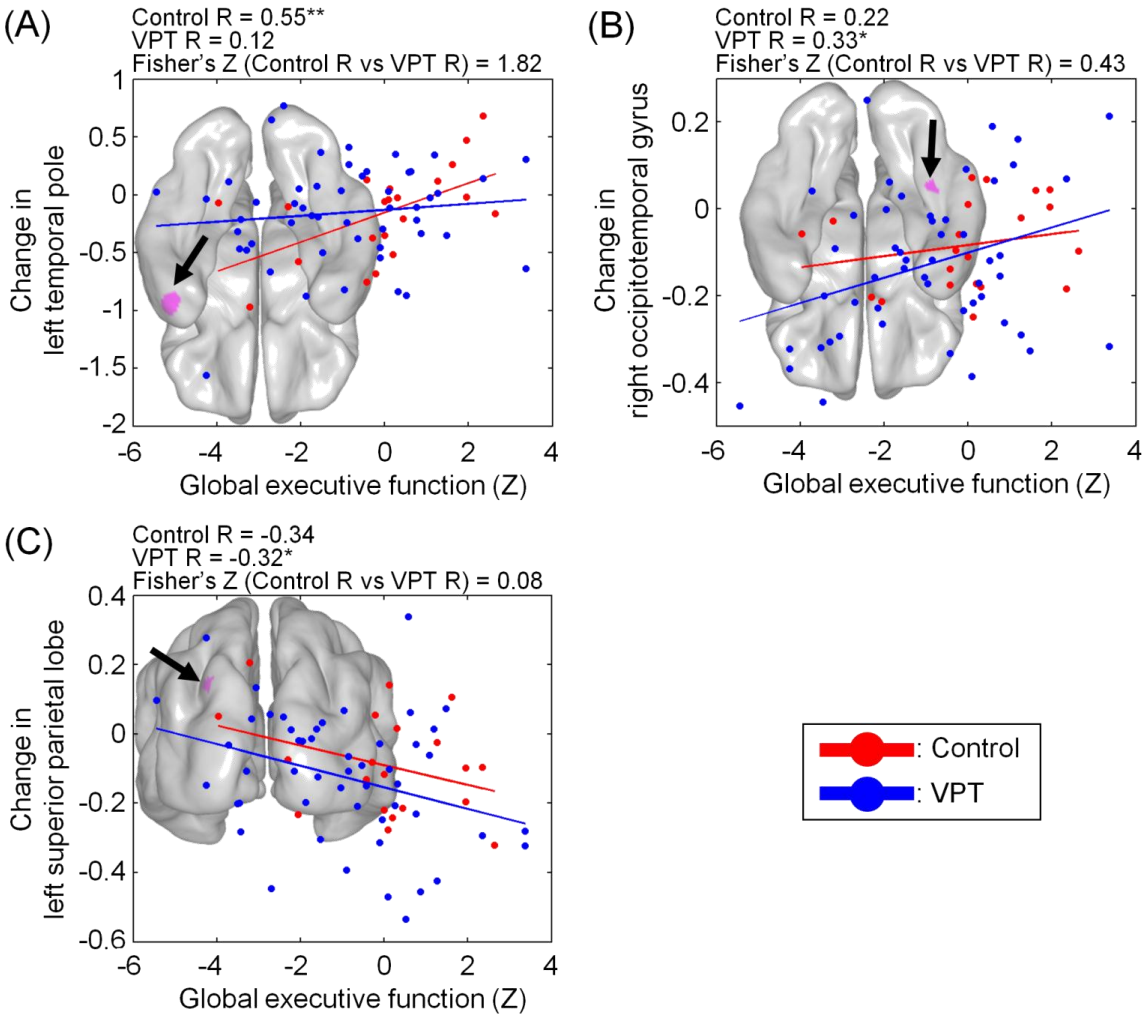
Controls' CT change in the left temporal pole (Figure 6-3A) was significantly and positively associated with global EF score ($r = 0.55$, $p = 0.009$). The preterm group displayed a non-significant positive correlation. The correlations did not significantly differ between groups, although the p value was at borderline significance levels (Fisher's $Z = 1.82$, $p = 0.068$). Adjusting for baseline CT (i.e. CT at Time 1) in left temporal pole did not alter these associations (controls, $r = 0.60$, $p = 0.006$; preterm, $r = 0.10$, $p = 0.48$).

The preterm group showed a significant positive correlation between global EF scores and CT change in the right occipitotemporal gyrus ($r = 0.33$, $p = 0.018$) (Figure 6-3B) and significant negative correlation in left superior parietal lobe ($r = -0.32$, $p = 0.020$) (Figure 6-3C). In both regions, the control group showed correlations which were non-significant and in the same direction as the preterm group. Controlling for baseline CT region-specific values did not alter these associations: the preterm group showed a significant positive correlation between global EF score and CT change in right occipitotemporal gyrus ($r = 0.30$, $p = 0.03$) whilst results were not statistically significant for controls ($r = 0.27$, $p = 0.24$); CT change in left superior parietal lobe was

significantly and negatively correlated with global EF score in preterm participants ($r = -0.28$, $p = 0.04$); results were non-significant for controls ($r = -0.32$, $p = 0.17$).

Figure 6-3

Correlation between CT change (mm) and global executive function scores.



*P < 0.05; **P < 0.01

6.2.2.3 Correlation between longitudinal cortical thickness change and gestational age

Results of the correlation analysis carried out in the preterm group between CT change in the 'top 1%' regions and gestational age identified only one significant cluster (< 20 vertices). This was centred in the left superior parietal lobe, where a negative correlation was observed between CT change and gestational age (r= -0.33; p=0.02).

6.3 Discussion

The results will be discussed sometimes in relation with cross-sectional and longitudinal analyses involving the participants scanned at both time points (Figure A-1 and Figure A-2 in Appendix). These should be distinguished from Chapter 4 and 5's analyses which involved all participants available, regardless of whether they were scanned at only one or both time points. Unless stated otherwise, references will be made to the cross-sectional and longitudinal analyses with the participants scanned twice rather than to Chapter 4 and 5's all-participants analyses.

Despite the apparent differences in longitudinal CT changes between preterm-born individuals and controls, conventional mass-univariate statistical methods investigating the interaction between group and time points did not reveal any between-group statistically significant differences in longitudinal CT changes – this was true both when involving all participants (Chapter 5) and when including only those scanned twice. This could be because mass-univariate methods apply overly stringent corrections for multiple comparisons to avoid Type I errors (Ecker et al., 2010). However, SVM, a multivariate approach which can more sensitively detect spatially distributed subtle effects, successfully classified brain images acquired at Time 2 with a classification

accuracy of 86.5%, based on spatially distributed differences in CT at Time 1. This suggests that the region specific cortical alterations following preterm birth are likely to persist during the second half of adolescence and still be present by early adulthood.

The spatially distributed regions in which CT best discriminated between the groups ('top 5%') included bilateral temporal poles and inferior temporal gyri, bilateral superior parietal lobes, right occipitotemporal and lingual gyri, as well as bilateral medial frontal cortex. In most of these areas, preterm individuals displayed greater relative decrease (i.e. greater decrease or smaller increase) in CT compared to controls, with the exception of left temporal pole in which preterm group displayed both greater and smaller relative decreases compared to controls (Figure 6-2). Considering the CT decreases observed in normative samples during adolescence (O'Donnell et al., 2005; Shaw et al., 2008; Tamnes et al., 2010), the observation that the relative CT thinning was greater in preterm participants in most of the 'top 5%' regions could reflect processes of cortical development 'catch-up' in this group.

Within the 'top 5%' regions, those with the highest discriminability ('top 1%') were selected again. Such selection was made so that structure-function associations could be investigated in the areas with the most prominent between-group differences in patterns of spatially discriminating features. Within these 'top 1%' regions, vertex-wise correlation analysis was carried out between CT change and global EF (acquired at Time 2). This yielded three clusters (left temporal pole, right occipitotemporal gyrus and left superior parietal lobe) where either control or preterm group showed significant 'CT change'-'Global EF' associations (i.e. there was no cluster in which both groups showed significant correlations). Among these regions (Figure 6-3), left temporal pole

displayed significant associations (between CT decrease and lower EF) in only the control group. On the other hand, only the preterm group displayed significant correlations between EF scores and CT change in right occipitotemporal gyrus and left superior parietal lobe. CT decrease was associated with worse EF in the right occipitotemporal gyrus and with better EF in the left superior parietal lobe. It is notable that, in these regions, only the preterm group showed significant CT decreases between Time 1 and Time 2 (Figure A-2).

As far as I am aware, this is the first study to investigate longitudinal CT changes and cognitive outcome following preterm birth. The correlations in the three clusters mentioned in the previous paragraph will be discussed in the subsections below, one for each region.

6.3.1 Left temporal pole

The finding of both greater and smaller relative decreases in CT in left temporal pole (Figure 6-2) is complex to interpret. Previous studies reported both decrease and increase in the temporal pole during adolescence. For example, Gogtay et al. (2004) acquired structural MRI images of the brain in a normative sample between ages 4 and 21 years, scanning every other year for 8-10 years, and observed constant CT decrease in temporal pole throughout the whole period. In contrast, Mills, Lalonde, Clasen, Giedd, & Blakemore (2012) reported temporopolar CT increase from age 11 until 19.4 years followed by decrease up to the age of 24 years (scanned 2-7 times). Also, Tamnes et al.'s (2010) cross-sectional study reported similar findings from participants between ages 8 and 30 years. After parcellating the brain into 33 regions, all regions showed

both significant linear and quadratic decrease (i.e. decrease which was rapid initially and slower at older age) in CT, with the exception of temporal pole and entorhinal cortex where statistically non-significant and tiny increase in CT was observed (Tamnes et al., 2010).

The inconsistency of these findings could reflect differential time-dependent trajectories of development for specific subdivisions of the temporal pole (Shaw et al., 2008), as has been observed in other regions including the hippocampus where volume was found to increase in its posterior region and decrease in its anterior region between ages 4 and 25 years (Gogtay et al., 2006), as well as thalamus, striatum and pallidum (Raznahan et al., 2014). Within the temporal pole, Shaw et al. (2008) observed three different CT development trajectories between ages 3.5 and 33 years (Figure 3-1). The ventral and posterior portion displayed cubic trajectory (increase during early childhood, rapid decrease until mid-20s when it stabilised), superior and lateral portion showed quadratic trajectory (increase followed by decrease, with the peak in late adolescence) and medial portion showed linear trajectory (constant decrease).

CT decrease in left temporal pole correlated with lower global EF scores in controls, whereas this association was non-significant for preterm-born individuals. Therefore, these findings could suggest that in normative samples greater CT decrease in left temporal pole between mid-adolescence and early adulthood is associated with worse cognitive outcome. However, this is not conclusive because, as indicated in the previous paragraph, this cluster could be subdivided into regions with differential CT development trajectories, both in terms of structure (Fan et al., 2013) and function (Fan et al., 2013; Pascual et al., 2013).

Fan et al. (2013) acquired structural and functional MRI images from participants aged between early 20s and early 30s. They segmented temporal poles into three subregions (dorsal, medial and lateral regions) based on their anatomical connectivity features, and identified structural connectivity (white matter (WM) fibre tracts branching out from each temporal pole subregion to other areas) and resting state functional connectivity (regions in which brain activity is correlated with that of each temporal pole subregion during resting state (i.e. when participants are not doing any task)). For the structural connectivity, the extent of connection was assessed between each temporal pole subregion and 43 brain areas excluding the cerebellum. The three temporal pole subregions showed significantly different structural connectivities to the 43 individual regions. Also, major WM fibre tracts (i.e. uncinate fasciculus, inferior longitudinal fasciculus, middle longitudinal fascicle, inferior fronto-occipital fasciculus, and inferior thalamic peduncle) differentially branched out from each temporal pole subregion (i.e. some regions had more fibres of certain types). In addition, there were 17 brain regions which were structurally connected with temporal pole areas in at least 50% of participants. These areas were connected to each temporopolar subregion with different strengths. In the left hemisphere, (1) lateral temporal pole showed stronger connections with superior frontal gyrus (orbital part), olfactory cortex, gyrus rectus, insula, putamen (lenticular nucleus), prefrontal-connected thalamus, and occipital-connected thalamus, (2) medial temporal pole was connected more with the parahippocampal gyrus, inferior temporal gyrus, fusiform gyrus, hippocampus, amygdala, and all the 3 thalamic subregions (prefrontal-, temporal- and occipital-connected thalami), and (3) dorsal temporal pole was most prominently connected with inferior frontal gyrus (orbital part), insular cortex, superior temporal gyrus, and middle temporal gyrus. In the right

hemisphere, (1) the lingual gyrus was most strongly connected to lateral temporal pole and (2) dorsal temporal pole was weakly connected with all the 3 thalamic subregions.

Fan et al.'s (2013) resting state functional connectivity analysis also revealed differential networks involving each temporal pole subregion (lateral, medial and dorsal). The patterns of connections were similar in both hemispheres, and two types of networks were identified: One showing positive correlations (i.e. regions which share similar activity patterns with temporal pole subregions) and the other displaying negative correlations (i.e. regions displaying increased activity when temporal pole subregions show decreased activity and vice versa). The positively correlated regions for lateral temporal pole included middle temporal gyrus, insula, posterior temporoparietal junction, and areas of the default mode network (DMN) encompassing the medial prefrontal cortex and posterior cingulate gyrus. Brain activities in medial temporal pole was positively correlated with those in ventral medial prefrontal cortex, subcallosal gyrus, orbitofrontal cortex, fusiform gyrus and medial temporal structures, including the parahippocampal gyrus, hippocampus, and amygdala. For dorsal temporal pole, the positively correlated regions were superior temporal gyrus, middle cingulate gyrus, supplement motor areas, anterior temporoparietal area, and perisylvian cortex, including the inferior frontal language areas and insula. On the other hand, regions showing negative correlation with lateral medial temporal pole were the bilateral dorsal prefrontal cortex, posterior parietal cortex, and dorsal precuneus. Medial temporal pole was negatively correlated with dorsal precuneus, part of the anterior cingulate gyrus, lateral middle frontal gyrus, and bilateral cerebellar Crus I/Crus II lobules and vermis areas. Dorsal temporal pole showed negative correlation with the DMN areas (including lateral inferior parietal lobule, posterior cingulate gyrus and precuneus) and bilateral cerebellar Crus I and Crus II lobules.

Also, significant differences in resting state functional connectivity was observed among temporal pole subregions, as revealed with paired t-tests (Fan et al., 2013). Compared to lateral temporal pole, medial temporal pole displayed stronger connections with the bilateral lateral orbital frontal cortex, posterior parietal cortex, and dorsal precuneus and also weaker connections to frontopolar, dorsomedial prefrontal cortex, and posterior cingulate cortex. Medial and lateral temporal poles, compared to dorsal temporal pole, showed better connectivity with DMN regions, including the posterior cingulate gyrus and precuneus, temporoparietal junction, and medial prefrontal cortex. Also compared to dorsal temporal pole, lateral temporal pole had better connection with the dorsomedial prefrontal cortex, whereas medial temporal pole were better connected with the orbital cortex. Regions which were more strongly connected with dorsal temporal pole compared to with medial temporal pole or lateral temporal pole were the supplementary motor area and perisylvian cortex.

It is notable that a number of regions named by Fan et al. (2013) in the previous three paragraphs (which were structurally and functionally connected to temporal pole) are related with language processing. For example, anterior temporal area including temporal pole is implicated in semantic processing (see Bonner & Price (2013)). Also, superior/middle/inferior frontal gyri, medial frontal, fusiform and inferior parietal areas were implicated in semantic association tasks which required participants to indicate whether a pair of presented words were semantically related to each other (Ghosh, Basu, Kumaran, & Khushu, 2010). Considering that the present study's HSCT task as it required judgement of semantic relationships between words, these past findings seem consistent with the present finding of EF scores being significantly lower in the preterm

group compared to controls. Additionally, preterm group's significantly lower EF seems to be reflected by the nearly significant group difference ($p = 0.068$ (see second paragraph of section "6.2.2.2") in 'CT change'-EF association. However, this link between the regions reported in (Fan et al., 2013) and language function is more speculative than conclusive. This is because the vast number of regions reported throughout the brain suggest its involvement in a wide range of functions rather than one particular set of functions, so it is inappropriate to limit their involvement to just language processing. Furthermore, present study's left temporal pole cluster did not overlap with the temporopolar seed regions used in (Fan et al., 2013).

On the other hand, the left temporal pole cluster overlapped with anterolateral temporal pole (described near the end of next paragraph) which covered some seed regions used in Pascual et al.'s (2013) resting state functional connectivity analysis (in adults aged 18-35 years). Forty seed regions (spheres with 2mm radius) were defined in the temporal pole. For this, temporal pole was divided into 6 coronal sections, with each section separated by 4mm, from the front end of the temporal lobe to the limen insulae (frontotemporal junction). On each section, seeds were placed at a regular interval. Then, regions were identified which were functionally connected to the temporopolar seed regions. Subsequently, the hierarchical clustering was conducted. Its procedure was (1) to group seed regions sharing similar functional connectivity topography together to form large groups, (2) and, in the same manner, continue dividing each group into subgroups and then divide the subgroups into smaller groups. The first level clustering identified two networks, each involving dorsal temporal pole and ventral temporal pole, respectively. The network involving ventral temporal pole could be subdivided into subnetworks including anterolateral or ventromedial temporal poles. These groupings were largely in agreement with manual segmentation, which was carried out before the

hierarchical clustering, into the cytoarchitectonic areas of temporal pole defined by Ding et al. (2009, as cited in Pascual et al., 2013), indicating concordance between structural and functional connectivities.

Then, Pascual et al. (2013) regrouped temporal pole into 4 subregions (dorsal, ventromedial, medial and anterolateral parts), considering altogether their functional connectivity, their locations in terms of cytoarchitectonic subregions, and the clustering analysis. (1) Dorsal temporal pole was functionally connected with regions resembling somatosensory-auditory network. The regions fully encompassed insula and central sulcus, which extended beyond post and precentral gyri, to superior temporal gyrus and dorsomedial prefrontal areas. The network included part of orbitofrontal areas, especially in the left hemisphere. Also, these regions covered regions considered to be language network (Pascual et al., 2013). (2) The ventromedial temporal pole showed functional connectivity with areas which were similar to visual network, located mostly in the ventral and middle-to-front parts of the brain. The regions extended posteriorly from the temporal poles ventrally and medially onto parahippocampal gyrus, medial and lateral occipitotemporal gyri, and laterally onto inferior and middle temporal gyri. Also included in the network were ventromedial prefrontal areas mainly encompassing gyrus rectus, orbitofrontal and superior frontal gyri. (3) Medial temporal pole was functionally connected with paralimbic regions. These areas were similar to the visual network associated with ventromedial temporal pole, but included supramarginal and superior temporal gyri as well as bigger portion of orbitofrontal area. (4) Lastly, the anterolateral temporal pole displayed functional connection with areas looking like default-semantic network; the regions resembled both semantic network (Binder et al., 2009, as cited in Pascual et al., 2013) and DMN. The regions covered almost the whole lateral as well as mid-anterior aspects of the temporal cortex, most of the medial and ventral sides of

prefrontal cortex as well as superior and inferior frontal gyri. Part of precuneus and postcingulate gyrus were also included.

Among these 4 subregions of temporal pole, the anterolateral part encompassed the left temporal pole cluster of the present study discussed in this section. The DMN, which resembled the functional network stemming from this subregion, is a group of regions which show activity decrease while carrying out a goal-directed task (Raichle et al., 2001) (e.g. executive control tasks). This network, as derived by resting state fMRI scanning in White et al. (2014), was found to cover similar regions between controls and preterm adults (gestational age (GA) < 33 weeks; mean age: 28-29 years) and displayed no group difference in the amplitude (i.e. extent of signal fluctuation) of the time series (i.e. a series of signal changes recorded throughout the fMRI scanning), between frequencies (i.e. gap between peaks in a time series) of 0.05 and 0.15 Hz. However, causal links (i.e. past activity of one network affects the current or future activity of the other network) between DMN and other functional networks were significantly weaker in the preterm group (White et al., 2014). Such weakened causal relationships in the preterm group included those (1) between a subdivision of salience network (which includes bilateral anterior insula and dorsal anterior cingulate area and is activated by cognitive, emotional or homeostatic salience (as described in White et al., 2014)) and DMN and also (2) between the posterior aspect of DMN (including mainly posterior cingulate gyrus and precuneus) affecting central executive network (including mostly lateral prefrontal and parietal areas and activated by tasks requiring externally-focused attention, working memory and response selection (Corbetta et al., 2002; Hester et al., 2007; Meda et al., 2008, all as cited in White et al., 2014).

These resting state fMRI findings, which suggest a functional connection between the present study's left temporal pole cluster and DMN, could be indirectly relevant to the current study for two reasons. First, CT and resting state functional connectivity has been found to be related. An example is provided by (van Tol et al., 2013). They observed smaller CT in right dorsomedial prefrontal cortex (which is part of DMN) in patients with major depressive disorder compared to in healthy controls. Then, they derived resting state functional network using this area as a seed region (i.e. they identified the regions where resting-state brain activity was associated with that in right dorsomedial prefrontal cortex). This was followed by a correlation analysis between the CT of the seed region and the strength of connectivity within its resting state functional network. The results showed a positive association between CT and functional connectivity in this region. That is, in the patient group and in the right dorsomedial profrontal cortex, the thinner the cortices were, the less coherent the functional network was. A second reason is the association between the DMN and the central executive network (comprising dorsolateral prefrontal and posterior parietal areas). Specifically, attention demanding tasks (Fox et al., 2006, as cited in Goulden et al., 2014) activate central executive network whereas it deactivates DMN, and therefore the two networks are anti-correlated with each other in a sense. It was also shown that transcranial magnetic stimulation to the posterior middle frontal gyrus, which is a region of the central executive network, supressed the DMN activity (Chen et al., 2013), suggesting an executive function task could affect DMN activity. Taking these together, I speculate that the preterm group's altered CT in the left temporal pole cluster (of the present study) could affect resting state connectivity within DMN, resulting in it being insufficiently suppressed by the central executive network during executive function tasks. Group difference in EF task performance observed in the present study could be attributed to the group difference in such chain of processes.

Overall, Fan et al. (2013) and Pascual et al. (2013) demonstrated that the temporal pole is a heterogeneous region and therefore its subregions should be considered separately. Also, temporopolar CT could be related with resting state functional connectivity of the DMN which is deactivated during attention-demanding tasks. Although speculative, difference in these links could result in a group difference of EF. However, there is another important question to ask: is CT a representative measure of temporopolar development? Evidence for this is scarce. In Tamnes et al.'s (2010) cross-sectional study mentioned above, the effect of age was biggest on CT compared to on WM measures (volume, fractional anisotropy and mean diffusivity) - that is, CT rather than WM measures most uniquely represented age-related changes - in all brain regions *except* in temporal pole (where age effect was weakest on CT and biggest on WM volume), entorhinal and parahippocampal cortices. This suggests that WM volume could reflect brain development better than CT in the temporal pole.

6.3.2 Right occipitotemporal gyrus

A number of studies showed the relevance between the EF tasks used in the present study and the right occipitotemporal gyrus. For example, brain activity in right occipitotemporal gyrus during semantic category judgement task (e.g. Are [CORN] and [RICE] in the same category?) was negatively correlated with level of reading skill (assessed with Word Attack test of pseudoword reading (Woodcock & Johnson, 1989, as cited in Shaywitz et al., 2002)) (Shaywitz et al., 2002). This could be relevant to the present study's HSCT task because, as described in the Methods section, one of the observed strategies for the task used by healthy controls was naming words from a chosen semantic category (Paul W. Burgess & Shallice, 1996).

Another relevant task is a Go-no-go task which measures inhibitory ability - the HSCT task in the present study also had an inhibition condition where participants were required to suppress the normal response. Watanabe et al. (2002) reported that, during Go-No-Go task (which required participants to click a mouse button when presented with a Go signal and make no response at a No-go signal), the right occipitotemporal area was activated during the no-go condition as compared against baseline or the go condition (Watanabe et al., 2002). The contrast of No-go against Go conditions measures inhibition, based on the assumption that response selection (Go) and response inhibition (No-go) are separate processes (as explained in (Simmonds, Pekar, & Mostofsky, 2008)). Rubia et al. (2006) also used a slightly different version of Go-No-Go task in which participants were required to press left and right buttons when presented with left- or right-pointing arrows, respectively, and inhibit response when an up-pointing arrow appeared. They observed that, between ages 10 and 38 years,

occipitotemporal activation in the No-go vs Go contrast was negatively correlated with age.

Occipitotemporal area was also shown to be activated during not auditory, but visual presentation of single words (Petersen, Fox, Posner, Mintun, & Raichle, 1988). This could be relevant to this study in that participants could have "pictured" the words in their minds although such link is only speculative.

CT decreases in the right occipitotemporal gyrus were significantly correlated with lower EF scores in the preterm group, whilst the association was non-significant for controls (Figure 6-3B). Considering that CT decrease in this region was significant only in the preterm group (Figure A-2), these associations demonstrate that preterm individuals' executive function was worse as CT changes deviated more (i.e. greater decrease) from those observed in controls. These results are in line with Nosarti et al.'s (2008) findings investigating grey and WM volumes in a preterm-born adolescent sample in relation to cognitive impairment, which showed that, in general, smaller rather than bigger volume in the preterm group was indicative of their worse cognitive function (global executive function and language measures). Among the areas in which the preterm individuals' brain volumes were altered compared to controls, Nosarti et al. (2008) selected, for each tissue class, 4 regions where the preterm group had smaller volumes and 4 regions where preterm individuals had excess volumes. In all eight regions in which preterm group had smaller volumes (grey matter (GM) in middle and inferior temporal gyri and fusiform gyrus; WM in brainstem, middle and inferior temporal gyri and occipitofrontal fasciculus), there was a significant association between every 25% decrease and worse cognitive impairment in the preterm individuals.

In contrast, in only two regions (WM in posterior cingulate gyrus and GM in middle temporal gyrus) out of the eight areas where preterm group had bigger volumes, quartile increase in volume was predictive of the preterm group's cognitive impairment. Therefore, Nosarti et al. (2008) demonstrated that, in the regions showing reduced volume in the preterm group compared to the controls, the more severely reduced volume indicated the worse cognitive outcome. However, these findings are only partly consistent with the current findings because they did not involve right occipitotemporal gyrus. Also, Nosarti et al. (2008) looked at regions showing smaller volume (measured cross-sectionally) in the preterm group at adolescence whereas I looked at CT in a region (i.e. right occipitotemporal gyrus) showing (1) longitudinal decreases within each group which did not statistically differ between groups and (2) which was not significantly thinner in the preterm compared to controls at either time point when measured cross-sectionally.

The significant CT decrease in right occipitotemporal gyrus within the preterm group (Figure A-2) is consistent with a previous finding of linear CT decrease in this region between ages 3.5 and 33 years (see Figure 3-1) (Shaw et al., 2008). However, the association between decreasing CT and worse EF in both groups (non-significant in controls) observed in the present study is not unanimously supported by previous reports. A finding which was consistent with the present one was reported by Hartberg et al. (2010) who observed, in 20-to-56-year-old healthy controls, an association between smaller CT in the right occipitotemporal gyrus and lower VIQ. The VIQ was measured with Vocabulary subtest of WAIS-R. This could be relevant with the current study in that the EF tasks used in the present study are vocabulary-based.

Also, opposing findings to the present ones were also reported (Westlye et al., 2011; Zelazo, Craik, & Booth, 2004). Westlye et al. (2011) reported that smaller CT in the right occipitotemporal gyrus was linearly associated with better executive control performance (which required inhibitory ability) in healthy adults (20-84 years), after controlling for gender and age. They used the Attention Network Test (ANT) which put together cued reaction time task (Posner 1980, as cited in Westlye et al., 2011) and the Eriksen flanker task (Eriksen & Eriksen, 1974, as cited in Westlye et al., 2011) to measure 3 largely independent components of attention: executive control, alerting, and orienting (Fan et al. 2009, as cited in Westlye et al., 2011). Executive control is related with the ability to resolve cognitively incongruent stimuli, the alerting with achieving and maintaining a vigilant state, and orienting with selecting and orienting toward sensory information (Posner and Petersen 1990; Posner 2008, both as cited in Westlye et al., 2011). During the task, participants were first presented with (1) no cue, (2) a cue in the centre of the screen, (3) double cue in the centre or (4) spatial cue (away from the centre). The cue was a fixation cross except for the double cue, which was double asterisks with or without a fixation cross. With the cue(s) remaining on the screen (when there was one), an arrow was presented below or above. Then, the direction of the arrow was required to be indicated by participants by pressing a left or right button. The arrow was sandwiched by (1) two incongruent arrows (e.g. ← → ←), (2) two congruent arrows (e.g. ← ← ←) or (3) two neutral lines. Alerting was indicated by reaction time difference between the no cue and the center cue conditions. Orienting was measured as the contrast between the center cue and the spatial cue conditions. Executive control was measured as the difference in reaction times between congruent versus incongruent conditions, which required motor inhibition. This could have indirect relevance to HSCT task used in the current study, which required cognitive inhibition.

An important thing to consider regarding Westlye et al. (2011) and Hartberg et al.'s (2010) studies, though, is that they cannot be directly compared to the present study. This is because they looked at cross-sectional differences in CT rather than longitudinal changes. In addition, they used older participants than those in the present study.

A lack of association, in the control group, between normal CT development (i.e. decrease) and EF improvement during adolescence is inconsistent with the report of EF improvement between childhood and adulthood (Zelazo et al., 2004). Zelazo et al. (2004) used three age groups: children (age 8.2-9.5 years), young adults (19.5-26.6 years) and elderly adults (65.8-74.2 years). The executive function tasks were visually cued colour-shape task and auditorily cued number-numeral tasks. During the visual task, participants were shown a row of 4 target items, each differing in shape and colour (red triangle, green circle, blue square, yellow diamond). On each trial, a test item was presented below the row, which shared the shape or colour from the row (e.g. green diamond). With the test item, either "X" or "Y" appeared, the former requiring sorting the test item according to the colour of the target items and the latter according to the shape. During the auditory task, participants watched a 2x2 grid. In each quadrant, there were from 1 to 4 small squares, together with a numeral (e.g. "4") between 1 and 4. The number of squares did not match the numerals. Participants heard numbers between 1 and 4 being read out in either male or female voice. Using four keys, each indicating each grid, participants were required to press a key corresponding to (1) the number of squares when hearing male voice or (2) the numeral when hearing female voice. The results of visual task showed significantly fewer perseverative errors made by young adult group compared to the children and elderly adults, indicating that executive

function improved from childhood to early adulthood and then declined by late adulthood. On the other hand, auditory task performance produced significantly more perseverative errors in children than the other two age groups, showing the executive function improvement between childhood and early adulthood, which was maintained until late adulthood. Overall, Zelazo et al. (2004) observed EF improvement between childhood and early adulthood.

I speculate that such lack of link between CT decrease and EF improvement observed in the present finding could be due to small sample size (Control n = 21). Also, it should be noted that Zelazo et al.'s (2004) findings looked at EF at different age groups, and therefore also cannot be directly compared to the present study which looked at EF at mean age 20 years only. Therefore, a complete interpretation of the present data from a developmental perspective would be possible only if EF at Time 1 were included. This will be investigated in a future study.

6.3.3 Left superior parietal lobe

The left superior parietal lobe has been implicated in executive processing assessed with tasks involving sentence comprehension (Otsuka, Osaka, & Osaka, 2008; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008), which was the basic requirement of the HSCT task used in the present study. The studies are described in the following two paragraphs.

Otsuka et al. (2008) measured executive function in elderly participants (62-76 years of age) using a Japanese version of reading span test (Otsuka et al., 2006, as cited in Otsuka et al., 2008). The test consisted of three phases: read + memory, recognition and baseline. During the "read + memory" phase, participants were shown 3 sentences and required to remember the underlined word. Additionally, to check whether the sentence was understood, participants were required to decide if the sentence was true or not (e.g. 'swimming is a field sport' – 'false') by pressing a left or right button. During the "recognition" phase, a word was presented at each trial and participants judged whether the word was presented in the "read + memory" phase by pressing a button. During the baseline, participants pressed any button after a visual cue. The results showed activation in left superior parietal lobe during "read + memory" phase, together with left anterior cingulate, dorsolateral prefrontal and ventrolateral cortices. Also, fMRI signal in the left superior parietal lobe as well as anterior cingulate cortex was positively and significantly correlated with the "read + memory" score. This appears to show the involvement of left superior parietal lobe in sentence comprehension as well as memory.

Meyler et al. (2008) classified children at age 11 years as good readers and poor readers, and the poor readers received 100 hours of intensive remedial instructions. Then, both groups were scanned with fMRI while performing a sentence comprehension task at three time points: before remediation (pre-remediation), immediately after the remediation (post-remediation) and at 1-year follow-up at age 12 years (follow-up). The task involved presentation of a sentence at each trial and required participants to judge whether they made sense by pressing a button (right-hand button for "sensible" and left-hand button for "not sensible"). There was a significant interaction between the effects of group and time points on task performance. That is, the poor readers showed significant improvement in sentence comprehension task performance from pre- to post-

remediation stages and also from post-remediation to follow-up. No significant improvement in performance was observed in the good readers. Both the area and extent of under-activation in the poor readers increasingly decreased across the three time points whereas an opposite pattern was observed for the over-activation in poor readers. Among such under-activated regions in the poor readers was the left superior parietal lobe, which showed decreased activation from pre- to post-remediation stages and finally disappeared at the follow-up, indicating normalisation of the activation. Such an association between increased involvement of left superior parietal lobe in sentence comprehension task and improved performance demonstrates the importance of this region in the task.

Although Otsuka et al. (2008) and Meyler et al. (2008) clearly demonstrated the involvement of left superior parietal lobe in sentence comprehension task, it should be considered that only COWAT scores and not HSCT scores were significantly different between groups in the participants included in the SVM analysis. COWAT tasks do not require sentence comprehension, but long-term memory retrieval which requires selective attention, mental set shifting, internal response generation, and self-monitoring (Patterson, 2011). A consistent finding from Wager & Smith (2003) suggests involvement of left superior parietal lobe in a more broad range of executive functions. Their meta-analysis of sixty functional neuroimaging studies (fMRI and positron emission tomography (PET)) revealed that superior parietal cortex was the only area which was activated in all three types of working memory (spatial, verbal and object) as well as three types of executive functions (continuous updating of working memory, memory for temporal order, and manipulation of information in working memory).

A negative correlation was found between CT change in left superior parietal lobe and executive function scores in both groups, although only in the preterm group results reached statistical significance. In other words, greater CT decrease in left superior parietal lobe was associated with better EF scores. In this cluster, CT decreased significantly within the preterm group (Figure A-2). Therefore, the findings showed an association between the normal course of CT development (i.e. decrease) and EF improvement. This is consistent with the findings in the normative samples which showed CT decrease in left superior parietal lobe (Shaw et al., 2008) and concurrent EF improvement (Zelazo et al., 2004) during adolescence. The lack of significant 'CT change'-EF association in the control group could be due to small sample size, as mentioned in the last paragraph of the previous section.

Within the preterm group, CT change in this cluster was further negatively associated with gestational age (i.e. greater CT decrease was associated with older gestational age). Considering that CT normally decreases during late adolescence in this region (Shaw et al., 2008; see Figure 3-1), this could indicate greater 'catch-up' in CT development by less premature subgroup of the preterm group. Such a possibility was already mentioned in the last part of section "4.3.1.3" in Chapter 4. To recap, cross-sectional CT difference between control and preterm groups came mostly from preterm subgroups with lower GA or birth weight (Bjuland et al., 2013; Martinussen et al., 2005), and such relationship was more prominent in early adulthood (Bjuland et al., 2013) than in adolescence (Martinussen et al., 2005). These suggest that the CT alteration could be more permanent in lower GA group whereas the higher GA group 'catches up' more with controls.

Such advantage of higher GA regarding preterm group's CT could be relevant with the association between higher GA and better connectivity among brain regions, especially the connectivity from and to the superior parietal lobe. A recent cross-sectional study reported a significant positive association between length of gestation (29-42 weeks) and local network efficiency particularly in bilateral superior parietal cortex (Kim et al., 2014). Kim et al. (2014) suggested that this association could affect the strength of interconnectivity among the "hubs" within the "rich club" which is critical for global neural communication and integration (Collin, Sporns, Mandl, & van den Heuvel, 2014) – "hubs" refer to heavily connected regions, and "rich club" refers to a group of highly interconnected hubs, as described in Collin et al. (2014). In addition, bilateral superior parietal cortices were identified to be part of the rich club in adulthood (mean age: 29 years) (Collin et al., 2014) although not during childhood (mean age: 8 years) (Kim et al., 2014). Collin et al. (2014) measured both structural and functional connectivities while Kim et al. (2014) examined only structural connectivity. Taken together, these past findings suggest that preterm individuals with high GA, compared to those with lower GA, make better use of the left superior parietal lobe as part of (1) a local network during childhood (Kim et al., 2014) and (2) the rich club in adulthood (Kim et al., 2014). I speculate that such better use could contribute to the 'catch-up' in development of CT and cognitive functions in this region. Therefore, future research is warranted which divides the current sample according to GA.

6.3.4 Summary

The SVM method identified spatially distributed groups of regions where control and preterm individuals showed CT difference at Time 1. Based on the spatial patterns of

difference from Time 1, the group membership of brain images acquired at Time 2 could be predicted with high accuracy. The regions showing largest group differences were bilateral temporal poles and inferior temporal gyri, bilateral superior parietal lobes, right occipitotemporal and lingual gyri and bilateral medial frontal areas. In these regions except in the left temporal pole, the preterm group showed greater relative decrease in CT than controls from Time 1 to Time 2. Left temporal pole displayed both greater and smaller relative CT decreases in preterm group compared to controls. This could reflect that subregions of the temporal pole have different development trajectories.

When global EF at Time 2 was correlated with CT change in these regions, a strong and significant association was found in the left temporal pole (positive association in control group). Significant, but weak associations were also observed in the right occipitotemporal gyrus (positive association in preterm group) and the left superior parietal lobe (negative association in preterm group). Significant associations observed in only one group per region could reflect low statistical power due to small sample size.

In the left temporal pole, CT decrease was associated with worse EF, but this was inconsistent with previous findings. This inconsistency could be attributed to the structural heterogeneity of the temporal pole. In addition, it was reported that left temporal pole in general was functionally and structurally connected with regions involved in semantic processing as well as the DMN, although those studies suggest that the present study's left temporal pole cluster in particular would be connected to the latter only. Altered CT in the preterm individuals could lead to insufficient suppression of the DMN activity when the central executive network is activated, resulting in

subnormal EF. Also, age effect was stronger on WM volume than on CT in this region, so WM volume rather than CT could be a more suitable measure to represent temporopolar development.

The association between CT decrease in right occipitotemporal gyrus and worse EF in the preterm group was consistent with past research findings. Also, this region is directly involved in the performance of HSCT task (requiring semantic processing and inhibition) used in the present study. I observed, only in the preterm group, (1) significant CT decrease in this region and (2) association between greater CT decrease and worse EF. These observations appear to indicate that greater deviation from the control group's development trajectory resulted in worse EF outcome. Also, such 'CT decrease'-'worse EF' relationship in the preterm group and control group's lack of 'CT change'-EF association is not fully consistent with previous research findings.

In the left superior parietal lobe, greater CT decrease was associated with better EF. This was consistent with past research findings. Also, within the preterm group, the less premature individuals showed greater CT decrease, which could indicate developmental 'catch-up'. Studies showed that less prematurity was associated with better connectivity between superior parietal area and other regions. This suggests that preterm born individuals with higher GA use the region more efficiently and this could lead to recovery of CT. Future research should be carried out to investigate differential CT development trajectories in different GA groups.

Chapter 7: Conclusions

In this work I described cross-sectional and longitudinal cortical thickness (CT) measurements in individuals who were born very preterm from mid-adolescence (Time 1) to early adulthood (Time 2). Results showed greater CT in the preterm group compared to controls at Time 1 in extensive areas including lateral occipitotemporal and prefrontal cortices. By Time 2, the number and magnitude of areas showing greater CT in the preterm group substantially decreased. These results suggest a delayed cortical maturational trajectory in the preterm sample (Nosarti et al., 2008), as has been observed in other neurodevelopmental conditions, such as attention deficit hyperactivity disorder (Shaw et al., 2007; Tamnes et al., 2010). The hypothesis of delayed cortical maturation is supported by the findings from the longitudinal analyses, which showed that CT decreases occurred to a greater extent and in wider regions in preterm individuals than in controls - in both groups CT generally decreased from Time 1 to Time 2, following developmental patterns observed in normative samples (Shaw et al., 2008).

However, these results further showed that at both time points CT was smaller in the preterm group compared to controls in parahippocampal and insular regions. This could indicate that these regions are particularly vulnerable to long-lasting structural alterations following preterm birth, and may be permanently damaged.

CT changes in regions identified by a pattern classification approach (support vector machine (SVM)) were associated with executive function (EF) scores of Time 2 (which were significantly lower in the preterm group), suggesting that CT alterations following very preterm birth not only continue into adolescence and early adult life, but also have significant functional long-term consequences.

The mechanisms underlying cortical alterations in the preterm group remain unclear but could reflect altered neuronal differentiation in the cortical plate, a transient structure which is exuberant in the third trimester of gestation, during which extensive afferent fibres migrate from the cortical plate into the cortex to form their final connections, and play a fundamental role in the establishment of early neuronal networks (Kostovic, Judas, & Sedmak, 2011). Evidence from both animal models of perinatal brain injury and neuroimaging investigations of infants born very preterm suggest that the cortical plate may be vulnerable to pre- and perinatal events (Miller & Ferriero, 2009). Environmental disturbances of such critical developmental processes may have subsequent life-long consequences for cortical development, as well as underlie an elevated risk for cognitive deficits and psychopathology (i.e., represent a 'pre-symptomatic signature') (Ben-Ari, 2008).

7.1 Strengths and limitations

The main strength of this study is the use of both univariate and multivariate analyses approaches, with SVM showing significant predictive power for group classification at Time 2 based on spatial CT patterns at Time 1.

Limitations of this study include the slight age difference between the preterm and the control groups, which was controlled for in the analyses. A further limitation is the inclusion of term-born controls from the general population, which could differ from our study group in variables that have not been measured, although similar to preterm born individuals in gender and socio-economic status.

Another caveat of the study is that the two participant cohorts were born between 1979 and 1984 and were studied at the mean age of 15 and 19 years. Thus most of the scans were performed over 10 years ago. This can be a disadvantage, considering that brain imaging techniques have substantially improved since then. One noticeable advance is the increased sensitivity of scanning methods. For example, the magnetic field in magnetic resonance imaging (MRI) scanner can be as strong as 7 tesla which is more than four times stronger than 1.5 tesla used in the present study – stronger magnetic field can provides sharper images. However, techniques have advanced for processing and analysing brain images as well, which allows this issue to be overcome to a certain extent. For instance, in the present study, the limited brain image resolution was overcome by (1) the Constrained Laplacian Anatomic Segmentation using Proximity (CLASP) algorithm used for cortical surface extraction and (2) the random field theory (RFT) employed to correct the statistical output for multiple comparisons.

The standard of neonatal care has improved too, resulting in reduced mortality of babies born very preterm (Fanaroff, Hack, & Walsh, 2003). Younger and younger babies are now surviving. Between 1987 and 2000, the survival rate increased in the babies registered at the National Institute of Child Health and Human Development Neonatal Research Network (Fanaroff et al., 2003). There was a 7% rise (23% to 30%) in the survival rate of babies born with gestational age (GA) ≤ 23 while the survival rates increased by 25% (34% to 59%) and 18% (54% to 72%) in those born with GA 24 and 25 weeks, respectively (Fanaroff et al., 2003). The cohort in the present study was born before this period and therefore may not fully represent the increased proportion of lower-GA babies in the contemporary cohorts. However, studies with younger samples have reported alterations in similar cortical areas (Murner-Lavanchy et al., 2014), supporting the idea of regional specificity in terms of neurodevelopmental vulnerability following very preterm birth.

The inclusion of the same participants in both training and testing phases of SVM could have posed a risk of type I error, which could have potentially favoured the prediction accuracy. However, we demonstrated that the use of different participants in training and testing phases, which was free of within-subject correlation, produced extremely similar results.

Also, a considerable amount of information was lost in SVM analysis due to the reduction of sample size in order to include only the participants scanned at both time points. This problem could be tackled in a future study, employing mixed-effects SVM (Luts, Molenberghs, Verbeke, Van Huffel, & Suykens, 2012) which will be able to deal with missing observations across the time points and therefore allow inclusion of all

images available at either time point. Similarly, mixed effects regression could be used to derive the relationship between CT and cognitive outcome in all available participants.

Having only two time points also limited the present study to examining only a linear change in CT instead of non-linear changes. In addition, the intrinsic problem with having only two time points is that the gap between Time 1 and Time 2 could be too short (e.g. regions showing quadratic developmental trajectory where CT decreases slowly and non-significantly between Time 1 and Time 2, and then increases rapidly and significantly in the next 3 years) or too long (e.g. regions showing cubic developmental trajectory (e.g. increase followed by decrease)) to observe true CT development trajectory. For this reason, it would be beneficial to include images from more time points in future research.

Lastly, CT could have been underestimated in regions with greater cortical myelination and overestimated in less myelinated areas (Glasser & Van Essen, 2011).

7.2 Summary and conclusion

To summarise, the findings of this study with regards to adolescent cortical development following very preterm birth do not entirely support either the 'delayed neurodevelopment' or the 'permanent impairment' model. Our results suggest that each model could be applicable to certain areas of the cortex. These findings could be useful in predicting which cognitive functions may be better candidates for focussed neuroplastic training in preterm-born individuals (Pascoe et al., 2013). For instance,

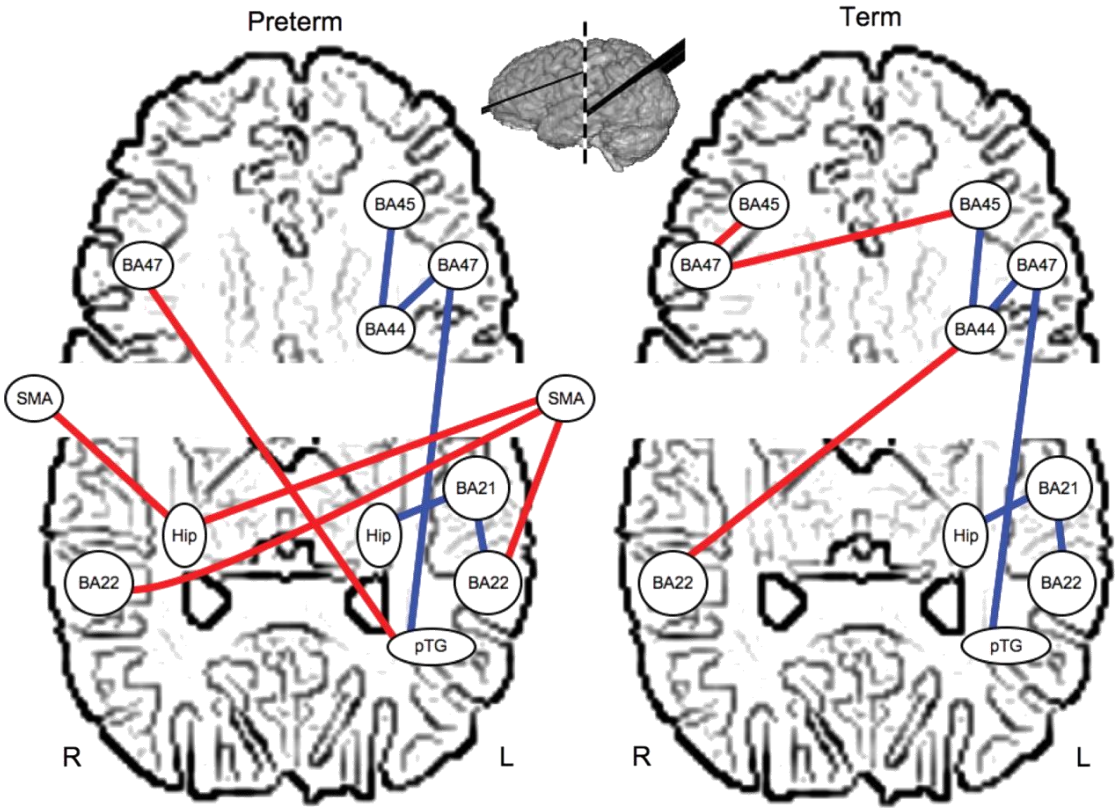
executive functions such as working memory and attention rely on areas of the prefrontal, parietal and cingulate cortices (Owen, McMillan, Laird, & Bullmore, 2005; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005), which do not show permanent structural deficits. So, these functions may be more responsive to such interventions than functions such as episodic memory, which depends on the parahippocampal areas (Eichenbaum & Lipton, 2008; Li, Lu, Li, & Zhong, 2010) that are more likely to remain structurally altered in adulthood. However, interventions may not have to be limited by this issue because, when a brain area is damaged, a homologous region in the other hemisphere could activate instead (Muller et al., 1998) or an alternative network could be developed to compensate for the damage (Just & Varma, 2007).

On the other hand, it could be important to consider this issue of 'delayed neurodevelopment' versus 'permanent impairment' not only in terms of structure, but also regarding the association between structure and function. Several functional MRI (fMRI) studies have provided such findings (Narberhaus et al., 2009; Salvan et al., 2013; Schafer et al., 2009). Without observing significant group difference in task performance, Salvan et al. (2013) reported significantly different patterns of activity change between control and preterm individuals across repeated trials of a verbal learning task (e.g. activation in right anterior cingulate and adjacent regions progressively increased in preterm group, but decreased in controls), while Narberhaus et al. (2009) observed a preterm group activating a different set of regions during a visual learning task (for details of these studies, see section "2.3.2"). Schafer et al. (2009) observed significant differences between controls and preterm children (GA 28.6 ± 2 weeks; age 12-13 years) in functional connectivity patterns within regions activated during a semantic association task (Figure 7-1) in the absence of group difference in (1)

task performance or (2) the regions activated by the task. These studies indicate that, for certain tasks, preterm individuals use (1) different sets of brain regions (Narberhaus et al., 2009) or (2) different strategies (Salvan et al., 2013) even when using the same set of regions as controls (Schafer et al., 2009). I speculate that such different use of the brain by the preterm group could reinforce structural alterations in their brains.

Figure 7-1

Functional connectivity in preterm and control groups, within the regions significantly activated during semantic association task. Blue lines represent significant connectivity between regions observed in both groups. Red lines represent group-specific connectivity. This figure has been adopted from Schafer et al. (2009).



These studies are important in highlighting the exquisite capacity of the preterm brain to adapt to a suboptimal neurodevelopment. Results such as these could be used to inform the development of neuroplastic training, which could focus either on the recovery of the original network or on the enhancement of alternative networks. The two types of training would require different sets of cognitive strategies involving different networks.

The findings of this study further suggest that CT changes in regions displaying patterns of spatially discriminating features between preterm-born individuals and controls at adolescence are associated with functional outcome at early adulthood. Mapping dynamic cortical changes throughout critical phases of development following very preterm birth could aid the identification of individuals at high-risk for cognitive impairment, who could be prospectively identified and closely monitored – to decide if, when and what interventions may be appropriate.

Appendix

Figure A-1

Cross-sectional differences in cortical thickness using only 72 participants scanned at both time points. Age and gender were controlled for. Blue-turquoise regions represent clusters (cluster $p \leq 0.05$) and red-yellow regions represent cluster peaks (vertex $p < 0.05$).

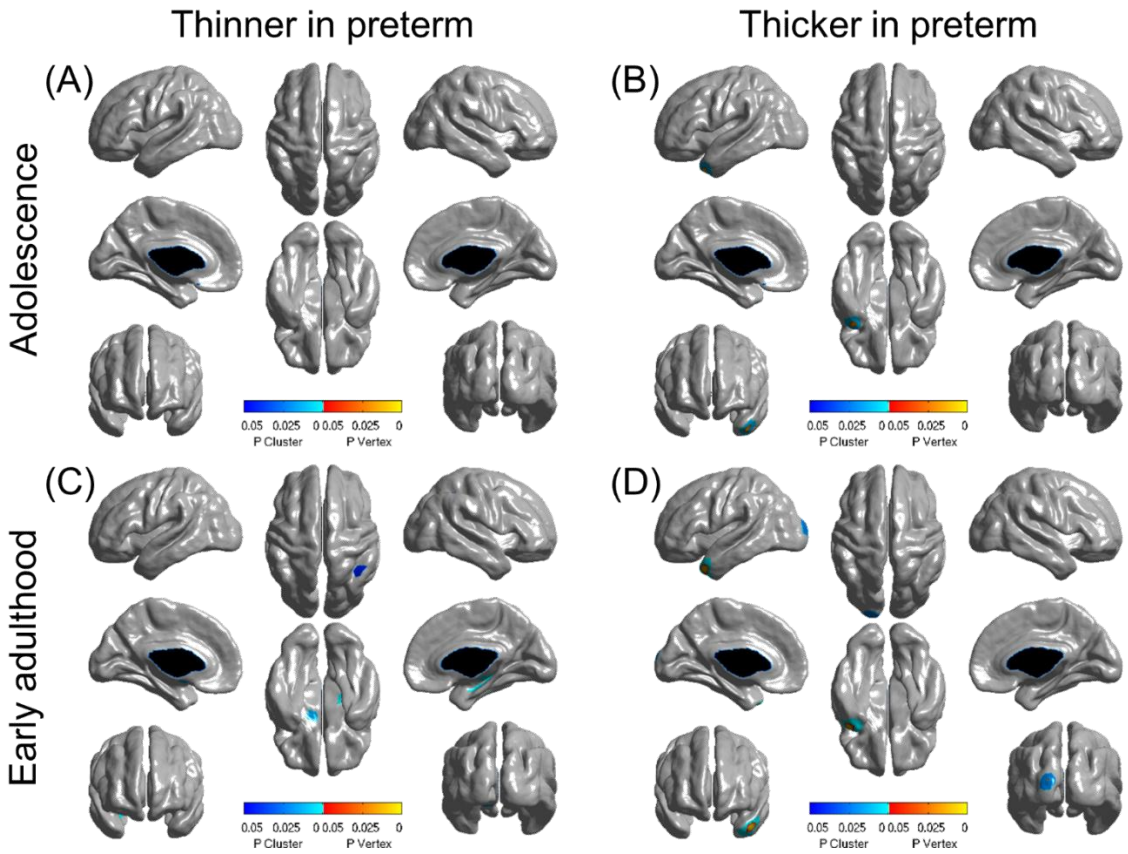


Figure A-2

Within-group longitudinal changes in cortical thickness using only 72 participants scanned at both time points. Gender was controlled for. Blue-turquoise regions represent clusters (cluster $p < 0.05$) and red-yellow regions represent cluster peaks (vertex $p < 0.05$).

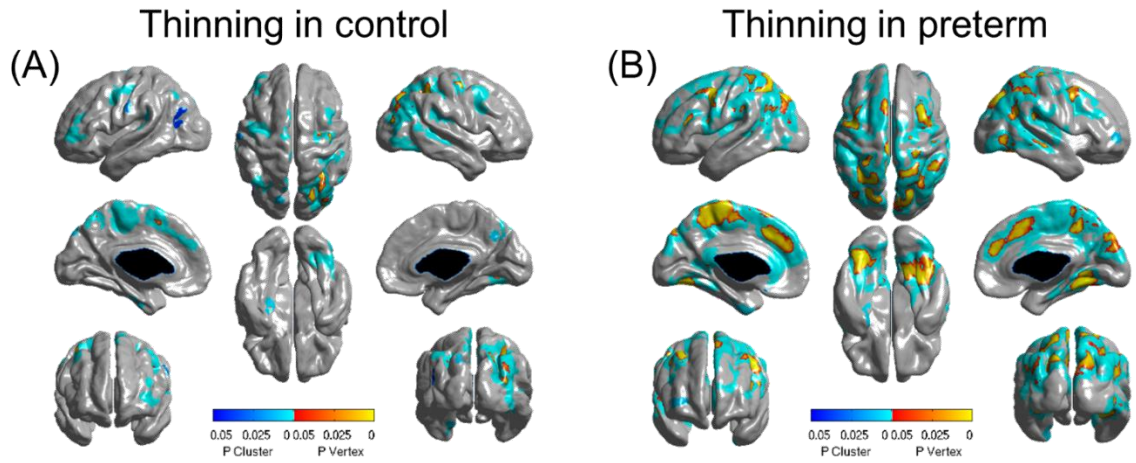


Table A-1

Areas displaying significant between-group differences in mean cortical thickness (in millimeters) at mid-adolescence and early adulthood.

Mid-adolescence			
Region	**VPT (n= 160), mean (95%CI)**	**Control (n= 88), mean (95%CI)**	**Cohen's d**
Right parahippocampus	2.96 (2.91-3.02)	3.21 (3.14-3.28)	-0.68
Left parahippocampus	2.55 (2.51-2.59)	2.76 (2.70-2.82)	-0.80
Left vmPFC/mOFC/Cingulate	3.55 (3.51-3.59)	3.37 (3.33-3.42)	0.75
Right temporal pole	3.86 (3.81-3.91)	3.63 (3.58-3.69)	0.76
Right vmPFC/dmPFC/mOFC	3.81 (3.76-3.85)	3.62 (3.57-3.67)	0.68
Left lingual/fusiform gyri	3.24 (3.20-3.27)	3.12 (3.08-3.15)	0.63
Left temporal pole	3.83 (3.77-3.89)	3.55 (3.48-3.61)	0.78
Left superior frontal gyrus	2.72 (2.68-2.77)	2.58 (2.53-2.63)	0.51
Left anterior insula	4.54 (4.46-4.63)	4.24 (4.15-4.34)	0.59
Right central sulcus	2.87 (2.84-2.91)	2.75 (2.70-2.81)	0.50
Left postcentral gyrus	2.43 (2.38-2.47)	2.29 (2.25-2.33)	0.54
Left central sulcus	2.81 (2.77-2.85)	2.68 (2.63-2.72)	0.50
Right middle frontal gyrus	2.93 (2.88-2.98)	2.79 (2.74-2.85)	0.46
Right occipito-temporal sulcus	3.59 (3.54-3.64)	3.46 (3.41-3.51)	0.47
Early Adulthood			
Region	**VPT (n= 67), mean (95%CI)**	**Control (n= 42), mean (95%CI)**	**Cohen's d**
Right parahippocampus	2.99 (2.90-3.08)	3.32 (3.22-3.42)	0.94
Left parahippocampus	2.89 (2.81-2.97)	3.21 (3.09-3.33)	0.89
Right temporo-parietal junction	3.2 (3.15-3.25)	3.41 (3.35-3.47)	1.04
Left Insula	3.88 (3.80-3.97)	4.16 (4.09-4.22)	0.91
Right inferior frontal sulcus	3.09 (3.04-3.14)	3.32 (3.26-3.38)	1.09
Left temporal pole	3.71 (3.63-3.80)	3.39 (3.29-3.49)	-0.95
Right medial orbitofrontal cortex	2.82 (2.73-2.90)	2.57 (2.48 -2.66)	-0.77

* vmPFC = ventromedial prefrontal cortex; mOFC = medial orbitofrontal cortex; dmPFC = dorsomedial prefrontal cortex

References

Aarnoudse-Moens, C. S., Weisglas-Kuperus, N., van Goudoever, J. B., & Oosterlaan, J. (2009). Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics, 124*(2), 717-728. doi: 10.1542/peds.2008-2816

Abernethy, L. J., Palaniappan, M., & Cooke, R. W. I. (2002). Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight. *Archives of Disease in Childhood, 87*(4), 279-283. doi: 10.1136/Adc.87.4.279

Ad-Dab'bagh, Y., Lyttelton, O., Muehlboeck, J., Lepage, C., Einarson, D., Mok, K., Ivanov, O., Vincent, R., Lerch, J., & Fombonne, E. (2006). *The CIVET image-processing environment: a fully automated comprehensive pipeline for anatomical neuroimaging research.* Paper presented at the Proceedings of the 12th annual meeting of the organization for human brain mapping.

Allin, M., Kontis, D., Walshe, M., Wyatt, J., Barker, G. J., Kanaan, R. A., McGuire, P., Rifkin, L., Murray, R. M., & Nosarti, C. (2011). White matter and cognition in adults who were born preterm. *PloS One, 6*(10), e24525. doi: 10.1371/journal.pone.0024525

Allin, M., Nosarti, C., Narberhaus, A., Walshe, M., Frearson, S., Kalpakidou, A., Wyatt, J., Rifkin, L., & Murray, R. (2007). Growth of the corpus callosum in adolescents born preterm. *Archives of Pediatrics and Adolescent Medicine, 161*(12), 1183-1189. doi: 10.1001/archpedi.161.12.1183

Allin, M., Salaria, S., Nosarti, C., Wyatt, J., Rifkin, L., & Murray, R. M. (2005). Vermis and lateral lobes of the cerebellum in adolescents born very preterm. *Neuroreport, 16*(16), 1821-1824. doi: 10.1097/01.wnr.0000185014.36939.84

Allin, M., Walshe, M., Fern, A., Nosarti, C., Cuddy, M., Rifkin, L., Murray, R., Rushe, T., & Wyatt, J. (2008). Cognitive maturation in preterm and term born

adolescents. *Journal of Neurology, Neurosurgery and Psychiatry, 79*(4), 381-386. doi: 10.1136/jnnp.2006.110858

Allin, M., Walshe, M., & Nosarti, C. (2010). Magnetic resonance imaging findings from adolescence to adulthood. In C. Nosarti, R. M. Murray & M. Hack (Eds.), *Neurodevelopmental Outcomes of Preterm Birth*: Cambridge University Press.

Ananth, C. V., & Vintzileos, A. M. (2006). Epidemiology of preterm birth and its clinical subtypes. *Journal of Maternal-Fetal & Neonatal Medicine, 19*(12), 773-782. doi: 10.1080/14767050600965882

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology, 8*(2), 71-82. doi: 10.1076/chin.8.2.71.8724

Anderson, P., Doyle, L. W., & Grp, V. I. C. (2004). Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. *Pediatrics, 114*(1), 50-57. doi: 10.1542/peds.114.1.50

Anderson, P., Doyle, L. W., & Victorian Infant Collaborative Study, G. (2003). Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. *JAMA, 289*(24), 3264-3272. doi: 10.1001/jama.289.24.3264

Arffa, S. (2007). The relationship of intelligence to executive function and non-executive function measures in a sample of average, above average, and gifted youth. *Archives of Clinical Neuropsychology, 22*(8), 969-978. doi: 10.1016/j.acn.2007.08.001

Atkinson, R. C., & Shiffrin, R. M. (1968). Human Memory: A Proposed System and its Control Processes. *2*, 89-195. doi: 10.1016/s0079-7421(08)60422-3

Attention deficit hyperactivity disorder (ADHD) - NHS Choices. (2014). Retrieved 21 July 2014, from http://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder/Pages/Introduction.aspx

Axelrod, B. N. (2002). Validity of the Wechsler Abbreviated Scale of Intelligence and Other Very Short Forms of Estimating Intellectual Functioning. *Assessment, 9*(1), 17-23. doi: 10.1177/1073191102009001003

Baddeley, A. (1992). Working memory. *Science, 255*(5044), 556-559. doi: 10.1126/science.1736359

Baddeley, A., Papagno, C., & Vallar, G. (1988). When Long-Term Learning Depends on Short-Term Storage. *Journal of Memory and Language, 27*(5), 586-595. doi: 10.1016/0749-596x(88)90028-9

Baldwin, B. T., & Stecher, L. I. (1922). Additional data from consecutive Stanford Binet tests. *Journal of Educational Psychology, 13*(9), 556-560. doi: 10.1037/H0071148

Banich, M. T. (2009). Executive Function: The Search for an Integrated Account. *Current Directions in Psychological Science, 18*(2), 89-94. doi: 10.1111/j.1467-8721.2009.01615.x

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin, 121*(1), 65-94.

Baron, I. S., Erickson, K., Ahronovich, M. D., Litman, F. R., & Brandt, J. (2010). Spatial location memory discriminates children born at extremely low birth weight and late-preterm at age three. *Neuropsychology, 24*(6), 787-794. doi: 10.1037/a0020382

Bayley, N. (1993). *Bayley Scales of Infant Development* (2nd ed.). San Antonio, TX: Harcourt Brace.

Bayley, N. (2006). *Bayley Scales of Infant and Toddler Development* (3rd ed.). San Antonio, TX: Harcourt Assessment Inc.

Beauchamp, M. H., Thompson, D. K., Howard, K., Doyle, L. W., Egan, G. F., Inder, T. E., & Anderson, P. J. (2008). Preterm infant hippocampal volumes correlate with later working memory deficits. *Brain, 131*(Pt 11), 2986-2994. doi: 10.1093/brain/awn227

Beckwith, L., & Parmelee, A. H. (1986). EEG Patterns of Preterm Infants, Home Environment, and Later IQ. *Child Development, 57*(3), 777. doi: 10.2307/1130354

Behrman, R. E., & Butler, A. S. (2007). Medical and Pregnancy Conditions Associated with Preterm Birth. In R. E. Behrman & A. S. Butler (Eds.), *Preterm birth: causes, consequences, and prevention*: National Academies Press.

Ben-Ari, Y. (2008). Neuro-archaeology: pre-symptomatic architecture and signature of neurological disorders. *Trends in Neurosciences, 31*(12), 626-636. doi: 10.1016/j.tins.2008.09.002

Benes, F. M. (1989). Myelination of cortical-hippocampal relays during late adolescence. *Schizophrenia Bulletin, 15*(4), 585-593.

Benetti, S., Mechelli, A., Picchioni, M., Broome, M., Williams, S., & McGuire, P. (2009). Functional integration between the posterior hippocampus and prefrontal cortex is impaired in both first episode schizophrenia and the at risk mental state. *Brain, 132*(Pt 9), 2426-2436. doi: 10.1093/brain/awp098

Benetti, S., Pettersson-Yeo, W., Hutton, C., Catani, M., Williams, S. C., Allen, P., Kambeitz-Ilankovic, L. M., McGuire, P., & Mechelli, A. (2013). Elucidating neuroanatomical alterations in the at risk mental state and first episode psychosis: a combined voxel-based morphometry and voxel-based cortical thickness study. *Schizophrenia Research, 150*(2-3), 505-511. doi: 10.1016/j.schres.2013.08.030

Benton, A. L., & Hamsher, K. d. (1976). *Multilingual Aphasia Examination*. Iowa City: University of Iowa.

Bielak, A. A., Mansueti, L., Strauss, E., & Dixon, R. A. (2006). Performance on the Hayling and Brixton tests in older adults: norms and correlates. *Archives of Clinical Neuropsychology, 21*(2), 141-149. doi: 10.1016/j.acn.2005.08.006

Bjuland, K. J., Lohaugen, G. C., Martinussen, M., & Skranes, J. (2013). Cortical thickness and cognition in very-low-birth-weight late teenagers. *Early Human Development, 89*(6), 371-380. doi: 10.1016/j.earlhumdev.2012.12.003

Bland, J. M., & Altman, D. G. (1995). Calculating correlation coefficients with repeated observations: Part 1--Correlation within subjects. *BMJ (Clinical research ed.), 310*(6977), 446.

Bless, J. J., Hugdahl, K., Westerhausen, R., Lohaugen, G. C., Eidheim, O. C., Brubakk, A. M., Skranes, J., Gramstad, A., & Haberg, A. K. (2013). Cognitive control deficits in adolescents born with very low birth weight (</= 1500 g): evidence from dichotic listening. *Scandinavian Journal of Psychology, 54*(3), 179-187. doi: 10.1111/sjop.12032

Bonner, M. F., & Price, A. R. (2013). Where is the anterior temporal lobe and what does it do? *Journal of Neuroscience, 33*(10), 4213-4215. doi: 10.1523/JNEUROSCI.0041-13.2013

Borgwardt, S. J., Riecher-Rossler, A., Dazzan, P., Chitnis, X., Aston, J., Drewe, M., Gschwandtner, U., Haller, S., Pfluger, M., Rechsteiner, E., D'Souza, M., Stieglitz, R. D., Radu, E. W., & McGuire, P. K. (2007). Regional gray matter volume abnormalities in the at risk mental state. *Biological Psychiatry, 61*(10), 1148-1156. doi: 10.1016/j.biopsych.2006.08.009

Botting, N., Powls, A., Cooke, R. W. I., & Marlow, N. (1997). Attention Deficit Hyperactivity Disorders and Other Psychiatric Outcomes in Very Low Birthweight Children at 12 Years. *Journal of Child Psychology and Psychiatry, 38*(8), 931-941. doi: 10.1111/j.1469-7610.1997.tb01612.x

Bourgeois, J.-P., Goldman-Rakic, P. S., & Rakic, P. (1994). Synaptogenesis in the Prefrontal Cortex of Rhesus Monkeys. *Cerebral Cortex, 4*(1), 78-96. doi: 10.1093/cercor/4.1.78

Boyle, M. H., Miskovic, V., Van Lieshout, R., Duncan, L., Schmidt, L. A., Hoult, L., Paneth, N., & Saigal, S. (2011). Psychopathology in young adults born at extremely low birth weight. *Psychological Medicine, 41*(8), 1763-1774. doi: 10.1017/S0033291710002357

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage, 5*(1), 49-62. doi: 10.1006/nimg.1996.0247

Brett, M., Penny, W., & Kiebel, S. (2004). An Introduction to Random Field Theory. In K. J. Friston, C. D. Frith, R. J. Dolan, C. J. Price, S. Zeki, J. T. Ashburner, W. D. Penny & R. S. J. Frackowiak (Eds.), *Human Brain Function*: Elsevier Science.

Brunnemann, N., Kipp, K. H., Gortner, L., Meng-Hentschel, J., Papanagiotou, P., Reith, W., & Shamdeen, M. G. (2013). Alterations in the relationship between hippocampal volume and episodic memory performance in preterm children. *Developmental Neuropsychology, 38*(4), 226-235. doi: 10.1080/87565641.2013.773003

Burgess, P. W., & Shallice, T. (1996). Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia, 34*(4), 263-272. doi: 10.1016/0028-3932(95)00104-2

Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton Tests*. Bury St Edmunds, UK: Thames Valley Test Company.

Burnett, A. C., Anderson, P. J., Cheong, J., Doyle, L. W., Davey, C. G., & Wood, S. J. (2011). Prevalence of psychiatric diagnoses in preterm and full-term children,

adolescents and young adults: a meta-analysis. *Psychological Medicine, 41*(12), 2463-2474. doi: 10.1017/S003329171100081X

Burnett, A. C., Davey, C. G., Wood, S. J., Wilson-Ching, M., Molloy, C., Cheong, J. L., Doyle, L. W., & Anderson, P. J. (2013). Extremely preterm birth and adolescent mental health in a geographical cohort born in the 1990s. *Psychological Medicine*, 1-12. doi: 10.1017/S0033291713002158

Burnett, A. C., Scratch, S. E., & Anderson, P. J. (2013). Executive function outcome in preterm adolescents. *Early Human Development, 89*(4), 215-220. doi: 10.1016/j.earlhumdev.2013.01.013

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience, 12*(1), 1-47. doi: 10.1162/08989290051137585

Caine, D., & Watson, J. D. (2000). Neuropsychological and neuropathological sequelae of cerebral anoxia: a critical review. *Journal of the International Neuropsychological Society, 6*(1), 86-99.

Caplan, B., DeLuca, J., & Kreutzer, J. S. (n.d.-a). Full Scale IQ. Retrieved 12 June 2014 http://www.springerreference.com/docs/html/chapterdbid/184247.html

Caplan, B., DeLuca, J., & Kreutzer, J. S. (n.d.-b). Performance IQ. Retrieved 12 June 2014 http://www.springerreference.com/docs/html/chapterdbid/183810.html

Caplan, B., DeLuca, J., & Kreutzer, J. S. (n.d.-c). Verbal IQ. Retrieved 12 June 2014 http://www.springerreference.com/docs/html/chapterdbid/183816.html

Caravale, B., Tozzi, C., Albino, G., & Vicari, S. (2005). Cognitive development in low risk preterm infants at 3-4 years of life. *Archives of Disease in Childhood: Fetal and Neonatal Edition, 90*(6), F474-479. doi: 10.1136/adc.2004.070284

Carpenter, W. T., Jr. (1987). Approaches to knowledge and understanding of schizophrenia. *Schizophrenia Bulletin, 13*(1), 1-8.

Catani, M., Jones, D. K., & ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology, 57*(1), 8-16. doi: 10.1002/ana.20319

Chen, A. C., Oathes, D. J., Chang, C., Bradley, T., Zhou, Z. W., Williams, L. M., Glover, G. H., Deisseroth, K., & Etkin, A. (2013). Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proceedings of the National Academy of Sciences of the United States of America, 110*(49), 19944-19949. doi: 10.1073/pnas.1311772110

Cheong, J. L., Anderson, P. J., Roberts, G., Burnett, A. C., Lee, K. J., Thompson, D. K., Molloy, C., Wilson-Ching, M., Connelly, A., Seal, M. L., Wood, S. J., & Doyle, L. W. (2013). Contribution of brain size to IQ and educational underperformance in extremely preterm adolescents. *PloS One, 8*(10), e77475. doi: 10.1371/journal.pone.0077475

Cherry, K. (2014a, 11 June 2014). What Is Cognition? Retrieved 4 September 2014, from http://psychology.about.com/od/cindex/g/def_cognition.htm

Cherry, K. (2014b). What Is the Average IQ? Is Your IQ Above Average? Retrieved 23 August 2014, from http://psychology.about.com/od/intelligence/f/average-iq.htm

Chorna, O., Solomon, J. E., Slaughter, J. C., Stark, A. R., & Maitre, N. L. (2014). Abnormal sensory reactivity in preterm infants during the first year correlates with adverse neurodevelopmental outcomes at 2 years of age. *Archives of Disease in Childhood: Fetal and Neonatal Edition*. doi: 10.1136/archdischild-2014-306486

Christoff, K., & Gabrieli, J. D. E. (2000). The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology, 28*(2), 168-186. doi: 10.3758/bf03331976

Chung, M. K., & Taylor, J. (2004, 15-18 April 2004). *Diffusion smoothing on brain surface via finite element method.* Paper presented at the Biomedical Imaging: Nano to Macro, 2004. IEEE International Symposium on, Arlington, VA, USA.

Clinical depression - NHS Choices. (2012). Retrieved 21 July 2014, from http://www.nhs.uk/conditions/depression/Pages/Introduction.aspx

Collin, G., Sporns, O., Mandl, R. C., & van den Heuvel, M. P. (2014). Structural and functional aspects relating to cost and benefit of rich club organization in the human cerebral cortex. *Cerebral Cortex, 24*(9), 2258-2267. doi: 10.1093/cercor/bht064

Collins, D. L., Holmes, C. J., Peters, T. M., & Evans, A. C. (1995). Automatic 3-D model-based neuroanatomical segmentation. *Human Brain Mapping, 3*(3), 190-208. doi: 10.1002/hbm.460030304

Colman, A. M. (Ed.) (n.d.) A Dictionary of Psychology. Oxford University Press.

Conrad, A. L., Richman, L., Lindgren, S., & Nopoulos, P. (2010). Biological and environmental predictors of behavioral sequelae in children born preterm. *Pediatrics, 125*(1), e83-89. doi: 10.1542/peds.2009-0634

Counsell, S. J., Shen, Y. J., Boardman, J. P., Larkman, D. J., Kapellou, O., Ward, P., Allsop, J. M., Cowan, F. M., Hajnal, J. V., Edwards, A. D., & Rutherford, M. A. (2006). Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. *Pediatrics, 117*(2), 376-386. doi: 10.1542/peds.2005-0820

Crews, F., He, J., & Hodge, C. (2007). Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacology, Biochemistry and Behavior, 86*(2), 189-199. doi: 10.1016/j.pbb.2006.12.001

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology, 50*(8), 873-880.

Curtis, W. J., Lindeke, L. L., Georgieff, M. K., & Nelson, C. A. (2002). Neurobehavioural functioning in neonatal intensive care unit graduates in late childhood and early adolescence. *Brain, 125*(Pt 7), 1646-1659. doi: 10.1093/brain/awf159

Curtis, W. J., Zhuang, J., Townsend, E. L., Hu, X., & Nelson, C. A. (2006). Memory in early adolescents born prematurely: a functional magnetic resonance imaging investigation. *Developmental Neuropsychology, 29*(2), 341-377. doi: 10.1207/s15326942dn2902_4

D'Esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Atlas, S., & Grossman, M. (1995). The neural basis of the central executive system of working memory. *Nature, 378*(6554), 279-281. doi: 10.1038/378279a0

Dalziel, S. R., Lim, V. K., Lambert, A., McCarthy, D., Parag, V., Rodgers, A., & Harding, J. E. (2007). Psychological functioning and health-related quality of life in adulthood after preterm birth. *Developmental Medicine and Child Neurology, 49*(8), 597-602. doi: 10.1111/j.1469-8749.2007.00597.x

Davatzikos, C., Ruparel, K., Fan, Y., Shen, D. G., Acharyya, M., Loughead, J. W., Gur, R. C., & Langleben, D. D. (2005). Classifying spatial patterns of brain activity with machine learning methods: application to lie detection. *Neuroimage, 28*(3), 663-668. doi: 10.1016/j.neuroimage.2005.08.009

Davis, J. M., & Auten, R. L. (2010). Maturation of the antioxidant system and the effects on preterm birth. *Seminars in Fetal & Neonatal Medicine, 15*(4), 191-195. doi: 10.1016/j.siny.2010.04.001

Deary, I. J., Whalley, L. J., Lemmon, H., Crawford, J. R., & Starr, J. M. (2000). The Stability of Individual Differences in Mental Ability from Childhood to Old Age: Follow-up of the 1932 Scottish Mental Survey. *Intelligence, 28*(1), 49-55. doi: 10.1016/s0160-2896(99)00031-8

Definition of MDI. (2012). Retrieved 20 June 2014 http://www.medterms.com/script/main/art.asp?articlekey=25818

Delahunty, C., Falconer, S., Hume, R., Jackson, L., Midgley, P., Mirfield, M., Ogston, S., Perra, O., Simpson, J., Watson, J., Willatts, P., Williams, F., & Scottish Preterm Thyroid Group (2010). Levels of neonatal thyroid hormone in preterm infants and neurodevelopmental outcome at 5 1/2 years: millennium cohort study. *Journal of Clinical Endocrinology and Metabolism, 95*(11), 4898-4908. doi: 10.1210/jc.2010-0743

Delis, D. C., Cullum, C. M., Butters, N., Cairns, P., & Prifitera, A. (1988). Wechsler memory scale-revised and california verbal learning test: Convergence and divergence. *Clinical Neuropsychologist, 2*(2), 188-196. doi: 10.1080/13854048808520100

Dellis, D., Kramer, J., Kaplan, E., & Ober, B. (1987). *The California Verbal Learning Test*. San Antonio, TX: The Psychological Corporation.

Doesburg, S. M., Ribary, U., Herdman, A. T., Miller, S. P., Poskitt, K. J., Moiseev, A., Whitfield, M. F., Synnes, A., & Grunau, R. E. (2011). Altered long-range alpha-band synchronization during visual short-term memory retention in children born very preterm. *Neuroimage, 54*(3), 2330-2339. doi: 10.1016/j.neuroimage.2010.10.044

Doria, V., Beckmann, C. F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F. E., Counsell, S. J., Murgasova, M., Aljabar, P., Nunes, R. G., Larkman, D. J., Rees, G., & Edwards, A. D. (2010). Emergence of resting state networks in the preterm human brain. *Proceedings of the National Academy of Sciences of the United States of America, 107*(46), 20015-20020. doi: 10.1073/pnas.1007921107

Duerden, E. G., Card, D., Lax, I. D., Donner, E. J., & Taylor, M. J. (2013). Alterations in frontostriatal pathways in children born very preterm. *Developmental Medicine and Child Neurology, 55*(10), 952-958. doi: 10.1111/dmcn.12198

Ecker, C., Ginestet, C., Feng, Y., Johnston, P., Lombardo, M. V., Lai, M. C., Suckling, J., Palaniyappan, L., Daly, E., Murphy, C. M., Williams, S. C., Bullmore, E. T., Baron-Cohen, S., Brammer, M., & Murphy, D. G. (2013). Brain surface anatomy in adults with autism: the relationship between surface area, cortical thickness, and autistic symptoms. *JAMA Psychiatry, 70*(1), 59-70. doi: 10.1001/jamapsychiatry.2013.265

Ecker, C., Rocha-Rego, V., Johnston, P., Mourao-Miranda, J., Marquand, A., Daly, E. M., Brammer, M. J., Murphy, C., Murphy, D. G., & Consortium, M. A. (2010). Investigating the predictive value of whole-brain structural MR scans in autism: a pattern classification approach. *Neuroimage, 49*(1), 44-56. doi: 10.1016/j.neuroimage.2009.08.024

Edgin, J. O., Inder, T. E., Anderson, P. J., Hood, K. M., Clark, C. A. C., & Woodward, L. J. (2008). Executive functioning in preschool children born very preterm: Relationship with early white matter pathology. *Journal of the International Neuropsychological Society, 14*(1), 90-101. doi: 10.1017/S1355617708080053

Eichenbaum, H., & Lipton, P. A. (2008). Towards a functional organization of the medial temporal lobe memory system: role of the parahippocampal and medial entorhinal cortical areas. *Hippocampus, 18*(12), 1314-1324. doi: 10.1002/hipo.20500

Eikenes, L., Lohaugen, G. C., Brubakk, A. M., Skranes, J., & Haberg, A. K. (2011). Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI. *Neuroimage, 54*(3), 1774-1785. doi: 10.1016/j.neuroimage.2010.10.037

El-Dib, M., Massaro, A. N., Bulas, D., & Aly, H. (2010). Neuroimaging and neurodevelopmental outcome of premature infants. *American Journal of Perinatology, 27*(10), 803-818. doi: 10.1055/s-0030-1254550

Engle, R. W., Tuholski, S. W., Laughlin, J. E., & Conway, A. R. (1999). Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. *Journal of Experimental Psychology: General, 128*(3), 309-331. doi: 10.1037/0096-3445.128.3.309

Fan, L., Wang, J., Zhang, Y., Han, W., Yu, C., & Jiang, T. (2013). Connectivity-Based Parcellation of the Human Temporal Pole Using Diffusion Tensor Imaging. *Cerebral Cortex*. doi: 10.1093/cercor/bht196

Fanaroff, A. A., Hack, M., & Walsh, M. C. (2003). The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. *Seminars in Perinatology, 27*(4), 281-287. doi: 10.1016/s0146-0005(03)00055-7

Fearon, P., O'Connell, P., Frangou, S., Aquino, P., Nosarti, C., Allin, M., Taylor, M., Stewart, A., Rifkin, L., & Murray, R. (2004). Brain volumes in adult survivors of very low birth weight: A sibling-controlled study. *Pediatrics, 114*(2), 367-371. doi: 10.1542/peds.114.2.367

Foulder-Hughes, L. A., & Cooke, R. W. I. (2007). Motor, cognitive, and behavioural disorders in children born very preterm. *Developmental Medicine and Child Neurology, 45*(2), 97-103. doi: 10.1111/j.1469-8749.2003.tb00912.x

Frye, R. E., Malmberg, B., Swank, P., Smith, K., & Landry, S. (2010). Preterm birth and maternal responsiveness during childhood are associated with brain morphology in adolescence. *Journal of the International Neuropsychological Society, 16*(5), 784-794. doi: 10.1017/S1355617710000585

Gadian, D. G., Aicardi, J., Watkins, K. E., Porter, D. A., Mishkin, M., & Vargha-Khadem, F. (2000). Developmental amnesia associated with early hypoxic-ischaemic injury. *Brain, 123 Pt 3*, 499-507.

Gadin, E., Lobo, M., Paul, D. A., Sem, K., Steiner, K. V., Mackley, A., Anzilotti, K., & Galloway, C. (2012). Volumetric MRI and MRS and early motor development of infants born preterm. *Pediatric Physical Therapy, 24*(1), 38-44. doi: 10.1097/PEP.0b013e31823e069d

Gale, C. R., O'Callaghan, F. J., Bredow, M., & Martyn, C. N. (2006). The influence of head growth in fetal life, infancy, and childhood on intelligence at the ages of 4 and 8 years. *Pediatrics, 118*(4), 1486-1492. doi: 10.1542/peds.2005-2629

Gale, C. R., O'Callaghan, F. J., Godfrey, K. M., Law, C. M., & Martyn, C. N. (2004). Critical periods of brain growth and cognitive function in children. *Brain, 127*(Pt 2), 321-329. doi: 10.1093/brain/awh034

Gaonkar, B., & Davatzikos, C. (2013). Analytic estimation of statistical significance maps for support vector machine based multi-variate image analysis and classification. *Neuroimage, 78*, 270-283. doi: 10.1016/j.neuroimage.2013.03.066

Generalised anxiety disorder - Symptoms - NHS Choices. (2014). Retrieved 21 July 2014, from http://www.nhs.uk/Conditions/Anxiety/Pages/Symptoms.aspx

Geschwind, D. H. (2009). Advances in autism. *Annual Review of Medicine, 60*, 367-380. doi: 10.1146/annurev.med.60.053107.121225

Ghosh, S., Basu, A., Kumaran, S. S., & Khushu, S. (2010). Functional mapping of language networks in the normal brain using a word-association task. *Indian Journal of Radiology & Imaging, 20*(3), 182-187. doi: 10.4103/0971-3026.69352

Gilbert, S. J., & Burgess, P. W. (2008). Executive function. *Current Biology, 18*(3), R110-114. doi: 10.1016/j.cub.2007.12.014

Gimenez, M., Junque, C., Vendrell, P., Caldu, X., Narberhaus, A., Bargallo, N., Falcon, C., Botet, F., & Mercader, J. M. (2005). Hippocampal functional magnetic resonance imaging during a face-name learning task in adolescents with antecedents of prematurity. *Neuroimage, 25*(2), 561-569. doi: 10.1016/j.neuroimage.2004.10.046

Glasser, M. F., & Van Essen, D. C. (2011). Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. *Journal of Neuroscience, 31*(32), 11597-11616. doi: 10.1523/JNEUROSCI.2180-11.2011

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F., 3rd, Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L., & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America, 101*(21), 8174-8179. doi: 10.1073/pnas.0402680101

Gogtay, N., Nugent, T. F., 3rd, Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., Clasen, L., Toga, A. W., Giedd, J. N., Rapoport, J. L., & Thompson, P. M. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus, 16*(8), 664-672. doi: 10.1002/hipo.20193

Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. *Lancet, 371*(9606), 75-84. doi: 10.1016/S0140-6736(08)60074-4

Gonzalez, N., Moll, L. C., & Amanti, C. (2013). *Funds of Knowledge: Theorizing Practices in Households, Communities, and Classrooms*: Taylor & Francis.

Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is responsible for switching between the default mode network and the central executive network:

Replication from DCM. *Neuroimage, 99*, 180-190. doi: 10.1016/j.neuroimage.2014.05.052

Griffiths, S. T., Gundersen, H., Neto, E., Elgen, I., Markestad, T., Aukland, S. M., & Hugdahl, K. (2013). fMRI: blood oxygen level-dependent activation during a working memory-selective attention task in children born extremely preterm. *Pediatric Research, 74*(2), 196-205. doi: 10.1038/pr.2013.79

Gu, X., Hof, P. R., Friston, K. J., & Fan, J. (2013). Anterior insular cortex and emotional awareness. *Journal of Comparative Neurology, 521*(15), 3371-3388. doi: 10.1002/cne.23368

Hack, M., Taylor, H. G., Drotar, D., Schluchter, M., Cartar, L., Wilson-Costello, D., Klein, N., Friedman, H., Mercuri-Minich, N., & Morrow, M. (2005). Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatrics, 116*(2), 333-341. doi: 10.1542/peds.2005-0173

Hack, M., Taylor, H. G., Klein, N., Eiben, R., Schatschneider, C., & Mercuri-Minich, N. (1994). School-age outcomes in children with birth weights under 750 g. *New England Journal of Medicine, 331*(12), 753-759. doi: 10.1056/NEJM199409223311201

Haier, R. J., Jung, R. E., Yeo, R. A., Head, K., & Alkire, M. T. (2004). Structural brain variation and general intelligence. *Neuroimage, 23*(1), 425-433. doi: 10.1016/j.neuroimage.2004.04.025

Hallin, A. L., Hellstrom-Westas, L., & Stjernqvist, K. (2010). Follow-up of adolescents born extremely preterm: cognitive function and health at 18 years of age. *Acta Paediatrica, 99*(9), 1401-1406. doi: 10.1111/j.1651-2227.2010.01850.x

Halsey, C. L. (1996). Extremely Low-Birth-Weight Children and Their Peers. *Archives of Pediatrics and Adolescent Medicine, 150*(8), 790. doi: 10.1001/archpedi.1996.02170330016003

Happe, F., & Ronald, A. (2008). The 'fractionable autism triad': a review of evidence from behavioural, genetic, cognitive and neural research. *Neuropsychology Review, 18*(4), 287-304. doi: 10.1007/s11065-008-9076-8

Hartberg, C. B., Lawyer, G., Nyman, H., Jonsson, E. G., Haukvik, U. K., Saetre, P., Bjerkan, P. S., Andreassen, O. A., Hall, H., & Agartz, I. (2010). Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults. *Psychiatry Research, 182*(2), 123-133. doi: 10.1016/j.pscychresns.2010.01.001

Harvey, J. M., O'Callaghan, M. J., & Mohay, H. (1999). Executive function of children with extremely low birthweight: a case control study. *Developmental Medicine and Child Neurology, 41*(5), 292-297. doi: 10.1017/s0012162299000663

Hays, J. R., Reas, D. L., & Shaw, J. B. (2002). Concurrent validity of the Wechsler abbreviated scale of intelligence and the Kaufman brief intelligence test among psychiatric inpatients. *Psychological Reports, 90*(2), 355-359. doi: 10.2466/pr0.2002.90.2.355

He, Y., Chen, Z. J., & Evans, A. C. (2007). Small-World Anatomical Networks in the Human Brain Revealed by Cortical Thickness from MRI. *Cerebral Cortex, 17*(10), 2407-2419. doi: 10.1093/cercor/bhl149

Healy, E., Reichenberg, A., Nam, K., Allin, M., Walshe, M., Rifkin, L., Murray, R., Taylor, E., & Nosarti, C. (2012). Social immaturity in adolescents who were born very preterm is associated with increased grey matter volume in the fusiform gyri. *Neuropsychiatrie de l'Enfance et de l'Adolescence, 60*(5, Supplement), S177. doi: http://dx.doi.org/10.1016/j.neurenf.2012.04.287

Healy, E., Reichenberg, A., Nam, K. W., Allin, M. P., Walshe, M., Rifkin, L., Murray, S. R., & Nosarti, C. (2013). Preterm birth and adolescent social functioning-alterations in emotion-processing brain areas. *Journal of Pediatrics, 163*(6), 1596-1604. doi: 10.1016/j.jpeds.2013.08.011

Heinonen, K., Pesonen, A. K., Lahti, J., Pyhala, R., Strang-Karlsson, S., Hovi, P., Jarvenpaa, A. L., Eriksson, J. G., Andersson, S., Kajantie, E., & Raikkonen, K. (2013). Self- and parent-rated executive functioning in young adults with very low birth weight. *Pediatrics, 131*(1), e243-250. doi: 10.1542/peds.2012-0839

Hensch, T. K. (2004). Critical period regulation. *Annual Review of Neuroscience, 27*, 549-579. doi: 10.1146/annurev.neuro.27.070203.144327

Hille, E. T. M., den Ouden, A. L., Saigal, S., Wolke, D., Lambert, M., Whitaker, A., Pinto-Martin, J. A., Hoult, L., Meyer, R., Feldman, J. F., Verloove-Vanhorick, S. P., & Paneth, N. (2001). Behavioural problems in children who weigh 1000 g or less at birth in four countries. *The Lancet, 357*(9269), 1641-1643. doi: 10.1016/s0140-6736(00)04818-2

Hughes, A., Greisen, G., Arce, J. C., & Thornton, S. (2014). Late preterm birth is associated with short-term morbidity but not with adverse neurodevelopmental and physical outcomes at 1 year. *Acta Obstetricia et Gynecologica Scandinavica, 93*(1), 109-112. doi: 10.1111/aogs.12258

Husby, I. M., Skranes, J., Olsen, A., Brubakk, A. M., & Evensen, K. A. (2013). Motor skills at 23 years of age in young adults born preterm with very low birth weight. *Early Human Development, 89*(9), 747-754. doi: 10.1016/j.earlhumdev.2013.05.009

Indredavik, M. S., Vik, T., Heyerdahl, S., Kulseng, S., Fayers, P., & Brubakk, A. M. (2004). Psychiatric symptoms and disorders in adolescents with low birth weight.

Archives of Disease in Childhood: Fetal and Neonatal Edition, 89(5), F445-450. doi: 10.1136/adc.2003.038943

intelligence: definition of intelligence in Oxford dictionary (British & World English). (2014). from http://www.oxforddictionaries.com/definition/english/intelligence

Isaacs, E. B., Edmonds, C. J., Chong, W. K., Lucas, A., Morley, R., & Gadian, D. G. (2004). Brain morphometry and IQ measurements in preterm children. *Brain, 127*(Pt 12), 2595-2607. doi: 10.1093/brain/awh300

Isaacs, E. B., Lucas, A., Chong, W. K., Wood, S. J., Johnson, C. L., Marshall, C., Vargha-Khadem, F., & Gadian, D. G. (2000). Hippocampal volume and everyday memory in children of very low birth weight. *Pediatric Research, 47*(6), 713-720. doi: 10.1203/00006450-200006000-00006

Jandl, M., Steyer, J., & Kaschka, W. P. (2012). Adolescent attention deficit hyperactivity disorder and susceptibility to psychosis in adulthood: a review of the literature and a phenomenological case report. *Early Interv Psychiatry, 6*(1), 11-20. doi: 10.1111/j.1751-7893.2011.00293.x

Johnson, S. (2007). Cognitive and behavioural outcomes following very preterm birth. *Seminars in Fetal & Neonatal Medicine, 12*(5), 363-373. doi: 10.1016/j.siny.2007.05.004

Johnson, S., Hollis, C., Kochhar, P., Hennessy, E., Wolke, D., & Marlow, N. (2010a). Autism spectrum disorders in extremely preterm children. *Journal of Pediatrics, 156*(4), 525-531 e522. doi: 10.1016/j.jpeds.2009.10.041

Johnson, S., Hollis, C., Kochhar, P., Hennessy, E., Wolke, D., & Marlow, N. (2010b). Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(5), 453-463 e451.

Johnson, S., & Marlow, N. (2011). Preterm birth and childhood psychiatric disorders. *Pediatric Research, 69*(5 Pt 2), 11R-18R. doi: 10.1203/PDR.0b013e318212faa0

Johnson, S., Moore, T., & Marlow, N. (2014). Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? *Pediatric Research, 75*(5), 670-674. doi: 10.1038/pr.2014.10

Johnson, S., & Wolke, D. (2013). Behavioural outcomes and psychopathology during adolescence. *Early Human Development, 89*(4), 199-207. doi: 10.1016/j.earlhumdev.2013.01.014

Just, M. A., & Varma, S. (2007). The organization of thinking: What functional brain imaging reveals about the neuroarchitecture of complex cognition. *Cognitive, Affective, & Behavioral Neuroscience, 7*(3), 153-191. doi: 10.3758/cabn.7.3.153

Kalpakidou, A. K., Allin, M. P., Walshe, M., Giampietro, V., Nam, K. W., McGuire, P., Rifkin, L., Murray, R. M., & Nosarti, C. (2012). Neonatal brain injury and neuroanatomy of memory processing following very preterm birth in adulthood: an fMRI study. *PloS One, 7*(4), e34858. doi: 10.1371/journal.pone.0034858

Kangas, J., & Bradway, K. (1971). Intelligence at middle age: A thirty-eight year follow-up. *Developmental Psychology, 5*(2), 333.

Kesler, S. R., Ment, L. R., Vohr, B., Pajot, S. K., Schneider, K. C., Katz, K. H., Ebbitt, T. B., Duncan, C. C., Makuch, R. W., & Reiss, A. L. (2004). Volumetric analysis of regional cerebral development in preterm children. *Pediatric Neurology, 31*(5), 318-325. doi: 10.1016/j.pediatrneurol.2004.06.008

Kesler, S. R., Reiss, A. L., Vohr, B., Watson, C., Schneider, K. C., Katz, K. H., Maller-Kesselman, J., Silbereis, J., Constable, R. T., Makuch, R. W., & Ment, L. R. (2008). Brain volume reductions within multiple cognitive systems in male preterm children at age twelve. *Journal of Pediatrics, 152*(4), 513-520, 520 e511. doi: 10.1016/j.jpeds.2007.08.009

Keunen, K., Kersbergen, K. J., Groenendaal, F., Isgum, I., de Vries, L. S., & Benders, M. J. (2012). Brain tissue volumes in preterm infants: prematurity, perinatal risk factors and neurodevelopmental outcome: a systematic review. *Journal of Maternal-Fetal & Neonatal Medicine, 25 Suppl 1*, 89-100. doi: 10.3109/14767058.2012.664343

Kibby, M. Y., & Cohen, M. J. (2008). Memory functioning in children with reading disabilities and/or attention deficit/hyperactivity disorder: a clinical investigation of their working memory and long-term memory functioning. *Child Neuropsychology, 14*(6), 525-546. doi: 10.1080/09297040701821752

Kilbride, H. W., Thorstad, K., & Daily, D. K. (2004). Preschool outcome of less than 801-gram preterm infants compared with full-term siblings. *Pediatrics, 113*(4), 742-747. doi: 10.1542/peds.113.4.742

Kim, D. J., Davis, E. P., Sandman, C. A., Sporns, O., O'Donnell, B. F., Buss, C., & Hetrick, W. P. (2014). Longer gestation is associated with more efficient brain networks in preadolescent children. *Neuroimage, 100*, 619-627. doi: 10.1016/j.neuroimage.2014.06.048

Kim, J. S., Singh, V., Lee, J. K., Lerch, J., Ad-Dab'bagh, Y., MacDonald, D., Lee, J. M., Kim, S. I., & Evans, A. C. (2005). Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. *Neuroimage, 27*(1), 210-221. doi: DOI: 10.1016/j.neuroimage.2005.03.036

Kloppel, S., Draganski, B., Golding, C. V., Chu, C., Nagy, Z., Cook, P. A., Hicks, S. L., Kennard, C., Alexander, D. C., Parker, G. J., Tabrizi, S. J., & Frackowiak, R. S. (2008). White matter connections reflect changes in voluntary-guided saccades in pre-symptomatic Huntington's disease. *Brain, 131*(Pt 1), 196-204. doi: 10.1093/brain/awm275

Kloppel, S., Stonnington, C. M., Chu, C., Draganski, B., Scahill, R. I., Rohrer, J. D., Fox, N. C., Jack, C. R., Jr., Ashburner, J., & Frackowiak, R. S. (2008). Automatic classification of MR scans in Alzheimer's disease. *Brain, 131*(Pt 3), 681-689. doi: 10.1093/brain/awm319

Konrad, A., Dielentheis, T. F., El Masri, D., Bayerl, M., Fehr, C., Gesierich, T., Vucurevic, G., Stoeter, P., & Winterer, G. (2010). Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder. *European Journal of Neuroscience, 31*(5), 912-919. doi: 10.1111/j.1460-9568.2010.07110.x

Koolschijn, P. C., & Crone, E. A. (2013). Sex differences and structural brain maturation from childhood to early adulthood. *Developmental Cognitive Neuroscience, 5C,* 106-118. doi: 10.1016/j.dcn.2013.02.003

Kostovic, I., Judas, M., & Sedmak, G. (2011). Developmental history of the subplate zone, subplate neurons and interstitial white matter neurons: relevance for schizophrenia. *International Journal of Developmental Neuroscience, 29*(3), 193-205. doi: 10.1016/j.ijdevneu.2010.09.005

Koutsouleris, N., Meisenzahl, E. M., Davatzikos, C., Bottlender, R., Frodl, T., Scheuerecker, J., Schmitt, G., Zetzsche, T., Decker, P., Reiser, M., Moller, H. J., & Gaser, C. (2009). Use of Neuroanatomical Pattern Classification to Identify Subjects in At-Risk Mental States of Psychosis and Predict Disease Transition. *Archives of General Psychiatry, 66*(7), 700-712.

Kulseng, S., Jennekens-Schinkel, A., Naess, P., Romundstad, P., Indredavik, M., Vik, T., & Brubakk, A.-M. (2007). Very-low-birthweight and term small-for-gestational-age adolescents: Attention revisited. *Acta Paediatrica, 95*(2), 224-230. doi: 10.1111/j.1651-2227.2006.tb02211.x

Lange, N., Froimowitz, M. P., Bigler, E. D., Lainhart, J. E., & Grp, B. D. C. (2010). Associations Between IQ, Total and Regional Brain Volumes, and Demography in a Large Normative Sample of Healthy Children and Adolescents. *Developmental Neuropsychology*, *35*(3), 296-317. doi: 10.1080/87565641003696833

Lawrence, E. J., McGuire, P. K., Allin, M., Walshe, M., Giampietro, V., Murray, R. M., Rifkin, L., & Nosarti, C. (2010). The very preterm brain in young adulthood: the neural correlates of verbal paired associate learning. *Journal of Pediatrics, 156*(6), 889-895. doi: 10.1016/j.jpeds.2010.01.017

Lawrence, E. J., Rubia, K., Murray, R. M., McGuire, P. K., Walshe, M., Allin, M., Giampietro, V., Rifkin, L., Williams, S. C. R., & Nosarti, C. (2009). The neural basis of response inhibition and attention allocation as mediated by gestational age. *Human Brain Mapping, 30*(3), 1038-1050. doi: 10.1002/hbm.20564

Lax, I. D., Duerden, E. G., Lin, S. Y., Mallar Chakravarty, M., Donner, E. J., Lerch, J. P., & Taylor, M. J. (2013). Neuroanatomical consequences of very preterm birth in middle childhood. *Brain Struct Funct, 218*(2), 575-585. doi: 10.1007/s00429-012-0417-2

Lewis, B. A., Singer, L. T., Fulton, S., Salvator, A., Short, E. J., Klein, N., & Baley, J. (2002). Speech and language outcomes of children with bronchopulmonary dysplasia. *Journal of Communication Disorders, 35*(5), 393-406.

Li, M., Lu, S., Li, J., & Zhong, N. (2010). The Role of the Parahippocampal Cortex in Memory Encoding and Retrieval: An fMRI Study. *6334*, 377-386. doi: 10.1007/978-3-642-15314-3_36

Libby, L. A., Ekstrom, A. D., Ragland, J. D., & Ranganath, C. (2012). Differential connectivity of perirhinal and parahippocampal cortices within human hippocampal subregions revealed by high-resolution functional imaging.

Journal of Neuroscience, 32(19), 6550-6560. doi: 10.1523/JNEUROSCI.3711-11.2012

Lind, A., Parkkola, R., Lehtonen, L., Munck, P., Maunu, J., Lapinleimu, H., Haataja, L., & Group, P. S. (2011). Associations between regional brain volumes at term-equivalent age and development at 2 years of age in preterm children. *Pediatric Radiology, 41*(8), 953-961. doi: 10.1007/s00247-011-2071-x

Lindstrom, K., Lindblad, F., & Hjern, A. (2009). Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. *Pediatrics, 123*(1), e47-53. doi: 10.1542/peds.2008-1654

Lindstrom, K., Lindblad, F., & Hjern, A. (2011). Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. *Pediatrics, 127*(5), 858-865. doi: 10.1542/peds.2010-1279

Lindstrom, M. J., & Bates, D. M. (1988). Newton-Raphson and EM Algorithms for Linear Mixed-Effects Models for Repeated-Measures Data. *Journal of the American Statistical Association, 83*(404), 1014. doi: 10.2307/2290128

Linnet, K. M., Wisborg, K., Agerbo, E., Secher, N. J., Thomsen, P. H., & Henriksen, T. B. (2006). Gestational age, birth weight, and the risk of hyperkinetic disorder. *Archives of Disease in Childhood, 91*(8), 655-660. doi: 10.1136/adc.2005.088872

Litt, J. S., Gerry Taylor, H., Margevicius, S., Schluchter, M., Andreias, L., & Hack, M. (2012). Academic achievement of adolescents born with extremely low birth weight. *Acta Paediatrica, 101*(12), 1240-1245. doi: 10.1111/j.1651-2227.2012.02790.x

Loe, I. M., Lee, E. S., Luna, B., & Feldman, H. M. (2011). Behavior problems of 9-16 year old preterm children: biological, sociodemographic, and intellectual

contributions. *Early Human Development, 87*(4), 247-252. doi: 10.1016/j.earlhumdev.2011.01.023

Lohaugen, G. C., Gramstad, A., Evensen, K. A., Martinussen, M., Lindqvist, S., Indredavik, M., Vik, T., Brubakk, A. M., & Skranes, J. (2010). Cognitive profile in young adults born preterm at very low birthweight. *Developmental Medicine and Child Neurology, 52*(12), 1133-1138. doi: 10.1111/j.1469-8749.2010.03743.x

Lohaugen, G. C., Martinussen, M., Evensen, K. A., Vangberg, T., Haraldseth, O., Dale, A., Brubakk, A. M., & Skranes, J. (2009). Regional Cerebral Cortical Thinning and Neuropsychological Impairments in Very Low Birth Weight (VLBW) Adolescents. *Neuroimage, 47*(Supplement 1), S110. doi: 10.1016/s1053-8119(09)70985-1

Lohaugen, G. C., Martinussen, M., Haraldseth, O., Dale, A. M., Brubakk, A. M., & Skranes, J. (2009). Can Entorhinal Cortical Thinning Explain Reduced Cognitive Performance in Very Low Birth Weight Adolescents? *Neuroimage, 47*(Supplement 1), S179. doi: 10.1016/s1053-8119(09)71957-3

Luciana, M., Lindeke, L., Georgieff, M., Mills, M., & Nelson, C. A. (2007). Neurobehavioral evidence for working-memory deficits in school-aged children with histories of prematurity. *Developmental Medicine and Child Neurology, 41*(8), 521-533. doi: 10.1111/j.1469-8749.1999.tb00652.x

Luts, J., Molenberghs, G., Verbeke, G., Van Huffel, S., & Suykens, J. A. K. (2012). A mixed effects least squares support vector machine model for classification of longitudinal data. *Computational Statistics & Data Analysis, 56*(3), 611-628. doi: 10.1016/j.csda.2011.09.008

Luu, T. M., Ment, L., Allan, W., Schneider, K., & Vohr, B. R. (2011). Executive and memory function in adolescents born very preterm. *Pediatrics, 127*(3), e639-646. doi: 10.1542/peds.2010-1421

Lv, B., Li, J., He, H., Li, M., Zhao, M., Ai, L., Yan, F., Xian, J., & Wang, Z. (2010). Gender consistency and difference in healthy adults revealed by cortical thickness. *Neuroimage, 53*(2), 373-382. doi: 10.1016/j.neuroimage.2010.05.020

Martin, R. J., Wang, K., Koroglu, O., Di Fiore, J., & Kc, P. (2011). Intermittent hypoxic episodes in preterm infants: do they matter? *Neonatology, 100*(3), 303-310. doi: 10.1159/000329922

Martins, I. P., Vieira, R., Loureiro, C., & Santos, M. E. (2007). Speech rate and fluency in children and adolescents. *Child Neuropsychology, 13*(4), 319-332. doi: 10.1080/09297040600837370

Martinussen, M., Fischl, B., Larsson, H. B., Skranes, J., Kulseng, S., Vangberg, T. R., Vik, T., Brubakk, A. M., Haraldseth, O., & Dale, A. M. (2005). Cerebral cortex thickness in 15-year-old adolescents with low birth weight measured by an automated MRI-based method. *Brain, 128*(Pt 11), 2588-2596. doi: 10.1093/brain/awh610

Mazziotta, J. C., Toga, A. W., Evans, A., Fox, P., & Lancaster, J. (1995). A Probabilistic Atlas of the Human Brain: Theory and Rationale for Its Development. *Neuroimage, 2*(2), 89-101. doi: 10.1006/nimg.1995.1012

McCarthy, D. (1972). *Manual for the McCarthy scales of children's abilities*. New York: Psychological Corporation, Harcourt Brace Jovanovich.

McCarthy Scales of Children's Abilities. (2013). *Wikipedia, The Free Encyclopedia.* Retrieved 25 August 2014, from http://en.wikipedia.org/w/index.php?title=McCarthy_Scales_of_Children%27s_Abilities&oldid=557143298

McGaugh, J. L. (2000). Memory--a Century of Consolidation. *Science, 287*(5451), 248-251. doi: 10.1126/science.287.5451.248

McLeod, S. A. (2008). Working Memory. Retrieved 29 August 2014, from http://www.simplypsychology.org/working%20memory.html

Ment, L. R., Kesler, S., Vohr, B., Katz, K. H., Baumgartner, H., Schneider, K. C., Delancy, S., Silbereis, J., Duncan, C. C., Constable, R. T., Makuch, R. W., & Reiss, A. L. (2009). Longitudinal brain volume changes in preterm and term control subjects during late childhood and adolescence. *Pediatrics, 123*(2), 503-511. doi: 10.1542/peds.2008-0025

Mesulam, M. (1998). From sensation to cognition. *Brain, 121*(6), 1013-1052. doi: 10.1093/brain/121.6.1013

Meyler, A., Keller, T. A., Cherkassky, V. L., Gabrieli, J. D., & Just, M. A. (2008). Modifying the brain activation of poor readers during sentence comprehension with extended remedial instruction: a longitudinal study of neuroplasticity. *Neuropsychologia, 46*(10), 2580-2592. doi: 10.1016/j.neuropsychologia.2008.03.012

Miller, S. P., & Ferriero, D. M. (2009). From selective vulnerability to connectivity: insights from newborn brain imaging. *Trends in Neurosciences, 32*(9), 496-505. doi: 10.1016/j.tins.2009.05.010

Mills, K. L., Lalonde, F., Clasen, L. S., Giedd, J. N., & Blakemore, S. J. (2012). Developmental changes in the structure of the social brain in late childhood and adolescence. *Social Cognitive and Affective Neuroscience*. doi: 10.1093/scan/nss113

Molloy, C. S., Wilson-Ching, M., Doyle, L. W., Anderson, V. A., Anderson, P. J., & for the Victorian Infant Collaborative Study, G. (2013). Visual Memory and Learning in Extremely Low-Birth-Weight/Extremely Preterm Adolescents

Compared With Controls: A Geographic Study. *Journal of Pediatric Psychology*. doi: 10.1093/jpepsy/jst088

Moster, D., Lie, R. T., & Markestad, T. (2008). Long-term medical and social consequences of preterm birth. *New England Journal of Medicine, 359*(3), 262-273. doi: 10.1056/NEJMoa0706475

Mulder, H., Pitchford, N. J., & Marlow, N. (2011). Processing Speed Mediates Executive Function Difficulties in Very Preterm Children in Middle Childhood. *Journal of the International Neuropsychological Society, 17*(3), 1-10. doi: 10.1017/S1355617711000373

Muller, K. E., & Barton, C. N. (1989). Approximate Power for Repeated-Measures ANOVA Lacking Sphericity. *Journal of the American Statistical Association, 84*(406), 549-555. doi: 10.1080/01621459.1989.10478802

Muller, R. A., Rothermel, R. D., Behen, M. E., Muzik, O., Mangner, T. J., Chakraborty, P. K., & Chugani, H. T. (1998). Brain organization of language after early unilateral lesion: a PET study. *Brain and Language, 62*(3), 422-451. doi: 10.1006/brln.1997.1931

Murner-Lavanchy, I., Steinlin, M., Nelle, M., Rummel, C., Perrig, W. J., Schroth, G., & Everts, R. (2014). Delay of cortical thinning in very preterm born children. *Early Human Development, 90*(9), 443-450. doi: 10.1016/j.earlhumdev.2014.05.013

Murray, R. M., Lappin, J., & Di Forti, M. (2008). Schizophrenia: from developmental deviance to dopamine dysregulation. *European Neuropsychopharmacology, 18 Suppl 3*, S129-134. doi: 10.1016/j.euroneuro.2008.04.002

Nagy, Z., Lagercrantz, H., Forssberg, H., & Hutton, C. (2009). Investigating The Long–Term Effects Of Preterm Birth On Cortical Thickness. *Neuroimage, 47, Supplement 1*(0), S68. doi: http://dx.doi.org/10.1016/S1053-8119(09)70388-X

Nagy, Z., Lagercrantz, H., & Hutton, C. (2011). Effects of preterm birth on cortical thickness measured in adolescence. *Cerebral Cortex, 21*(2), 300-306. doi: 10.1093/cercor/bhq095

Narberhaus, A., Lawrence, E., Allin, M. P., Walshe, M., McGuire, P., Rifkin, L., Murray, R., & Nosarti, C. (2009). Neural substrates of visual paired associates in young adults with a history of very preterm birth: alterations in fronto-parieto-occipital networks and caudate nucleus. *Neuroimage, 47*(4), 1884-1893. doi: 10.1016/j.neuroimage.2009.04.036

Narberhaus, A., Segarra, D., Caldu, X., Gimenez, M., Pueyo, R., Botet, F., & Junque, C. (2008). Corpus callosum and prefrontal functions in adolescents with history of very preterm birth. *Neuropsychologia, 46*(1), 111-116. doi: 10.1016/j.neuropsychologia.2007.08.004

Narr, K. L., Bilder, R. M., Toga, A. W., Woods, R. P., Rex, D. E., Szeszko, P. R., Robinson, D., Sevy, S., Gunduz-Bruce, H., Wang, Y. P., DeLuca, H., & Thompson, P. M. (2005). Mapping cortical thickness and gray matter concentration in first episode schizophrenia. *Cerebral Cortex, 15*(6), 708-719. doi: 10.1093/cercor/bhh172

Narr, K. L., Woods, R. P., Thompson, P. M., Szeszko, P., Robinson, D., Dimtcheva, T., Gurbani, M., Toga, A. W., & Bilder, R. M. (2007). Relationships between IQ and Regional Cortical Gray Matter Thickness in Healthy Adults. *Cerebral Cortex, 17*(9), 2163-2171. doi: 10.1093/cercor/bhl125

Norman, D. A., & Shallice, T. (1986). Attention to action: willed and automatic control of behaviour. In S. G.E. & S. D. (Eds.), *Consciousness and self-regulation* (Vol. 4). New York: Plenum Press.

Northam, G. B., Liegeois, F., Chong, W. K., Wyatt, J. S., & Baldeweg, T. (2011). Total brain white matter is a major determinant of IQ in adolescents born preterm. *Annals of Neurology, 69*(4), 702-711. doi: 10.1002/ana.22263

Nosarti, C. (2013). Structural and functional brain correlates of behavioral outcomes during adolescence. *Early Human Development, 89*(4), 221-227. doi: 10.1016/j.earlhumdev.2013.02.002

Nosarti, C., Al-Asady, M. H. S., Frangou, S., Stewart, A. L., Rifkin, L., & Murray, R. M. (2002). Adolescents who were born very preterm have decreased brain volumes. *Brain, 125*(Pt 7), 1616-1623. doi: 10.1093/Brain/Awf157

Nosarti, C., Allin, M. P., Frangou, S., Rifkin, L., & Murray, R. M. (2005). Hyperactivity in adolescents born very preterm is associated with decreased caudate volume. *Biological Psychiatry, 57*(6), 661-666. doi: 10.1016/j.biopsych.2004.12.003

Nosarti, C., Giouroukou, E., Healy, E., Rifkin, L., Walshe, M., Reichenberg, A., Chitnis, X., Williams, S. C., & Murray, R. M. (2008). Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain, 131*(Pt 1), 205-217. doi: 10.1093/brain/awm282

Nosarti, C., Giouroukou, E., Micali, N., Rifkin, L., Morris, R. G., & Murray, R. M. (2007). Impaired executive functioning in young adults born very preterm. *Journal of the International Neuropsychological Society, 13*(4), 571-581. doi: 10.1017/S1355617707070725

Nosarti, C., Nam, K., Walshe, M., Murray, R. M., Cuddy, M., Rifkin, L., & Allin, M. (2014). Preterm birth and structural brain alterations in early adulthood. *NeuroImage: Clinical*. doi: 10.1016/j.nicl.2014.08.005

Nosarti, C., Reichenberg, A., Murray, R. M., Cnattingius, S., Lambe, M. P., Yin, L., MacCabe, J., Rifkin, L., & Hultman, C. M. (2012). Preterm birth and psychiatric

disorders in young adult life. *Archives of General Psychiatry, 69*(6), E1-8. doi: 10.1001/archgenpsychiatry.2011.1374

Nosarti, C., Rubia, K., Smith, A. B., Frearson, S., Williams, S. C., Rifkin, L., & Murray, R. M. (2006). Altered functional neuroanatomy of response inhibition in adolescent males who were born very preterm. *Developmental Medicine and Child Neurology, 48*(4), 265-271. doi: 10.1017/S0012162206000582

Nosarti, C., Rushe, T. M., Woodruff, P. W. R., Stewart, A. L., Rifkin, L., & Murray, R. M. (2004). Corpus callosum size and very preterm birth: Relationship to neuropsychological outcome. *Brain, 127*(9), 2080-2089. doi: 10.1093/brain/awh230

Nosarti, C., Shergill, S. S., Allin, M. P., Walshe, M., Rifkin, L., Murray, R. M., & McGuire, P. K. (2009). Neural substrates of letter fluency processing in young adults who were born very preterm: Alterations in frontal and striatal regions. *Neuroimage, 47*(4), 1904-1913. doi: 10.1016/j.neuroimage.2009.04.041

Numan, B., Sweet, J. J., & Ranganath, C. (2000). Use of the california verbal learning test to detect proactive interference in the traumatically brain injured. *Journal of Clinical Psychology, 56*(4), 553-562. doi: 10.1002/(sici)1097-4679(200004)56:4<553::aid-jclp8>3.0.co;2-q

O'Brien, F. (2004). The neurodevelopmental progress of infants less than 33 weeks into adolescence. *Archives of Disease in Childhood, 89*(3), 207-211. doi: 10.1136/adc.2002.006676

O'Brien, G., & Pearson, J. (2004). Autism and learning disability. *Autism, 8*(2), 125-140. doi: 10.1177/1362361304042718

O'Donnell, S., Noseworthy, M. D., Levine, B., & Dennis, M. (2005). Cortical thickness of the frontopolar area in typically developing children and adolescents. *Neuroimage, 24*(4), 948-954. doi: 10.1016/j.neuroimage.2004.10.014

Omizzolo, C., Scratch, S. E., Stargatt, R., Kidokoro, H., Thompson, D. K., Lee, K. J., Cheong, J., Neil, J., Inder, T. E., Doyle, L. W., & Anderson, P. J. (2014). Neonatal brain abnormalities and memory and learning outcomes at 7 years in children born very preterm. *Memory, 22*(6), 605-615. doi: 10.1080/09658211.2013.809765

Omizzolo, C., Thompson, D. K., Scratch, S. E., Stargatt, R., Lee, K. J., Cheong, J., Roberts, G., Doyle, L. W., & Anderson, P. J. (2013). Hippocampal volume and memory and learning outcomes at 7 years in children born very preterm. *Journal of the International Neuropsychological Society, 19*(10), 1065-1075. doi: 10.1017/S1355617713000891

Orru, G., Pettersson-Yeo, W., Marquand, A. F., Sartori, G., & Mechelli, A. (2012). Using Support Vector Machine to identify imaging biomarkers of neurological and psychiatric disease: a critical review. *Neuroscience and Biobehavioral Reviews, 36*(4), 1140-1152. doi: 10.1016/j.neubiorev.2012.01.004

Otsuka, Y., Osaka, N., & Osaka, M. (2008). Functional asymmetry of superior parietal lobule for working memory in the elderly. *Neuroreport, 19*(14), 1355-1359. doi: 10.1097/WNR.0b013e32830e000f

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping, 25*(1), 46-59. doi: 10.1002/hbm.20131

Paarlberg, K. M., Vingerhoets, A. J., Passchier, J., Dekker, G. A., Heinen, A. G., & van Geijn, H. P. (1999). Psychosocial predictors of low birthweight: a prospective study. *British Journal of Obstetrics and Gynaecology, 106*(8), 834-841.

Palmer, B. W., & Heaton, R. K. (2000). Executive dysfunction in schizophrenia. In T. Sharma & P. D. Harvey (Eds.), *Cognition in schizophre- nia: Impairments,*

importance and treatment strategies (pp. 51-72). Oxford, United Kingdom: Oxford University Press.

Parker, J., Mitchell, A., Kalpakidou, A., Walshe, M., Jung, H.-Y., Nosarti, C., Santosh, P., Rifkin, L., Wyatt, J., Murray, R. M., & Allin, M. (2008). Cerebellar growth and behavioural & neuropsychological outcome in preterm adolescents. *Brain, 131*(5), 1344-1351. doi: 10.1093/brain/awn062

Pascoe, L., Roberts, G., Doyle, L. W., Lee, K. J., Thompson, D. K., Seal, M. L., Josev, E. K., Nosarti, C., Gathercole, S., & Anderson, P. J. (2013). Preventing academic difficulties in preterm children: a randomised controlled trial of an adaptive working memory training intervention - IMPRINT study. *BMC Pediatrics, 13*, 144. doi: 10.1186/1471-2431-13-144

Pascual, B., Masdeu, J. C., Hollenbeck, M., Makris, N., Insausti, R., Ding, S. L., & Dickerson, B. C. (2013). Large-Scale Brain Networks of the Human Left Temporal Pole: A Functional Connectivity MRI Study. *Cerebral Cortex*. doi: 10.1093/cercor/bht260

Patterson, J. (2011). Controlled Oral Word Association Test. 703-706. doi: 10.1007/978-0-387-79948-3_876

Pearl, R., & Donahue, M. (1995). Four Years After a Preterm Birth: Children's Development and Their Mothers' Beliefs and Expectations. *Journal of Pediatric Psychology, 20*(3), 363-370. doi: 10.1093/jpepsy/20.3.363

Peng, Y., Huang, B., Biro, F., Feng, L., Guo, Z., & Slap, G. (2007). Outcome of low birthweight in China: A 16-year longitudinal study. *Acta Paediatrica, 94*(7), 843-849. doi: 10.1111/j.1651-2227.2005.tb01999.x

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., & Raichle, M. E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature, 331*(6157), 585-589. doi: 10.1038/331585a0

Peterson, B. S., Anderson, A. W., Ehrenkranz, R., Staib, L. H., Tageldin, M., Colson, E., Gore, J. C., Duncan, C. C., Makuch, R., & Ment, L. R. (2003). Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. *Pediatrics, 111*(5 Pt 1), 939-948.

Peterson, B. S., Vohr, B., Staib, L. H., Cannistraci, C. J., Dolberg, A., Schneider, K. C., Katz, K. H., Westerveld, M., Sparrow, S., Anderson, A. W., Duncan, C. C., Makuch, R. W., Gore, J. C., & Ment, L. R. (2000). Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA : the journal of the American Medical Association, 284*(15), 1939-1947.

Peterson, L. R., & Peterson, M. J. (1959). Short-term retention of individual verbal items. *Journal of Experimental Psychology, 58*(3), 193-198. doi: 10.1037/h0049234

Petrides, M. (2005). Lateral prefrontal cortex: architectonic and functional organization. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 360*(1456), 781-795. doi: 10.1098/rstb.2005.1631

Petrie Thomas, J. H., Whitfield, M. F., Oberlander, T. F., Synnes, A. R., & Grunau, R. E. (2012). Focused attention, heart rate deceleration, and cognitive development in preterm and full-term infants. *Developmental Psychobiology, 54*(4), 383-400. doi: 10.1002/dev.20597

Phillips, O. R., Clark, K. A., Luders, E., Azhir, R., Joshi, S. H., Woods, R. P., Mazziotta, J. C., Toga, A. W., & Narr, K. L. (2013). Superficial white matter: effects of age, sex, and hemisphere. *Brain Connect, 3*(2), 146-159. doi: 10.1089/brain.2012.0111

Porter, J. N., Collins, P. F., Muetzel, R. L., Lim, K. O., & Luciana, M. (2011). Associations between cortical thickness and verbal fluency in childhood,

adolescence, and young adulthood. *Neuroimage, 55*(4), 1865-1877. doi: 10.1016/j.neuroimage.2011.01.018

Pyhala, R., Lahti, J., Heinonen, K., Pesonen, A. K., Strang-Karlsson, S., Hovi, P., Jarvenpaa, A. L., Eriksson, J. G., Andersson, S., Kajantie, E., & Raikkonen, K. (2011). Neurocognitive abilities in young adults with very low birth weight. *Neurology, 77*(23), 2052-2060. doi: 10.1212/WNL.0b013e31823b473e

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98*(2), 676-682. doi: 10.1073/pnas.98.2.676

Ravizza, S. M., McCormick, C. A., Schlerf, J. E., Justus, T., Ivry, R. B., & Fiez, J. A. (2006). Cerebellar damage produces selective deficits in verbal working memory. *Brain, 129*(Pt 2), 306-320. doi: 10.1093/brain/awh685

Raznahan, A., Shaw, P., Lalonde, F., Stockman, M., Wallace, G. L., Greenstein, D., Clasen, L., Gogtay, N., & Giedd, J. N. (2011). How does your cortex grow? *Journal of Neuroscience, 31*(19), 7174-7177. doi: 10.1523/JNEUROSCI.0054-11.2011

Raznahan, A., Shaw, P. W., Lerch, J. P., Clasen, L. S., Greenstein, D., Berman, R., Pipitone, J., Chakravarty, M. M., & Giedd, J. N. (2014). Longitudinal four-dimensional mapping of subcortical anatomy in human development. *Proceedings of the National Academy of Sciences of the United States of America, 111*(4), 1592-1597. doi: 10.1073/pnas.1316911111

Reiss, A. L., Abrams, M. T., Singer, H. S., Ross, J. L., & Denckla, M. B. (1996). Brain development, gender and IQ in children. A volumetric imaging study. *Brain, 119 (Pt 5)*(5), 1763-1774. doi: 10.1093/brain/119.5.1763

Repovs, G., Csernansky, J. G., & Barch, D. M. (2011). Brain network connectivity in individuals with schizophrenia and their siblings. *Biological Psychiatry, 69*(10), 967-973. doi: 10.1016/j.biopsych.2010.11.009

Riddle, T., & Suhr, J. (2012). Extension of the Contingency Naming Test to adult assessment: psychometric analysis in a college student sample. *Clinical Neuropsychologist, 26*(4), 609-625. doi: 10.1080/13854046.2012.666265

Robbins, S. M. (2003). *Anatomical standardization of the human brain in euclidean 3-space and on the cortical 2-manifold.* McGill University. Retrieved from http://digitool.Library.McGill.CA:80/R/?func=dbin-jump-full&object_id=84315

Rogers, C. E., Lenze, S. N., & Luby, J. L. (2013). Late preterm birth, maternal depression, and risk of preschool psychiatric disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(3), 309-318. doi: 10.1016/j.jaac.2012.12.005

Rose, S. A., & Feldman, J. F. (1996). Memory and processing speed in preterm children at eleven years: A comparison with full-terms. *Child Development, 67*(5), 2005-2021. doi: 10.1111/j.1467-8624.1996.tb01840.x

Rubia, K., Smith, A. B., Woolley, J., Nosarti, C., Heyman, I., Taylor, E., & Brammer, M. (2006). Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. *Human Brain Mapping, 27*(12), 973-993. doi: 10.1002/hbm.20237

Rueda, M. R., Rothbart, M. K., McCandliss, B. D., Saccomanno, L., & Posner, M. I. (2005). Training, maturation, and genetic influences on the development of executive attention. *Proceedings of the National Academy of Sciences of the United States of America, 102*(41), 14931-14936. doi: 10.1073/pnas.0506897102

Rushe, T. M., Rifkin, L., Stewart, A. L., Townsend, J. P., Roth, S. C., Wyatt, J. S., & Murray, R. M. (2001). Neuropsychological outcome at adolescence of very preterm birth and its relation to brain structure. *Developmental Medicine and Child Neurology*, *43*(4), 226-233. doi: 10.1111/j.1469-8749.2001.tb00194.x

Saavalainen, P., Luoma, L., Bowler, D., Maatta, S., Kiviniemi, V., Laukkanen, E., & Herrgard, E. (2007). Spatial span in very prematurely born adolescents. *Developmental Neuropsychology*, *32*(3), 769-785. doi: 10.1080/87565640701539535

Saigal, S., Pinelli, J., Hoult, L., Kim, M. M., & Boyle, M. (2003). Psychopathology and social competencies of adolescents who were extremely low birth weight. *Pediatrics*, *111*(5 Pt 1), 969-975.

Saklofske, D. H., Caravan, G., & Schwartz, C. (2000). Concurrent Validity of the Wechsler Abbreviated Scale of Intelligence (WASI) with a Sample of Canadian Children. *Canadian Journal of School Psychology, 16*(1), 87-94. doi: 10.1177/082957350001600106

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S. R., Busa, E., Morris, J. C., Dale, A. M., & Fischl, B. (2004). Thinning of the Cerebral Cortex in Aging. *Cerebral Cortex, 14*(7), 721-730. doi: 10.1093/cercor/bhh032

Salvan, P., Froudist Walsh, S., Allin, M. P., Walshe, M., Murray, R. M., Bhattacharyya, S., McGuire, P. K., Williams, S. C., & Nosarti, C. (2013). Road work on memory lane-Functional and structural alterations to the learning and memory circuit in adults born very preterm. *Neuroimage*. doi: 10.1016/j.neuroimage.2013.12.031

Sansavini, A., Pentimonti, J., Justice, L., Guarini, A., Savini, S., Alessandroni, R., & Faldella, G. (2014). Language, motor and cognitive development of extremely preterm children: modeling individual growth trajectories over the first three

years of life. *Journal of Communication Disorders, 49*, 55-68. doi: 10.1016/j.jcomdis.2014.02.005

Schafer, R. J., Lacadie, C., Vohr, B., Kesler, S. R., Katz, K. H., Schneider, K. C., Pugh, K. R., Makuch, R. W., Reiss, A. L., Constable, R. T., & Ment, L. R. (2009). Alterations in functional connectivity for language in prematurely born adolescents. *Brain, 132*(Pt 3), 661-670. doi: 10.1093/brain/awn353

Schmidt, L. A., Miskovic, V., Boyle, M., & Saigal, S. (2010). Frontal electroencephalogram asymmetry, salivary cortisol, and internalizing behavior problems in young adults who were born at extremely low birth weight. *Child Development, 81*(1), 183-199. doi: 10.1111/j.1467-8624.2009.01388.x

Scott, F. E., Mechelli, A., Allin, M. P., Walshe, M., Rifkin, L., Murray, R. M., & Nosarti, C. (2011). Very preterm adolescents show gender-dependent alteration of the structural brain correlates of spelling abilities. *Neuropsychologia, 49*(9), 2685-2693. doi: 10.1016/j.neuropsychologia.2011.05.016

Seamon, J. G., & Kenrick, D. T. (1994). *Psychology*. Englewood Cliffs, NJ: Prentice Hall.

Shah, P. E., Robbins, N., Coelho, R. B., & Poehlmann, J. (2013). The paradox of prematurity: the behavioral vulnerability of late preterm infants and the cognitive susceptibility of very preterm infants at 36 months post-term. *Infant Behavior & Development, 36*(1), 50-62. doi: 10.1016/j.infbeh.2012.11.003

Shang, C. Y., Wu, Y. H., Gau, S. S., & Tseng, W. Y. (2013). Disturbed microstructural integrity of the frontostriatal fiber pathways and executive dysfunction in children with attention deficit hyperactivity disorder. *Psychological Medicine, 43*(5), 1093-1107. doi: 10.1017/S0033291712001869

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., Clasen, L., Evans, A., Giedd, J., & Rapoport, J. L. (2007). Attention-

deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences of the United States of America, 104*(49), 19649-19654. doi: 10.1073/pnas.0707741104

Shaw, P., Gilliam, M., Liverpool, M., Weddle, C., Malek, M., Sharp, W., Greenstein, D., Evans, A., Rapoport, J., & Giedd, J. (2011). Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: support for a dimensional view of attention deficit hyperactivity disorder. *The American journal of psychiatry, 168*(2), 143-151. doi: 10.1176/appi.ajp.2010.10030385

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., Evans, A., Rapoport, J., & Giedd, J. (2006). Intellectual ability and cortical development in children and adolescents. *Nature, 440*(7084), 676-679. doi: 10.1038/nature04513

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., Rapoport, J. L., Giedd, J. N., & Wise, S. P. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *Journal of Neuroscience, 28*(14), 3586-3594. doi: 10.1523/JNEUROSCI.5309-07.2008

Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Mencl, W. E., Fulbright, R. K., Skudlarski, P., Constable, R. T., Marchione, K. E., Fletcher, J. M., Lyon, G. R., & Gore, J. C. (2002). Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biological Psychiatry, 52*(2), 101-110. doi: 10.1016/s0006-3223(02)01365-3

Shum, D., Neulinger, K., O'Callaghan, M., & Mohay, H. (2008). Attentional problems in children born very preterm or with extremely low birth weight at 7-9 years. *Archives of Clinical Neuropsychology, 23*(1), 103-112. doi: 10.1016/j.acn.2007.08.006

Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2008). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia, 46*(1), 224-232. doi: 10.1016/j.neuropsychologia.2007.07.015

Simmons, A., Westman, E., Muehlboeck, S., Mecocci, P., Vellas, B., Tsolaki, M., Kloszewska, I., Wahlund, L. O., Soininen, H., Lovestone, S., Evans, A., & Spenger, C. (2011). The AddNeuroMed framework for multi-centre MRI assessment of Alzheimer's disease: experience from the first 24 months. *International Journal of Geriatric Psychiatry, 26*(1), 75-82. doi: 10.1002/gps.2491

Simmons, A., Westman, E., Muehlboeck, S., Mecocci, P., Vellas, B., Tsolaki, M., Kloszewska, I., Wahlund, L. O., Soininen, H., Lovestone, S., Evans, A., Spenger, C. (2009). MRI measures of Alzheimer's disease and the AddNeuroMed study. *Annals of the New York Academy of Sciences, 1180*, 47-55. doi: 10.1111/j.1749-6632.2009.05063.x

Skranes, J., Lohaugen, G. C., Evensen, K. A., Indredavik, M. S., Haraldseth, O., Dale, A. M., Brubakk, A. M., & Martinussen, M. (2012). Entorhinal cortical thinning affects perceptual and cognitive functions in adolescents born preterm with very low birth weight (VLBW). *Early Human Development, 88*(2), 103-109. doi: 10.1016/j.earlhumdev.2011.07.017

Skranes, J., Lohaugen, G. C., Martinussen, M., Haberg, A., Brubakk, A. M., & Dale, A. M. (2013). Cortical surface area and IQ in very-low-birth-weight (VLBW) young adults. *Cortex, 49*(8), 2264-2271. doi: 10.1016/j.cortex.2013.06.001

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging, 17*(1), 87-97. doi: 10.1109/42.668698

Smith, E. E., & Jonides, J. (1999). Neuroscience - Storage and executive processes in the frontal lobes. *Science, 283*(5408), 1657-1661. doi: 10.1126/science.283.5408.1657

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143-155. doi: 10.1002/hbm.10062

Soares, D. d. A., Cunha, A. B., & Tudella, E. (2014). Differences between late preterm and full-term infants: Comparing effects of a short bout of practice on early reaching behavior. *Research in Developmental Disabilities, 35*(11), 3096-3107. doi: 10.1016/j.ridd.2014.07.041

Somhovd, M. J., Hansen, B. M., Brok, J., Esbjorn, B. H., & Greisen, G. (2012). Anxiety in adolescents born preterm or with very low birthweight: a meta-analysis of case-control studies. *Developmental Medicine and Child Neurology, 54*(11), 988-994. doi: 10.1111/j.1469-8749.2012.04407.x

Soria-Pastor, S., Gimenez, M., Narberhaus, A., Falcon, C., Botet, F., Bargallo, N., Mercader, J. M., & Junque, C. (2008). Patterns of cerebral white matter damage and cognitive impairment in adolescents born very preterm. *International Journal of Developmental Neuroscience, 26*(7), 647-654. doi: 10.1016/j.ijdevneu.2008.08.001

Soria-Pastor, S., Padilla, N., Zubiaurre-Elorza, L., Ibarretxe-Bilbao, N., Botet, F., Costas-Moragas, C., Falcon, C., Bargallo, N., Mercader, J. M., & Junque, C. (2009). Decreased regional brain volume and cognitive impairment in preterm children at low risk. *Pediatrics, 124*(6), e1161-1170. doi: 10.1542/peds.2009-0244

Sowell, E. R., Thompson, P. M., Leonard, C. M., Welcome, S. E., Kan, E., & Toga, A. W. (2004). Longitudinal Mapping of Cortical Thickness and Brain Growth in

Normal Children. *The Journal of Neuroscience, 24*(38), 8223-8231. doi: 10.1523/jneurosci.1798-04.2004

Spittle, A. J., Anderson, P. J., Lee, K. J., Ferretti, C., Eeles, A., Orton, J., Boyd, R. N., Inder, T., & Doyle, L. W. (2010). Preventive care at home for very preterm infants improves infant and caregiver outcomes at 2 years. *Pediatrics, 126*(1), e171-178. doi: 10.1542/peds.2009-3137

Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review, 99*(2), 195-231. doi: 10.1037//0033-295x.99.2.195

Srinivasan, L., Dutta, R., Counsell, S. J., Allsop, J. M., Boardman, J. P., Rutherford, M. A., & Edwards, A. D. (2007). Quantification of deep gray matter in preterm infants at term-equivalent age using manual volumetry of 3-tesla magnetic resonance images. *Pediatrics, 119*(4), 759-765. doi: 10.1542/peds.2006-2508

Statistics, O. f. N. (2011). Release Edition Reference Tables (Text). Retrieved 2014-06-09 http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-320891

Steer, P. (2005). The epidemiology of preterm labour. *BJOG: An International Journal of Obstetrics and Gynaecology, 112 Suppl 1*, 1-3. doi: 10.1111/j.1471-0528.2005.00575.x

Strang-Karlsson, S., Andersson, S., Paile-Hyvarinen, M., Darby, D., Hovi, P., Raikkonen, K., Pesonen, A. K., Heinonen, K., Jarvenpaa, A. L., Eriksson, J. G., & Kajantie, E. (2010). Slower reaction times and impaired learning in young adults with birth weight <1500 g. *Pediatrics, 125*(1), e74-82. doi: 10.1542/peds.2009-1297

Strang-Karlsson, S., Raikkonen, K., Pesonen, A. K., Kajantie, E., Paavonen, E. J., Lahti, J., Hovi, P., Heinonen, K., Jarvenpaa, A. L., Eriksson, J. G., & Andersson, S.

(2008). Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. *The American journal of psychiatry, 165*(10), 1345-1353. doi: 10.1176/appi.ajp.2008.08010085

Stuss, D. T., & Alexander, M. P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 362*(1481), 901-915. doi: 10.1098/rstb.2007.2096

Stuss, D. T., & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. *Psychological Bulletin, 95*(1), 3-28.

Sullivan, M. C., Msall, M. E., & Miller, R. J. (2012). 17-year outcome of preterm infants with diverse neonatal morbidities: Part 1--Impact on physical, neurological, and psychological health status. *Journal for Specialists in Pediatric Nursing, 17*(3), 226-241. doi: 10.1111/j.1744-6155.2012.00337.x

Tamnes, C. K., Østby, Y., Fjell, A. M., Westlye, L. T., Due-Tønnessen, P., & Walhovd, K. B. (2010). Brain Maturation in Adolescence and Young Adulthood: Regional Age-Related Changes in Cortical Thickness and White Matter Volume and Microstructure. *Cerebral Cortex, 20*(3), 534-548. doi: 10.1093/cercor/bhp118

Tau, G. Z., & Peterson, B. S. (2010). Normal development of brain circuits. *Neuropsychopharmacology, 35*(1), 147-168. doi: 10.1038/npp.2009.115

Taylor, H. G., Klein, N., Minich, N. M., & Hack, M. (2000). Middle-School-Age Outcomes in Children with Very Low Birthweight. *Child Development, 71*(6), 1495-1511. doi: 10.1111/1467-8624.00242

Taylor, H. G., Minich, N., Bangert, B., Filpek, P. A., & Hack, M. (2004). Long-term neuropsychological outcomes of very low birth weight: Associations with early risks for periventricular brain insults. *Journal of the International*

Neuropsychological Society, 10(7), 987-1004. doi: 10.1017/S1355617704107078

Taylor, H. G., Minich, N. M., Klein, N., & Hack, M. (2004). Longitudinal outcomes of very low birth weight: neuropsychological findings. *Journal of the International Neuropsychological Society, 10*(2), 149-163. doi: 10.1017/S1355617704102038

Taylor, M. J., Donner, E. J., & Pang, E. W. (2012). fMRI and MEG in the study of typical and atypical cognitive development. *Neurophysiologie Clinique, 42*(1-2), 19-25. doi: 10.1016/j.neucli.2011.08.002

Therien, J. M., Worwa, C. T., Mattia, F. R., & DeRegnier, R.-A. O. (2004). Altered pathways for auditory discrimination and recognition memory in preterm infants. *Developmental Medicine and Child Neurology, 46*(12), 816-824. doi: 10.1111/j.1469-8749.2004.tb00447.x

Thompson, D. K., Wood, S. J., Doyle, L. W., Warfield, S. K., Lodygensky, G. A., Anderson, P. J., Egan, G. F., & Inder, T. E. (2008). Neonate hippocampal volumes: prematurity, perinatal predictors, and 2-year outcome. *Annals of Neurology, 63*(5), 642-651. doi: 10.1002/ana.21367

Thorndike, R. L., Hagen, E. P., & Sattler, J. M. (1986). *Stanford-Binet Intelligence Scales* (4th ed.). Itasca, IL: Riverside Publishing Company.

Tideman, E. (2000). Longitudinal follow-up of children born preterm: cognitive development at age 19. *Early Human Development, 58*(2), 81-90. doi: 10.1016/S0378-3782(00)00055-4

Tiemeier, H., Lenroot, R. K., Greenstein, D. K., Tran, L., Pierson, R., & Giedd, J. N. (2010). Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. *Neuroimage, 49*(1), 63-70. doi: 10.1016/j.neuroimage.2009.08.016

Tohka, J., Zijdenbos, A., & Evans, A. (2004). Fast and robust parameter estimation for statistical partial volume models in brain MRI. *Neuroimage, 23*(1), 84-97. doi: 10.1016/j.neuroimage.2004.05.007

Towusewi, E., & Pallotta, S. (n.d.). Commentary on "Volumetric MRI and MRS and early motor development of infants born preterm". *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association, 24*(1), 44-45. doi: 10.1097/PEP.0b013e31823e0abb

Treyvaud, K., Ure, A., Doyle, L. W., Lee, K. J., Rogers, C. E., Kidokoro, H., Inder, T. E., & Anderson, P. J. (2013). Psychiatric outcomes at age seven for very preterm children: rates and predictors. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 54*(7), 772-779. doi: 10.1111/jcpp.12040

Trochim, W. M. K. (2006, 20 October 2006). Convergent & Discriminant Validity. Retrieved 1 September 2014

Tucker, J., & McGuire, W. (2004). Epidemiology of preterm birth. *BMJ, 329*(7467), 675-678. doi: 10.1136/bmj.329.7467.675

Van Hus, J. W., Potharst, E. S., Jeukens-Visser, M., Kok, J. H., & Van Wassenaer-Leemhuis, A. G. (2014). Motor impairment in very preterm-born children: links with other developmental deficits at 5 years of age. *Developmental Medicine and Child Neurology, 56*(6), 587-594. doi: 10.1111/dmcn.12295

Van Kooij, B. J., Benders, M. J., Anbeek, P., Van Haastert, I. C., De Vries, L. S., & Groenendaal, F. (2012). Cerebellar volume and proton magnetic resonance spectroscopy at term, and neurodevelopment at 2 years of age in preterm infants. *Developmental Medicine and Child Neurology, 54*(3), 260-266. doi: 10.1111/j.1469-8749.2011.04168.x

van Noort-van der Spek, I. L., Franken, M. C., & Weisglas-Kuperus, N. (2012). Language functions in preterm-born children: a systematic review and meta-analysis. *Pediatrics, 129*(4), 745-754. doi: 10.1542/peds.2011-1728

van Tol, M. J., Li, M., Metzger, C. D., Hailla, N., Horn, D. I., Li, W., Heinze, H. J., Bogerts, B., Steiner, J., He, H., & Walter, M. (2013). Local cortical thinning links to resting-state disconnectivity in major depressive disorder. *Psychological Medicine*, 1-13. doi: 10.1017/S0033291713002742

Vapnik, V. N. (1995). *The nature of statistical learning theory*. New York: Springer-Verlag.

Volpe, J. J. (2009). Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *The Lancet Neurology, 8*(1), 110-124. doi: Doi: 10.1016/s1474-4422(08)70294-1

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory. *Cognitive, Affective, & Behavioral Neuroscience, 3*(4), 255-274. doi: 10.3758/cabn.3.4.255

Walhovd, K. B., Tamnes, C. K., Bjornerud, A., Due-Tonnessen, P., Holland, D., Dale, A. M., & Fjell, A. M. (2014). Maturation of Cortico-Subcortical Structural Networks--Segregation and Overlap of Medial Temporal and Fronto-Striatal Systems in Development. *Cerebral Cortex*. doi: 10.1093/cercor/bht424

Walsh, N. D., Dalgleish, T., Lombardo, M. V., Dunn, V. J., Van Harmelen, A. L., Ban, M., & Goodyer, I. M. (2014). General and specific effects of early-life psychosocial adversities on adolescent grey matter volume. *Neuroimage Clin, 4*, 308-318. doi: 10.1016/j.nicl.2014.01.001

Walshe, M., Rifkin, L., Rooney, M., Healy, E., Nosarti, C., Wyatt, J., Stahl, D., Murray, R. M., & Allin, M. (2008). Psychiatric disorder in young adults born very

preterm: Role of family history. *European Psychiatry, 23*(7), 527-531. doi: 10.1016/j.eurpsy.2008.06.004

Watanabe, J., Sugiura, M., Sato, K., Sato, Y., Maeda, Y., Matsue, Y., Fukuda, H., & Kawashima, R. (2002). The Human Prefrontal and Parietal Association Cortices Are Involved in NO-GO Performances: An Event-Related fMRI Study. *Neuroimage, 17*(3), 1207-1216. doi: 10.1006/nimg.2002.1198

Wechsler, D. (1987). *Wechsler Memory Scale - Revised*. New York: Psychological Corporation.

Wechsler, D. (1989). *Wechsler Preschool and Primary Scale of Intelligence – Revised*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997). *WAIS-III: Administration and Scoring Manual*: Harcourt Brace & Company.

Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence*. New York: Psychological Corporation.

Wechsler, D. (2008). *WAIS-IV administration and scoring manual*. San Antonio, TX: Pearson.

Weindrich, D., Jennen-Steinmetz, C., Laucht, M., & Schmidt, M. H. (2003). Late sequelae of low birthweight: mediators of poor school performance at 11 years. *Developmental Medicine and Child Neurology, 45*(7), 463-469.

Weisglas-Kuperus, N., Hille, E. T., Duivenvoorden, H. J., Finken, M. J., Wit, J. M., van Buuren, S., van Goudoever, J. B., & Verloove-Vanhorick, S. P. (2009). Intelligence of very preterm or very low birthweight infants in young adulthood. *Archives of disease in childhood. Fetal and neonatal edition, 94*(3), F196-200. doi: 10.1136/adc.2007.135095

Weschsler, D. (1991). *Wechsler Intelligence Scale for Children*. San Antonia, TX: The Psychological Corporation.

Westlye, L. T., Grydeland, H., Walhovd, K. B., & Fjell, A. M. (2011). Associations between regional cortical thickness and attentional networks as measured by the attention network test. *Cerebral Cortex, 21*(2), 345-356. doi: 10.1093/cercor/bhq101

White, T. P., Symington, I., Castellanos, N. P., Brittain, P. J., Froudist Walsh, S., Nam, K. W., Sato, J. R., Allin, M. P., Shergill, S. S., Murray, R. M., Williams, S. C., & Nosarti, C. (2014). Dysconnectivity of neurocognitive networks at rest in very-preterm born adults. *Neuroimage Clin, 4*, 352-365. doi: 10.1016/j.nicl.2014.01.005

WHO. (2013). Preterm birth. from http://www.who.int/mediacentre/factsheets/fs363/en/

Wierenga, L., Langen, M., Ambrosino, S., van Dijk, S., Oranje, B., & Durston, S. (2014). Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24. *Neuroimage, 96*, 67-72. doi: 10.1016/j.neuroimage.2014.03.072

Wilson-Ching, M., Molloy, C. S., Anderson, V. A., Burnett, A., Roberts, G., Cheong, J. L., Doyle, L. W., & Anderson, P. J. (2013). Attention difficulties in a contemporary geographic cohort of adolescents born extremely preterm/extremely low birth weight. *Journal of the International Neuropsychological Society, 19*(10), 1097-1108. doi: 10.1017/S1355617713001057

Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., Duggirala, R., & Glahn, D. C. (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage, 53*(3), 1135-1146. doi: 10.1016/j.neuroimage.2009.12.028

Woodward, L. J., Clark, C. A., Bora, S., & Inder, T. E. (2012). Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. *PloS One, 7*(12), e51879. doi: 10.1371/journal.pone.0051879

Woodward, L. J., Clark, C. A., Pritchard, V. E., Anderson, P. J., & Inder, T. E. (2011). Neonatal White Matter Abnormalities Predict Global Executive Function Impairment in Children Born Very Preterm. *Developmental Neuropsychology, 36*(1), 22-41. doi: 10.1080/87565641.2011.540530

Woodward, L. J., Edgin, J. O., Thompson, D., & Inder, T. E. (2005). Object working memory deficits predicted by early brain injury and development in the preterm infant. *Brain, 128*(Pt 11), 2578-2587. doi: 10.1093/brain/awh618

Worsley, K. J., Andermann, M., Koulis, T., MacDonald, D., & Evans, A. C. (1999). Detecting changes in nonisotropic images. *Human Brain Mapping, 8*(2-3), 98-101.

Wu, M., Lu, L. H., Lowes, A., Yang, S., Passarotti, A. M., Zhou, X. J., & Pavuluri, M. N. (2014). Development of superficial white matter and its structural interplay with cortical gray matter in children and adolescents. *Human Brain Mapping, 35*(6), 2806-2816. doi: 10.1002/hbm.22368

Yau, G., Schluchter, M., Taylor, H. G., Margevicius, S., Forrest, C. B., Andreias, L., Drotar, D., Youngstrom, E., & Hack, M. (2013). Bullying of extremely low birth weight children: associated risk factors during adolescence. *Early Human Development, 89*(5), 333-338. doi: 10.1016/j.earlhumdev.2012.11.004

Yuan, P., & Raz, N. (2014). Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 42*, 180-192. doi: 10.1016/j.neubiorev.2014.02.005

Zelazo, P. D., Craik, F. I., & Booth, L. (2004). Executive function across the life span. *Acta Psychologica, 115*(2-3), 167-183. doi: 10.1016/j.actpsy.2003.12.005

Zijdenbos, A., Forghani, R., & Evans, A. (1998). Automatic quantification of MS lesions in 3D MRI brain data sets: Validation of INSECT. In W. Wells, A. Colchester & S. Delp (Eds.), *Medical Image Computing and Computer-Assisted Interventation — MICCAI'98* (Vol. 1496, pp. 439-448): Springer Berlin / Heidelberg.

Zubiaurre-Elorza, L., Soria-Pastor, S., Junque, C., Sala-Llonch, R., Segarra, D., Bargallo, N., & Macaya, A. (2012). Cortical thickness and behavior abnormalities in children born preterm. *PloS One, 7*(7), e42148. doi: 10.1371/journal.pone.0042148

Zubiaurre-Elorza, L., Soria-Pastor, S., Junque, C., Segarra, D., Bargallo, N., Mayolas, N., Romano-Berindoague, C., & Macaya, A. (2011). Gray matter volume decrements in preterm children with periventricular leukomalacia. *Pediatric Research, 69*(6), 554-560. doi: 10.1203/PDR.0b013e3182182366