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Psychiatric and neurocognitive profile of adults born very preterm

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Psychiatric and neurocognitive profile of adults
born very preterm

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Thesis submitted for the degree of
Doctor of Philosophy
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Abstract

In recent decades, the rate of very preterm birth (<32 weeks of gestation) has increased, and it is now estimated as occurring in approximately 1 in 9 live births. Multiple lines of research suggest that very preterm birth is associated with a range of psychiatric and neurodevelopmental problems throughout childhood and adolescence. However, little is known about adult outcomes. This PhD sought to delineate the cognitive and psychiatric profile of adults born very preterm. It included four related studies.

Firstly, IQ trajectories were examined in order to understand whether IQ improves or remains stable from the age of 8 to the age 30 years. The results indicated that individuals who were born very preterm and especially those born at the lower end of the gestational age spectrum, continue to be at higher risk of cognitive impairment in adult life, affecting Performance IQ in particular.

Secondly, cognitive outcomes were compared between very preterm born adults and age-matched controls, with an emphasis on executive function. The influence of cognitive outcomes on social functioning and achievement was also examined. Individuals born very preterm performed worse than controls on measures of IQ and executive function. They also demonstrated significantly lower achievement levels in terms of years spent in education, employment status, and on a measure of functioning in work and social domains. Persisting executive function impairments in very preterm survivors were associated with achievement in several real-life domains.

Thirdly, considering that very preterm birth is associated with an increased rate of psychiatric disorders, a dimensional approach was utilized to examine psychiatric symptomatology in adults who were born very preterm and controls. Moreover, the

specificity of this risk was examined in order to better understand their adult clinical profile. Very preterm individuals demonstrated elevated psychiatric symptomatology compared to full-term controls. Psychiatric risk was characterized by a non-specific clinical profile and was associated with lower IQ.

Lastly, salience attribution, thought to underlie psychiatric symptomatology, was examined. Adults born very preterm displayed reduced capacity to process adaptive salience, indicating they may have difficulties in distinguishing between high and low probability stimuli features. Salience processing was associated with negative and positive psychotic-like symptoms, lending support to the hypothesis that very preterm individuals may be a distinct subgroup of high-risk individuals, characterized by increased 'cognitive' psychotic-like experiences.

This study aimed to understand the neuropsychiatric and cognitive profile of adults born very preterm. It demonstrated that in adulthood they experience similar difficulties to those that are evident earlier in life. These findings emphasize the need for cognitive remediation programmes to be delivered to vulnerable groups, which thus far have targeted specific executive function components (e.g. working memory, cognitive control), and may one day show generalizable benefits for a successful overall life adjustment.

Declaration of Originality

This thesis and the work presented here are my own and were conducted at King's College London between June 2013 and June 2017, all sources are appropriately referenced. This work has not been submitted to obtain any other degree at this University or any other institution.

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Karolis, V., Froudish-Walsh, S., **Kroll, J.**, Brittain, P., Nosarti, N. (2016). 'Rich-Club' Stability is Compromised Without More Equal Distribution of Resources: The Study of Whole Brain Connectome in Adults Born Very Preterm. *Cerebral Cortex*. 26(3):1322-1335.

Froudish-Walsh, S., Karolis, V., Caldinelli, C., Brittain, P., **Kroll, J.**, Colquhoun, M., Howes, O., Dell'Acqua, F., Murray, R., Williams, S., Nosarti, C. (2015). Very Early Brain Damage Leads to Remodeling of the Working Memory System in Adulthood: A Combined fMRI/Tractography Study. *The Journal of Neuroscience*. 35(48):15787-15799.

Conference Abstracts

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Brittain, P., Froudish-Walsh, S., **Kroll, J.**, Nosarti, C. (2014). Neurocognitive Outcomes in Adulthood Following Very Preterm Birth. *Pediatric Academic Society; Vancouver*.

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Contributions

Assessment: Philip Brittain conducted some of the neuropsychological and psychiatric assessments that form part of this thesis.

Chapter 3: The work described in this section was performed in collaboration with Vyacheslav Karolis.

Chapter 5: Sean Froudish-Walsh collaborated in conducting the data analysis in this section.

List of Abbreviations

ANCOVA - Analysis of Covariance
ADHD – Attention Deficit Hyperactivity Disorder
ASD – Autism Spectrum Disorder
BIC – Bayesian Information Criteria
BW - Birth Weight
CAARMS - Comprehensive Assessment of At-Risk Mental States
CCPT-EC - Continuous Performance Test - Errors of Commission
CIS-R - Clinical Interview Schedule – Revised
CBCL - Child Behaviour Checklist
CP – Cerebral Palsy
DSM-V – Diagnostic and Statistical Manual of Mental Disorders
EF – Executive Functions
FDR - False Discovery Rate
FSIQ - Full Scale IQ
GA – Gestational Age
GRFI - Global Role Functioning Index
IED - Intra-Extra Dimensional Set Shift
IQ – Intelligence Quotient
IUGR - intrauterine growth retardation
LME – Linear mixed-effect
MRI - magnetic resonance imaging
OR - odds ratios
PCA - Principal Component Analysis
PVH - periventricular haemorrhage
PVH +Dil - periventricular haemorrhage with ventricular dilatation
PVL - Periventricular Leukomalacia
RFS - Role Functioning Scale
SAS-SR - Social Adjustment Scale Self-Report
SAT - Saliency Attribution Test
SD - Standard Deviation
SES - Socioeconomic Status
SOC- Social Class
TMT-B - Trail Making Test
U-PVH – uncomplicated periventricular haemorrhage
WASI- Wechsler Abbreviated Scale of Intelligence
WAIS –R Wechsler Intelligence Scale for Children - Revised
WISC-IV - Wechsler Intelligence Scale for Children IV
WISC-R - Wechsler Intelligence Scale for Children - Revised
WPPSI-IV - Wechsler Preschool and Primary Scale of Intelligence IV
VAS - Visual Analogue Scale
VPT – Very Preterm

1. General Introduction

1.1 Preterm Birth

The rates of preterm birth, defined by the World Health Organization (WHO) as any live birth less than 37 weeks, varies slightly by country (WHO, 2010). A typical gestation in humans lasts between 38 and 42 weeks. Risk factors for premature birth include multiple pregnancies, in vitro fertilisation and maternal infection. Babies born premature are susceptible to adverse medical complications that are associated with neurodevelopmental alterations. Considering that the last trimester of gestation is a crucial time for brain development, including neuronal migration and gyrification, it is perhaps unsurprising that any disruption during this stage of gestation is associated with a range of difficulties. In addition to adverse brain alterations, preterm birth is associated severe disabilities such as cerebral palsy, mental retardation, and deafness. Fortunately, the majority of premature babies display no sign of disabilities; although there is growing evidence for subtle impairments that can have a cascade of effects throughout the individual's life. Hence, the focus of this thesis is to provide a neuropsychological profile of adults born preterm. The infants at highest risk of disabilities and of subtle impairments are those born at or before 32 weeks of gestation and will therefore be the focus of the studies presented.

1.2 Definitions

Further sub-divisions of preterm birth (Figure 1), based on gestational age, have been described by Lumley et al (1993) and can be summarised as follows:

Late Preterm Birth: 33-36 weeks completed gestation

Very Preterm Birth (VPT): 28-32 weeks completed gestation

Extremely preterm (EPT): 24-27 weeks completed gestation.

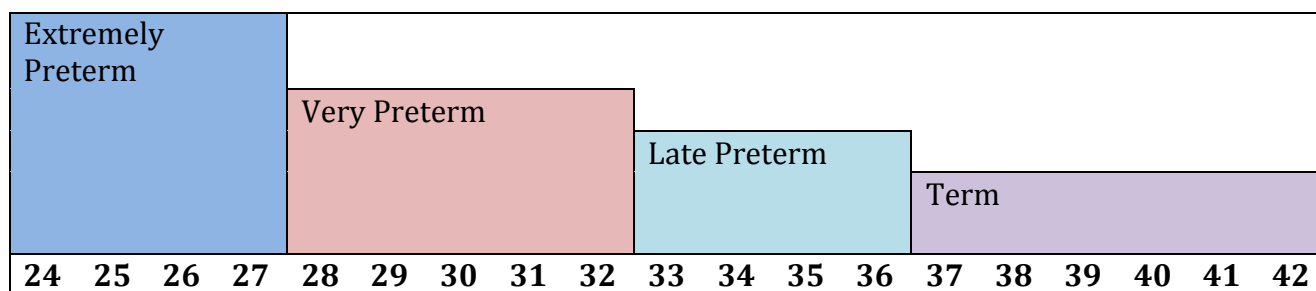


Figure 1: Gestational Age Spectrum

Subdivisions based on weeks of gestation, Extremely Preterm (24-27 weeks of gestation); Very Preterm (28-32 weeks of gestation); Late Preterm (33-36 weeks of gestation) and Term (>37 weeks of gestation)

These sub-divisions reflect differences in morbidity and mortality and include the level of support required during the neonatal period.

1.3 Prevalence

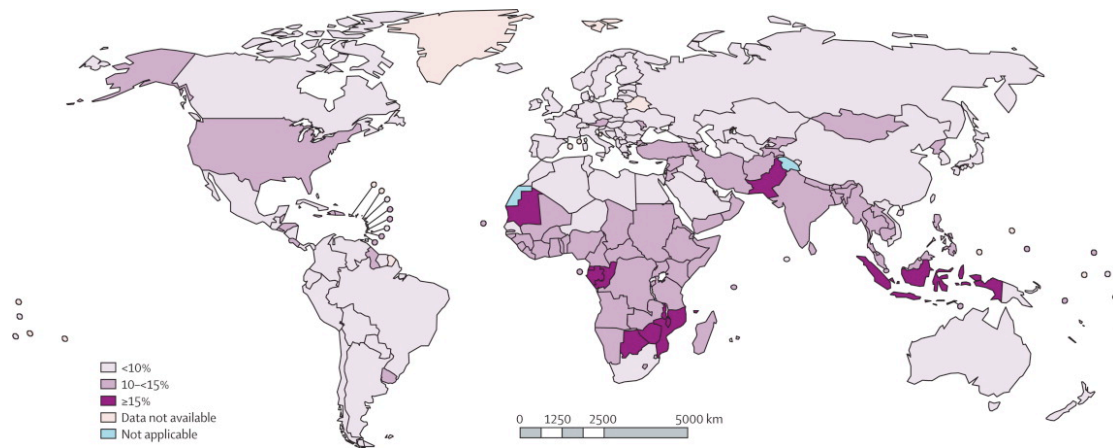
It is estimated that approximately 11% of all births worldwide are preterm (Blencowe et al., 2012) and the annual economic burden associated with preterm birth reaches \$26 billion in the United States alone (Allen, 2008). The UK is among the countries with the highest rates of preterm birth in Europe, where 1 in 13 births end before term. 80-90% of live preterm births occur between 27-32 weeks' gestation, 15% between 28-31 weeks and 5% below 28 weeks (Goldenberg, Culhane, Iams, & Romero, 2008). Estimating the exact nature and extent of premature birth is difficult due to inconsistent data collection. Estimated rates of premature birth in developed countries can range from as low as 5% in Northern European countries to 13% in the United States. Low-income countries have the highest rates of preterm birth, up to 18% in some African countries, and account for the majority of preterm birth worldwide (Figure 2).

Gestational age is ideally measured using an ultrasound during the first trimester of gestation. Despite this, there are still studies and hospitals that omit this measure, making it difficult to draw conclusions on widespread estimates. Similarly, while some countries report an increase in rates of preterm birth in the past decades, primarily in

the late gestational age group, these data need to be interpreted with caution, due to the varied methodologies employed to measure gestation. However, several factors may be used to explain the high prevalence rates of preterm birth; the list below includes some of the major contributors but is not exhaustive.

1. Rising maternal age and assisted conception has led to a large increase in multiple births, which carries a 10-fold risk of preterm birth (Smulian, Ananth, Kinzler, Kontopoulos, & Vintzileos, 2004).
2. Lifestyle factors such as stress, smoking and excessive physical work may be possible contributors (Smith et al., 2015).
3. Provider-initiated rates have increased including elective and urgent cases as compared to rapid delivery following abruption (Blencowe, Cousens, et al., 2013).
4. Maternal mental health such as depression and schizophrenia, in addition to psychiatric medication, may contribute to the risk of preterm birth (Grote et al., 2010).
5. Infections such as urinary tract infection and HIV have been demonstrated to contribute to preterm birth (Lambert et al., 2000).

Figure 2: International prevalence rates of preterm birth



Preterm Birth rates by country in 2010 (Blencowe et al., 2012). Darker colours indicate increased rates of premature birth worldwide.

1.4 Gestation Age or Birth Weight

In the past, birth weight was often measured instead of gestational age. Birth weight is highly correlated with length of gestation but the two measures cannot be used interchangeably, since each gestational age has a corresponding range of 'healthy' birth weight. Hence, using birth weight instead of gestational age may overestimate the prevalence of preterm birth. Using birth weight in research may also cause babies born 'small for gestational age' to be overlooked. This group may represent a unique high-risk population that may have a different developmental sequelae (Breeze & Lees, 2007).

1.5 Neonatal Brain Injury Following Very Preterm Birth

Very preterm neonates often suffer hypoxic-ischaemic events caused by their undeveloped respiratory and cardiovascular systems (Osborn, Evans, & Kluckow, 2007), such events can lead to damage in periventricular brain areas. This is often evident in the first few days after birth and in most cases occur within the first four days

of life (Perlman, 1998; Volpe, 2003). One of the most vulnerable areas of the developing brain is the germinal matrix, the main site of haemorrhage following preterm birth. This structure is situated between the caudate nucleus and the thalamus, and separated from the lateral ventricles by a single ependymal layer. During the third trimester of gestation, this system is particularly vulnerable to haemorrhaging; disruptions to the uterine environment such as premature birth may cause rupture of the germinal matrix, leading to the lateral cerebral ventricles filling with blood (Ballabh, 2010). Hence, the most common form of brain injury associated with preterm birth is periventricular haemorrhage (PVH) as shown in Figure 3. PVH can occur in isolation, uncomplicated PVH (UPVH); or with ventricular dilatation (PVH+D). PVH rarely occurs in infants born at 32 weeks gestation or after, but is more common in infants born at the lower end of the gestational age spectrum.

Although figures vary, it is estimated that 30-85% of preterm infants who experience PVH will develop major cognitive deficits and psychiatric difficulties (Vohr et al, 2003). Due to the site and extent of injury, it is hypothesized that PVH may impact the structural and functional integrity of the brain including key areas such as the basal ganglia, hippocampus and cerebellum (Cheong et al., 2013; Ghei et al., 2014; Kidokoro, Neil, & Inder, 2013; Nosarti et al., 2008). Damage to the basal ganglia is associated with deficits in sensory-motor, limbic and associative networks; all of which are believed to be mediated by dopamine neurons and correlate with adverse behavioural outcomes. Furthermore, such structural deficits are associated with functional network dysfunction influencing cognitive processing. Cognitive networks initially develop during the second half of gestation when the majority of preterm babies are born (Doria et al., 2010; Penn & Shatz, 1999). Hence, any disruption to network formation at this key stage of development may lead to the adverse outcomes described in the preterm literature.

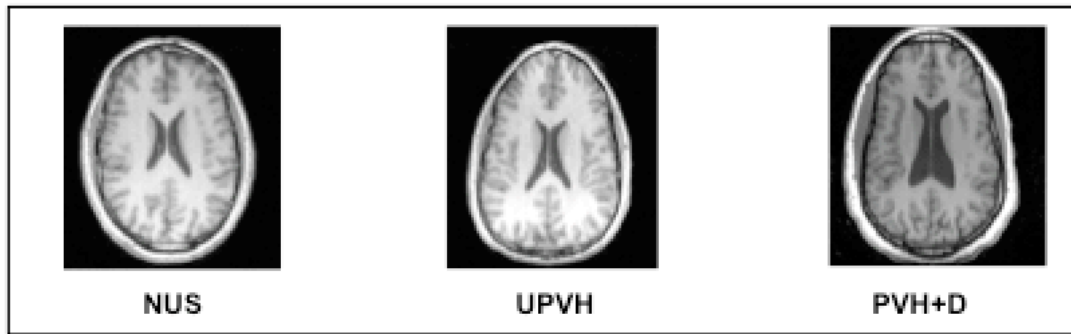


Figure 3: Examples of adult MRI scans from individuals belonging to the three ultrasound classification groups described above.

The most common form of cerebral injury in preterm populations. Normal ultrasound results (NUS) are presented on the left; PVH can occur in isolation, uncomplicated PVH (UPVH) in the middle image; or with ventricular dilatation (PVH+D) as shown on the right.

1.6 Why Study Preterm Birth?

Improvements in neonatal care, in the past few decades, have ensured increased survival of even the most vulnerable infants. Nonetheless, preterm birth is still a major cause of death and is second only to pneumonia in children under five (Blencowe, Cousens, et al., 2013), hence increasing our understanding of the preterm sequelae is particularly pertinent. Despite increased survival, there have been no improvements in the neurodevelopmental outcomes of these individuals (Moore et al., 2012; Wolke, Strauss, et al., 2015). Preterm birth is consistently associated with difficulties in a number of domains including cognitive, psychiatric, motor and sensory abilities. At the extreme end of the spectrum, 5-15% of preterm children will experience neurological disorders such as cerebral palsy, blindness and deafness (Woodward, Anderson, Austin, Howard, & Inder, 2006). However, research is increasingly indicating that *subtle* cognitive and behavioural problems may be significantly more widespread than previously thought and may affect those born very preterm (Anderson & Doyle, 2003). Up to 50% of children reported academic difficulties (Johnson et al., 2009) and 25% experience emotional and behavioural problems (Aarnoudse-Moens, Smidts,

Oosterlaan, Duivenvoorden, & Weisglas-Kuperus, 2009). The majority of studies have focused on children and adolescence, although; at present, and in large part due to healthcare improvements, large cohorts of preterm born individuals are reaching adulthood.

1.7 Adverse Outcomes following Preterm Birth

Considering the extensive neuroanatomical alterations often found in preterm born individuals, it is perhaps unsurprising that various cognitive and behavioural deficits have been described. These typically span over a number of domains, indicating that preterm birth is associated with a general, rather than a specific risk in cognitive and psychiatric outcomes (Nosarti, Murray, et al., 2012; Wolke & Meyer, 1999).

Cognitive deficits are evident in infancy and earlier studies have focused on detecting general cognitive impairment often reflected by lower IQ in preterm individuals (Moore et al., 2012). More recent efforts have examined domain-specific deficits, including processing speed, attentional difficulties and working memory impairments (Jaekel, Wolke, & Bartmann, 2013; Mulder, Pitchford, & Marlow, 2010). Moreover, individuals who were born at the lower end of the gestational spectrum, and in particular those who sustained perinatal brain injury, such as PVH, may be at a significantly higher risk of these deficits (Patra, Wilson-Costello, Taylor, Mercuri-Minich, & Hack, 2006). However, there is a paucity of adult studies and some initial evidence suggests that specific cognitive functions may improve with time (Luu, Vohr, Allan, Schneider, & Ment, 2011). This has increased the interest in utilising longitudinal studies to examine specific trajectories of cognitive functioning. Cognitive functions, such as IQ and executive function in childhood and adolescence, can reliably predict academic achievement, occupational choices and salary (Deary, 2012). Considering there is evidence that preterm individuals have worse cognitive skills and lower social

functioning and achievement compared to controls, it is perhaps surprising the relationship between the two has not been a main focus of research. Nonetheless, studies in children and adolescents have found executive function deficits to underlie academic performance (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, & Oosterlaan, 2013; Bhutta, Cleves, Casey, Cradock, & Anand, 2002) although this has yet to be examined in adults. Beyond lower academic achievement, poorer cognitive outcomes may also be associated with internalising problems, such as social withdrawal, anxiety and depression (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, et al., 2013; Alduncin, Huffman, Feldman, & Loe, 2014).

At a behavioural level, several studies have indicated an increase in depression, anxiety, autism spectrum and ADHD in children born preterm compared to controls (Johnson et al., 2010). Cognitive and psychiatric risks are overlapping and may have serious consequences on an individual's well-being and functioning, which will be described in subsequent chapters. These represent an enormous emotional and economic burden to family and society. It becomes clear that specific advice needs to be provided to families and educational providers and targeted interventions need to be the focus of future research. In order to better understand the difficulties these individuals face, efforts have focused on identifying patterns in their clinical profiles at a behavioural, psychiatric and cognitive level. Indeed, a "preterm behavioural phenotype" has been described in children and adolescents; this is characterised by inattention, socio-emotional difficulties and internalising problems (Johnson & Marlow, 2011) and it is likely that it will extend into adulthood (Hack et al., 2004). To date, very few studies have examined the cognitive and psychiatric profile of individuals born very preterm beyond adolescence. Hence, the focus of this thesis will be to delineate their profile in adulthood following natural age-related changes. The following chapters will examine the literature, which primarily focuses on childhood and adolescence. While cognitive

and psychiatric risk are often overlapping, these will be discussed separately in order to understand the specific difficulties adults born very preterm may face.

1.8 Rationale, Aims and Hypotheses

This thesis set out to investigate the profile of cognitive and behavioural outcomes in a longitudinal cohort of adults who were born very preterm and controls. The study also sought to characterise the cognitive and behavioural correlates of premature birth in adulthood. Considering the extensive evidence for neurocognitive and behavioural difficulties described in childhood and in adolescence outlined above (Anderson & Doyle, 2003; Rushe et al., 2001), it is crucial to determine whether these difficulties persist or ameliorate by adulthood. If there is evidence of an ‘adult preterm behavioural phenotype’ it is imperative to characterise this in order to determine whether preventive strategies may be implemented at younger ages. In addition, despite extensive findings of both cognitive and behavioural deficits in younger preterm populations (Johnson & Marlow, 2011), only a few studies to date have sought to integrate the two domains and delineate a cognitive *and* behavioural profile of very preterm individuals.

The main aims of this thesis are two-fold: firstly, to provide a comprehensive account of the cognitive profile of preterm born individuals in adult life and to explore the association between cognitive outcomes and real life functions, such as educational attainment and social adjustment (Chapter 3 & 4); secondly, to describe the psychiatric and behavioural difficulties experienced by preterm individuals in adult life (Chapter 5 & 6). An overall aim of the work is to integrate these disparate lines of research and examine the association between cognitive and psychiatric symptoms. Hence, the first studies presented in Chapter 3 & 4 will focus on describing cognitive outcomes in preterm adults, followed by an examination of psychopathology (Chapter 5) and its

relation to cognitive outcomes; the last study (Chapter 6) will integrate social, cognitive and psychological factors and examine salience processing and psychopathology. A more detailed summary of individual chapters is provided in the following sections.

Chapter 3 will investigate whether IQ trajectories from school-age to adulthood following very preterm birth differ from those observed in the general population over the lifetime (Salthouse, 2016). Possible contributing factors to the stability of IQ over time will be explored, including gestational age, neonatal ultrasound classification, sex and socio-economic status. It is hypothesised that the relationship between IQ and gestational age will be non-linear; specifically that preterm individual at the lower end of the gestational age spectrum will demonstrate disproportionately lower IQ scores compared to those born at later gestational ages. In addition to examining Full-scale IQ, Verbal and Performance IQ will also be explored. In the general population, Verbal and Performance IQ may fluctuate over time (Ramsden et al., 2011) despite Full-scale IQ remaining stable. Considering this, and given the evidence that preterm participants may be particularly vulnerable to deficits in Performance IQ (Saavalainen et al., 2007) it is imperative to examine whether specific cognitive difficulties, which may be masked when examining only Full-scale IQ (Aylward, 2005), can be also detected. Hence the second research aim of this section is to examine whether gestational age determines or mediates IQ and IQ subtests (i.e., relate to stability or changes over the lifetime). Lastly, it is hypothesised that gestational age will exert a stronger association with Performance IQ compared to Verbal IQ.

Chapter 4 will explore differences in neuropsychological functioning between preterm adults compared to full-term controls. This study will focus on executive function performance in adulthood considering the extensive evidence indicating deficits in this domain in younger populations compared to full-term controls (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, Oosterlaan, & van Goudoever, 2013; Anderson,

2002). However, it is also thought that executive function abilities continue to develop until the third decade of life (De Luca et al., 2003) hence exploring this in preterm adults, in their fourth decade of life, is warranted. Since preterm birth may adversely affect executive function, the focus of this chapter will be on different aspects of executive function including cognitive flexibility, planning, response inhibition as well as IQ to determine whether there are specific deficits or a general cognitive impairment. It is hypothesised that preterm adults will demonstrate a range of executive function deficits compared to full-term controls. Previous studies exploring executive function have not only shown a deficit in preterm samples but have also demonstrated a direct association between executive function abilities and social and academic functioning (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, et al., 2013) although it is unclear whether this association will remain in adulthood. Since it is hypothesised that preterm participants will perform worse than controls, exploring the associations between executive function deficits and wider aspects of everyday life is crucial. In addition to examining the association of premature birth and cognition in adulthood, the relationship between cognition and social functioning and achievement, including educational attainment, income, personal relationships and social adjustment, will also be explored.

The second half of this thesis focuses on psychiatric outcomes (Chapter 5) and their relationship with cognitive outcome, namely salience processing (Chapter 6).

Despite research indicating that preterm children and adolescents demonstrate increased psychiatric symptomatology, this has been seldomly examined cross-sectionally in preterm adults (Samantha Johnson & Dieter Wolke, 2013). In childhood and adolescence, there is a higher incidence of ADHD, ASD, and anxiety disorders in preterm individuals compared to full-term controls (Hack et al., 2009). Considering that anxiety and behavioural difficulties may be a precursor adult onset psychiatric

disorders it is perhaps unsurprising that population-based studies in preterm adults have found an increased incidence of depression and psychotic disorders (Nosarti, Murray, et al., 2012). While informative, population-based studies may disguise individuals who demonstrate increased symptomatology yet do not meet clinical criteria for psychiatric diagnosis or whose symptoms transcend current diagnostic boundaries. Hence, this study utilised a dimensional approach to explore psychiatric symptomatology in preterm adults. It is hypothesised that adults born preterm will demonstrate increased symptomatology compared to controls on the Comprehensive Assessment of At-Risk Mental States' (CAARMS; Yung et al., 2005); a tool that assess psychotic-like symptomatology. Secondly, it is also predicted that adults born preterm will display non-specific elevated psychopathology, i.e., on several psychopathology sub-scales.

Lastly, Chapter 6 will consider whether the outcomes and factors described in Chapters 3 & 4 are related to psychopathology using salience processing. Salience is both a social and cognitive construct that is hypothesised to underlie psychotic-like symptoms (Kapur, 2003) in both patients with schizophrenia and in those individuals with increased psychotic-like symptoms (Smieskova et al., 2015). This has yet to be explored in preterm populations despite evidence of cognitive and social difficulties and increased sub-clinical symptomatology (Johnson et al., 2010). Chapter 6 will therefore explore whether adults born preterm demonstrate worse salience processing performance compared to full-term controls. Specifically, this study will test the hypothesis that preterm individuals would demonstrate impairments in salience and that these impairments would underlie their psychiatric symptomatology studied in Chapter 5.

Finally, Chapter 7 will present a summary of the work presented in this thesis, integrate findings and discuss potential future directions.

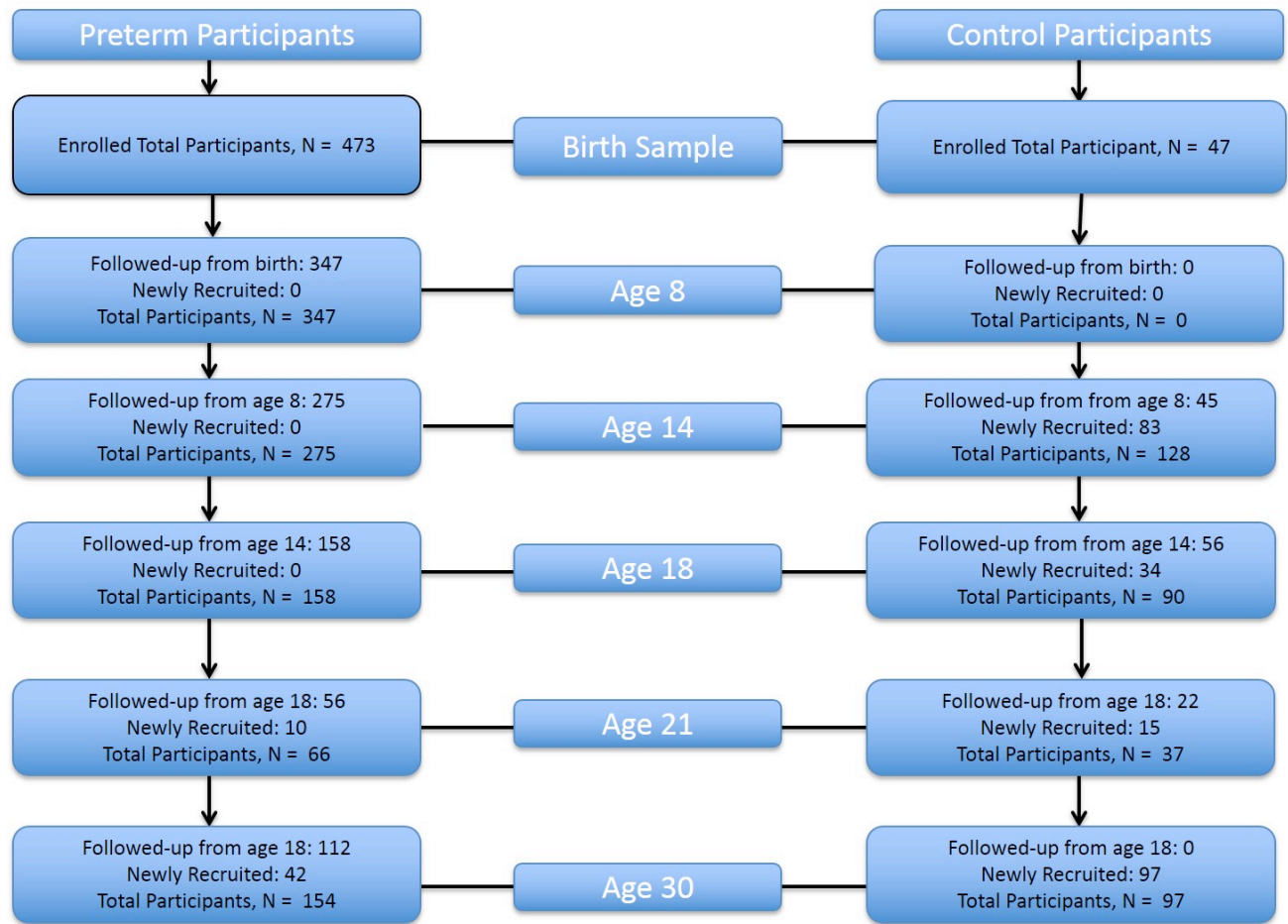
Chapter 2: Study Population

2.1 Preterm Study population

Between 1979 and 1984, 473 infants who were born before 33 weeks' gestation were admitted to the neonatal unit of University College Hospital, London (UCHL). In the first five days after birth they were enrolled for participation in the current longitudinal study. Participants that entered the follow-up study were reassessed periodically throughout their lives (Nam, Castellanos, Simmons, Froudish-Walsh, et al., 2015; Stewart et al., 1989a). Neonatal variables were collected at birth and included: birth weight, gestational age and severity of perinatal brain injury, based on neonatal cranial ultrasound classification, summarized as a) normal, no-periventricular haemorrhage (no-PVH), b) uncomplicated periventricular haemorrhage without ventricular dilatation (PVH), and c) periventricular haemorrhage with ventricular dilatation (PVH+DIL) for exact classification details please refer to (Nosarti et al., 2011). Neurodevelopmental assessments of 450 children were completed at ages one and four and 347 at age 8 (Roth et al., 1993; Roth et al., 1994; Stewart et al., 1989).

At ages 14-15, 275 individuals from the original cohort were traced and 269 were assessed (please refer to (Nosarti et al., 2008) for further details). Similarly, at age 18, 158 participants were assessed and underwent a cognitive and psychiatric assessment (Walshe et al., 2008). A flow chart of each assessment is presented below in Figure 4, describing the different assessment phases. A detailed description of each follow-up is described in Appendix C.

Figure 4: Flowchart of participants throughout the study



The cohort of participants described in this thesis are a subset of the participants recruited at birth. Each study presented will contain a brief description of the participant's characteristics including any inclusion and exclusion criteria.

2.2 Full-term controls

A term-born control group consisted of 96 individuals recruited from advertisements in the local community (see Appendix B, Section 3). Inclusion criteria were full-term birth (38-42 weeks), gender and birth weight >2500 grams. Exclusion criteria were a history of neurological conditions including meningitis, head injury, cerebral infections and birth complications. All study participants were native English speakers.

2.3 Current Assessment

Between 2012 and 2016 the original preterm cohort and a matched control group were recruited and assessed. In total, 154 preterm participants and 97 full-term controls were assessed. The assessment battery included neuropsychological, psychiatric and behavioural tests. In addition, participants received an MRI scan and a subset underwent a PET scan. Details of the current participants are presented in Table 1 and of the full assessment battery in Appendix C Figure C1. The preterm and control participants did not differ in terms of ethnicity and age of assessment. However, there were slightly more males in the preterm group compared to the control group ($\chi^2=4.09$, $df=1$, $p=.043$) as described in Table 1.

Table 1: Participants' Perinatal and Socio-Demographic data

Demographic and Neonatal risk variables	Term (n=97)	Preterm (n=154)
Gestational age (weeks)	-	29.26 (SD 2.08)
Birth weight (grams)	-	1311.32 (SD 346.78)
Neonatal Cranial Ultrasound Classification (% no-PVH/PVH/PVH+DIL)	-	49/22/28
Gender (N (% male))	45.4	58.4*
Ethnicity (% Caucasian, African, Afro-Caribbean, Indian-Subcontinent, Other)	117/3/8/9/10/1	67/7/4/2/8/1
Age at current assessment (years)	30.52 (5.24)	31.61 (2.46)

Ultrasound Classification: no-PVH: normal neonatal cranial ultrasound, PVH: uncomplicated periventricular haemorrhage without ventricular dilatation, PVH+DIL: periventricular haemorrhage with ventricular dilatation. Means and standard deviations (SD) and percentages are presented. * $p<0.05$ using Student's t-test, Pearson Chi-Square or Fisher's exact test as appropriate.

The current studies recruited participants that are part of a longitudinal follow-up study that started at birth (Froudish-Walsh et al., 2015; Stewart et al., 1989). During each assessment period a decision was made to reduce the sample to allow for a comprehensive assessment to take place while preserving sufficient statistical power. Hence, each subsequent chapter will include a subset of the total sample, and will be described in the following paragraphs.

Chapter 3 utilises a longitudinal design to assess IQ in preterm participants only. It was unfeasible to include a full-term control group for comparison due to different control participants being assessed at each follow-up. This study included 258 preterm participants assessed at age 8, 161 at age 15, 158 at age 18, 66 at age 22 and 103 at adult assessment at age 30.

Chapter 4 is a cross-sectional study examining neuropsychological and social functioning in preterm (n=122) and full-term adults (n=89). This study was conducted in 2016 before the full sample was recruited and assessed.

Chapter 5 also utilised a cross sectional design to assess differences in psychopathology between preterm (n=152) and full-term participants (n=96).

Chapter 6 describes the salience attribution study and has significantly less participants compared to previous chapters due to the fact that the salience task was introduced in late 2014; hence, participants assessed between 2012-2014 were not included. In total, 38 full-term and 67 preterm participants took part in this cross-sectional study.

2.4 Ethical Approval

Ethical approval for the study was granted by the King's College Hospital Ethics Committee (PNM/12/13-10). All participants gave their written informed consent to undergo assessments. Travel expenses were reimbursed and refreshments were provided for all participants. All information is confidential and numerical codes are used to identify participants electronically. Details of assessments and statistical analyses will be included in individual chapters. Further details regarding the current ethical approval are presented in Appendix A.

Chapter 3: Long-term Trajectories and Predictors of Cognitive Outcomes in Adults Born Very Preterm

Research Question 1: What is the course of IQ trajectories from childhood to adulthood in individuals born very preterm?

3.1 Introduction

Standardized intelligence quotient (IQ) is a commonly used measure thought to capture a wide range of cognitive abilities. IQ tests are multi-faceted, often incorporating various cognitive subtests. Full-scale IQ consists of two main sub-scales: Performance IQ which reflects fluid reasoning and the “ability to arrive at understanding relations among stimuli using a number of non-verbal reasoning skills, such as abstract thought and reasoning, and may be associated, to an extent, with executive function abilities (Roca et al., 2010). Crystallised intelligence, captured by Verbal IQ, examines verbal skills, such as expressive vocabulary, and relies on acquired knowledge (Duncan, Emslie, Williams, Johnson, & Freer, 1996), which indicates the “depth of the knowledge of the dominant culture” (Horn, 1997). Each IQ subtest is thought to measure specific cognitive abilities. A combination of the two subtests provides a Full-scale IQ score, which is thought to capture general intellectual abilities.

In normative samples, Full-scale IQ remains fairly stable across the lifetime, with a gradual decline in later life (Bielak, Anstey, Christensen, & Windsor, 2012; T. A. Salthouse, 2016). On the contrary, IQ subdivisions may follow distinct trajectories, with Performance IQ fluctuating across the lifespan and gradually declining with age, and Verbal IQ showing minimal or no change, or increasing with time (Ryan, Sattler, & Lopez, 2000; Salthouse, 2012). Such findings highlight the need to examine specific IQ subtests as they may differ in their developmental trajectory.

There is a growing consensus that both environmental and genetic factors contribute to the stability in IQ subtests (Beaver et al., 2013), although the relative influence of exogenous and endogenous factors may fluctuate over the lifetime (Deary et al., 2012). The environment may be particularly crucial for neural development during early childhood (Hackman & Farah, 2009; Hackman, Farah, & Meaney, 2010), with a direct affect on specific aspects of cognition, such as language development (Ronfani et al., 2015). The developing brain may also endure sensitive periods when it is particularly responsive to environmental input (Shaw et al., 2006) or periods, such as in adolescence, when environmental influences may decrease in importance (Brant et al., 2013).

There are numerous theories concerning the gene/environment interaction and its influence on IQ; however, two theories are particularly relevant to those born very preterm. Although most agree that IQ is in part environmentally influenced, early experiences may also determine future abilities. The fetal programming theory posits that prenatal and neonatal environments have long-lasting effects on the individual (Tucker-Drob & Briley, 2014); while the developmental cascade theory proposes that early acquisition of skills confer the building blocks for later learning, such that early cognitive performance will have substantial effects on later cognitive abilities (Duncan et al., 2007). These theories may help to shed light on findings in the preterm literature considering the atypical, and often traumatic events many neonates endure in the first few months and even years of life. Indeed, various aspects of development such as neuronal maturation, cognitive and social functioning

3.1.1 Intelligence in Preterm Individuals

A growing population thought to be at high risk of long-term neurodevelopmental impairments, including decreased IQ, are individuals born very preterm (Breeman,

Jaekel, Baumann, Bartmann, & Wolke, 2015; Mwaniki, Atieno, Lawn, & Newton, 2012). Understanding neurocognitive abilities in adult preterm survivors is important. Despite robust evidence that very preterm individuals have lower IQ compared to controls in childhood (Bhutta et al., 2002), adolescence (van der Pal-de Bruin, van der Pal, Verloove-Vanhorick, & Walther, 2015) and early adulthood (Nam, Castellanos, Simmons, Froudust-Walsh, et al., 2015), little is known about very preterm individuals' IQ in adult life. Results of longitudinal studies are inconsistent; some showed that very preterm participants continue to display cognitive deficits, including in IQ scores, in their twenties (Breeman et al., 2015; Karolis et al., 2016), whereas others have suggested an improvement in specific cognitive functions such as verbal abilities and working memory (Froudust-Walsh et al., 2015; Thuy Mai Luu, Laura Ment, Walter Allan, Karen Schneider, & Betty R. Vohr, 2011; Taylor, Minich, Klein, & Hack, 2004). Although a 'catch-up' has been reported in some domains (Rose & Feldman, 1995; Taylor, Klein, Minich, & Hack, 2000), for Full-scale IQ, deficits have been shown to persist into young adulthood (Breeman et al., 2015; de Jong, Verhoeven, & van Baar, 2012; Eryigit Madzwamuse, Baumann, Jaekel, Bartmann, & Wolke, 2015; Hack et al., 2009; Nosarti et al., 2007).

Despite these findings, the precise nature of any ameliorative effect of time is unclear and merits further investigation. This process may be a reflection of neuromaturation (brain maturation with age) and can lead to an improvement or 'catch-up' in cognitive outcomes whereby decreasing the gap in IQ between the very preterm and control groups (Kormos, Wilkinson, Davey, & Cunningham, 2014; Peng et al., 2005). In contrast, other studies have found this gap to remain the same (Madzwamuse, Baumann, Jaekel, Bartmann, & Wolke, 2015) or even to widen over time (Saigal, Hoult, Streiner, Stoskopf, & Rosenbaum, 2000). Specific skills such as sensorimotor abilities may be particularly vulnerable to a developmental delay (Coker-Bolt et al., 2014); thus, cognitive tests in

early development may not accurately reflect a child's true abilities. Even in the absence of overt disability, psychomotor function is a significant contributor to cognitive performance in infants (Simard, Lambert, Lachance, Audibert, & Gosselin, 2011). Since the majority of studies examined considerably younger cohorts the magnitude of the effect of premature birth in adulthood remains unknown. Such findings emphasize the need for longitudinal studies to determine the 'delay-deficit dilemma' (Baron et al., 2014); that is, do IQ deficits indicate a developmental delay or an impairment that will persist over the lifespan. Longitudinal studies may shed light on whether cognitive functions improve or even deteriorate. If early functions set the stage for the next developmental stage as has been hypothesised, then we can predict to see a stability of IQ scores with time.

3.1.2 Are all preterm individuals at equal risk?

Large cohort or meta-analytic studies have shown that very preterm individuals often demonstrate approximately a 0.7-0.8 standard deviation reduction in IQ scores compared to full-term controls (Bhutta et al., 2002; Kerr-Wilson, Mackay, Smith, & Pell, 2012). The average IQ in the general population is 100 and the standard deviation is 15 points, meaning that the majority of preterm individuals score within a normative range, despite having significantly lower IQ compared to controls. However, the risk may not be equal for all those born preterm. It has been proposed that the relationship between IQ and gestational age may be non-linear; very preterm individuals at the lower end of the gestational age spectrum may be at a disproportionately higher risk of impairment (Jaekel et al., 2013; Volpe, 2009). Indeed, individuals born before 28 weeks' gestation, described as extremely preterm, often display a substantially larger deficit on IQ tests compared to those born between 28 and 32 weeks, who often perform within the population norm range (Johnson, 2007). This effect may be explained by increased

obstetric complications associated with earlier gestational ages, which are also associated with atypical brain development. Individuals who sustained early brain injury, for example, such as PVH, appear to have lower Full-scale IQ than those who do not sustain early brain injury (Cooke, 2005) and the severity of the cognitive impairments are proportional to the level of injury (Sherlock, Anderson, & Doyle, 2005). However, another study found that low-grade PVH was not a predictor of long-term outcomes (Ann Wy et al., 2015) making the relationship between brain alterations and IQ unclear. More subtle brain alterations, such as cortical grey matter reduction and white matter injury may also explain lower cognitive scores in preterm samples (Martinussen et al., 2009; Nosarti et al., 2014). Similarly, white matter connections such as thalamocortical connectivity, often established early in development (Ball et al., 2015) may be directly associated with cognitive performance in adulthood even when controlling for SES and gestational age (Karolis et al., 2016) .

Nonetheless, in the absence of a disability, environmental factors may be better predictors of cognitive outcomes compared to biological ones (Hack, 2009). Environmental influences affect IQ in preterm samples in a similar way to the general population. Preterm participants with low socio-economic status may be at a 'double jeopardy' compared to full-term participants with high SES (Breeman et al., 2015). Considering the increased risk of lower IQ in preterm populations, coupled with environmental risks, it has been shown that their IQ may be as low as 2.25 standard deviations below those of individuals with high SES (Madzwamuse et al., 2015). Further studies are required to replicate this finding as the effect of SES on IQ may differ with age (Wolke & Meyer, 1999) and it remains unclear what the relationship between preterm birth, SES and IQ will be in adulthood.

3.1.3 IQ Subtests

It is difficult to directly compare the results of different studies, as some that have examined Full-scale IQ have reported no significant improvements with time, despite changes in IQ subtests (Ramsden et al., 2011), possibly masking specific difficulties (Aylward, 2002). Hence, although very preterm individuals seem to demonstrate a global, rather than a specific, cognitive deficit (Lohaugen et al., 2010; Wolke & Meyer, 1999) further studies are required to delineate the IQ profile of this heterogeneous group (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Goudoever, & Oosterlaan, 2012). It has been suggested that very preterm individuals may be particularly susceptible to impairments in Performance IQ (Saavalainen et al., 2007), although deficits in verbal domains have also been reported (Allin et al., 2008; Luu et al., 2009; Rushe et al., 2004) including in the current cohort (Kroll et al., 2017; Nam, Castellanos, Simmons, Froudish Walsh, et al., 2015).

Neonatal white and grey matter alterations may influence Performance IQ; a dose-dependent relationship has been demonstrated between the severity of white matter damage and performance based tasks (Clark & Woodward, 2010). Skills associated with Performance IQ, such as fine motor function and visuospatial abilities, may be distinctly compromised in very preterm populations (Geldof, van Wassenae, de Kieviet, Kok, & Oosterlaan, 2012; Spittle et al., 2013). Indeed, the tasks comprising Performance IQ require higher-level cognitive skills and may be related to executive function abilities. Deficits in Performance IQ have also been described in studies examining small for gestational age groups (Lohaugen et al., 2013; Tideman, 2000). Deficits in processing speed and visual attention, which are evaluated to estimate Performance IQ, have been often studied in very preterm samples. Indeed impairments in processing speed and visual attention have been reported as early as in the first year of life (Rose, Feldman, &

Jankowski, 2001, 2002) and are important predictors of higher order cognitive function, such as executive function (Mulder et al., 2010).

3.1.4 Aims and Hypotheses

Here we aimed to examine the developmental trajectory of IQ and its subtypes in very preterm individuals from childhood to adult life. We were interested in answering the following questions: (1) Do very preterm individuals at the lowest end of the gestational age spectrum demonstrate disproportionately lower IQ compared to those born at later gestational age? (2) Does gestational age determine or mediate IQ (i.e., relate to stability or changes over the lifetime)? and (3) Do very preterm individuals demonstrate different Performance IQ and Verbal IQ trajectories?

3.2 Methods

3.2.1 Study Participants

Inclusion criteria for the current study were an IQ assessment at baseline (age 8) and at least one more assessment at any further follow-up. From the cohort described in Chapter 2, in this study the following participants were included: 258 at age 8, 161 at age 15, 158 at age 18; 66 at age 22 and 103 at age 30.

3.2.2 Materials

Socio-demographic and perinatal details, including gestation age and birth weight, were collected for all participants at the time of birth. Parental occupation at birth was used to define participants' SES (Her Majesty's Stationary, 1991). SES was collapsed into two groups: a high SES category consisted of professional and managerial roles (levels 1-2); a low SES category comprised all other occupations (levels 3-5 and included missing variables).

At baseline each participant completed the Wechsler Intelligence Scale for Children – Revised (WISC – R; Wechsler, 1974). Participants who returned for assessment at age 15 were tested using the Wechsler Intelligence Scale for Children – Revised (WISC – R; Wechsler, 1974); and at age 18 using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). An abbreviated version of the WAIS was used at age 22 (Wechsler, 1981). The WAIS – R consists of 13 subtests divided into four indices. During their latest assessment (age 30), the abbreviated version of the WASI was used, consisting of four subtests that are equivalent to those included in the WAIS. Scores on these widely used measures were standardised to age-appropriate norms. Individual subtest scores were generated to estimate Verbal IQ and Performance IQ.

3.2.3 Statistical Analysis

Linear mixed-effect (LME) modelling with random intercept and a model selection procedure (i.e., Bayesian Information Criterion (BIC)) were implemented in order to systematically identify factors affecting IQ trajectories in very preterm individuals. All models were fitted using maximum likelihood criterion. Time of assessment was included in all tested models as a variable of no interest. Initially, we tested the predictive power of gestational age, log-transformed gestational age (with zero-coordinate shifted to 23 weeks), birth weight, and log-transformed birth weight (with zero-coordinate shifted to 500 grams). Due to the high covariance between gestational age and birth weight, we used two separate model-selection pipelines, one for each variable. For analysis of Full-scale IQ, we tested the model by sequentially including the following factors: 1) ultrasound results, SES and sex; 2) two-way interactions between all possible pairwise combinations of the main factors (i.e., gestational age/birth weight, ultrasound results, SES and sex); 3) all two-way interactions between time of assessment and each main factor; 4) three-way interactions between time of

assessment and all possible pairwise combinations of the main factors. A likelihood ratio test was used to decide whether any additional factor should be added to the model.

For analysis of IQ subtests, data for Verbal IQ and Performance IQ were concatenated. The model selection pipeline mimicked the procedure used for Full-scale IQ, but included four additional sets of factors: 1) IQ subtest as a main factor; 2) the interaction between IQ subtest and time of assessment; 3) two-way interactions between IQ subtest and all other main factors; 4) three-way interactions between IQ subtest, time of assessment and all other main factors.

3.3 Results

Perinatal, socio-demographic variables and IQ are presented in Table 2, for all assessment time points.

Table 2: Participants' Perinatal, Socio-Demographic data and IQ

	Age 8 (<i>baseline</i>)	15	18	22	31
N	258	161	158	66	103
Age at assessment ¹	8.23 (0.35)	15.39 (0.47)	18.44 (0.83)	22.02 (1.18)	31.08 (2.27)
Gestational age (week) ¹	29.24 (2.18)	28.95 (2.31)	29.23 (2.06)	29.55 (2.01)	29.26 (2.10)
Birth weight (gram) ¹	1298 (347.84)	1286.6 (277.06)	1287.2 (325.35)	1322.5 (338.17)	1317.8 (255.93)
Low SES (%) ²	65	61	69	59	56
Gender (Males)	54	56	50	59	62
Neonatal Cranial Ultrasound Classification ³ (% no-PVH/PVH/PVH+DIL)	50/31/19	45/34/22	52/28/20	53/32/15	50/24/26
IQ¹	WISC-R	WISC-R	WASI	WAIS-R	WASI
Full-scale IQ	103.21 (16.35)	97.02 (17.2)	102.00 (14.88)	102.67 (11.85)	103.71 (14.26)
Performance IQ	98.92 (15.24)	97.75 (20.12)	103.07 (15.61)	107.23 (13.64)	105.16 (14.99)
Verbal IQ	106.49 (17.56)	96.57 (15.33)	101.91 (15.41)	98.08 (12.24)	101.53 (15.21)
Verbal - Performance IQ	7.57 (15.37)	-1.18 (16.68)	-1.16 (15.21)	-9.15 (14.69)	-3.62 (16.19)

- 1 Means and standard deviations are presented for age, gestational age, birth weight and IQ scores at each time of assessment.
- 2 SES was collapsed into two groups; the percent of participants belonging to the low SES category (levels 3-5) is presented.
- 3 Ultrasound Classification: no-PVH: normal neonatal cranial ultrasound, PVH: uncomplicated periventricular haemorrhage, PVH+DIL: periventricular haemorrhage with ventricular dilatation.

3.3.1 Perinatal, Socio-Demographic Data and Full-scale IQ

The selection procedure identified an optimal model to explain Full-scale IQ, which included three factors: SES, sex and log gestational age (Table 3). There was no significant interaction between these factors and time of assessment, which indicates that Full-scale IQ did not change over the lifetime as a result of a modulatory effect of other factors. Low SES negatively affected IQ and males had a higher mean Full-scale IQ compared to females. As predicted, very preterm individuals with lower gestational age demonstrated lower Full-scale IQ scores, with log-transformed gestational age fitting the data better than linearly scaled gestational age. Similar results were obtained for the best-fitting model that contained birth weight as a predictor instead of gestational age, with log-transformed birth weight outperforming linearly scaled birth weight. The birth weight model, however, provided a slightly worse fit to the data than the gestational age model (BIC = 5770 vs. 5767 for gestational age model) and did not contain sex as a predictor. This may be attributed to a statistically significant interdependence between birth weight and sex, with males having a higher birth weight, $t(740) = 5.51$, $p < .001$, $\beta = 137.7$, $CI = [88.7-186.7]$. In contrast, sex differences in gestational age were not significant, $p = .87$. Considering this, and the fact that the current sample was selected on the basis of gestation age, not birth weight, further analyses were run using gestational age only.

Table 3: Statistics for the best-fit model for Full-Scale IQ

Factors	t (df =738)	β [95% CI]	p
SES	5.52	9.25 [5.96 12.54]	<.001
Sex	2.23	3.58 [0.42 6.74]	.026
GA	5.67	9.81 [6.41 13.20]	<.001

3.3.2 Verbal and Performance IQ Trajectories

The optimal model for the prediction of Verbal and Performance IQ contained SES, sex and log gestational age as main factors (Table 4), as was also the case for Full-scale IQ.

Table 4: Significant predictors for Verbal and Performance IQ

Factors	F	df	β [95% CI]	p
SES	14.69	1, 1475	6.08 [2.97 9.19]	<.001
Sex	4.99	1, 1475	3.24 [.40 6.09]	.025
GA	39.74	1, 1475	10.55 [7.27 13.83]	<.001
IQ subtest: GA	6.43	1, 1475	3.07 [.69 5.44]	.011
IQ subtest: Time	22.17	4, 1475	NA	< .001
IQ subtest: SES: Time	5.80	4, 1475	NA	< .001

Three additional interactive factors were also identified. Firstly, a significant interaction was observed between IQ subtype and gestational age (GA), indicating that gestational age had a greater influence on Performance IQ compared to Verbal IQ. Secondly, IQ subtype significantly interacted with time. At age 8 there was a relatively higher discrepancy between Verbal and Performance IQ, with 34% of the total sample demonstrating a clinically defined discrepancy (15 points or more; Blackburn et al,

2007); by the age of 15 this discrepancy diminished (Figure 5). Thirdly, there was a significant three-way interaction among IQ subtest, SES and time, which indicated that Verbal IQ was relatively greater than Performance IQ in individuals with a higher SES at age 8; the difference between SES stratifications disappeared at adolescence, and gradually re-appeared at later ages.

Figure 5: IQ subtype by time and SES

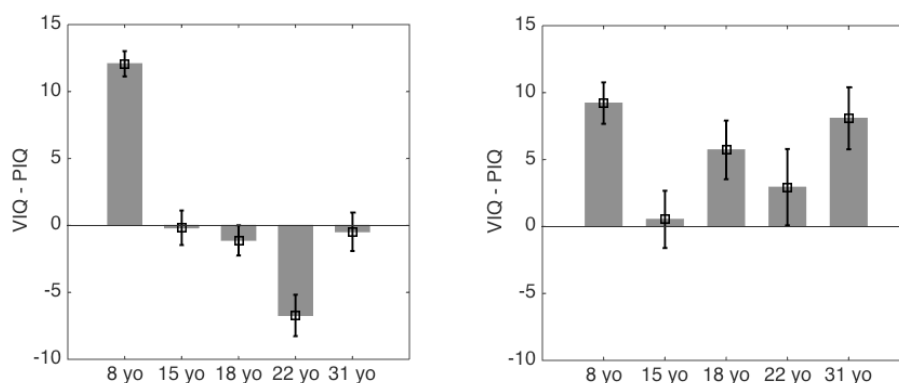


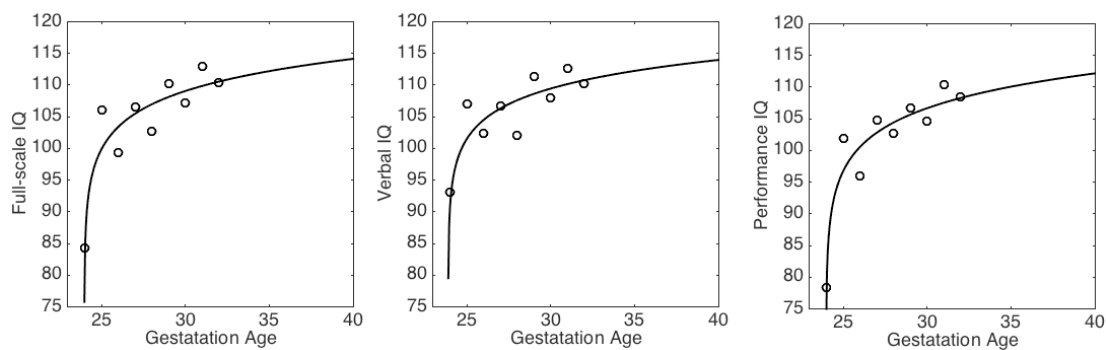
Figure 5: Left - IQ subtype by time interaction: the y-axis represents the difference between Verbal IQ and Performance IQ. Right – the effect of higher SES on the difference between Verbal and Performance IQ.

3.3.3 Post-Hoc Analysis

The logarithmic function fitting scores for each IQ scale are shown in Figure 6. The overall trend suggests the logarithmic trend may be driven by individuals who were born at 24 weeks' gestational age. In order to verify this, we utilised the models that were identified as the best-fitting in previous analyses (Table 3 and Table 4) and tested whether log gestational age still outperformed the model using linear gestational age in a reduced sample, obtained after removing participants born at 24 weeks' gestational age. Analyses showed that this was no longer the case for both Full-scale IQ and IQ subscales models, with models containing linear gestational age marginally

outperforming models with log gestational age (BIC for Full-scale IQ: 5640.2 vs. 5639, respectively; BIC for the analysis of IQ subscales: 11650 vs. 11649, respectively). In both analyses, the effect of linear gestational age was significant (Full-scale IQ: $\beta = 1.39$ [0.64-2.15] $t(723) = 3.61$, $p < .001$; IQ subscales: $\beta = 1.32$ [0.64 2.01], $t(1445) = 3.79$, $p < .001$), as well as the effect of sex ($\beta = 2.85$ [0.02 5.67], $t(1445) = 1.97$, $p < .05$) and SES ($\beta = 6.69$ [3.60 9.78], $t(1445) = 4.25$, $p < .001$). In the analysis of IQ subscales, the interaction between IQ subscale and time and the three-way interaction between SES, time and IQ subscale remained significant ($F(4,1445) = 21.23$, $p < .001$, and $F(4,1445) = 6.10$, $p < .001$), but the interaction between IQ subscale and gestational age did not ($F(4,1445) = 1.42$, $p = .23$). Notably, the latter was also true for the model with log gestational age ($p = .16$), indicating that this interaction was predominantly driven by the subsample of individuals born at 24 weeks' gestational age.

Figure 6: The Log Function Fitting Each IQ Subtype



3.4 Discussion

The current study demonstrated a significant association between gestational age, SES, gender and IQ scores. Specifically, lower gestational age and lower SES were associated with lower IQ scores, and males had higher IQ scores compared to females. After removing those individuals who were born at the further end of the gestational spectrum, i.e., at 24 weeks, we noticed a linear association between IQ and gestational

age. This result indicates that only the group born at 24 weeks of gestation was at a disproportionately higher risk of IQ deficits compared to the rest of very preterm born individuals. Furthermore, an interaction was shown between gestational age and IQ subtest, with gestational age exerting a greater influence on Performance IQ compared to Verbal IQ.

The main objective of this study was to explore the developmental trajectory of IQ and its subtypes in very preterm individuals from childhood to adult life. Our observation of a linear association between gestational age and IQ is in line with the results of previous investigations (Clark, Woodward, Horwood, & Moor, 2008; Kerr-Wilson et al., 2012). However, other studies focusing on specific aspects of cognition, rather than general intellectual abilities, found a disproportionate risk of cognitive deficits at the lower end of the gestational age spectrum (Jaekel et al., 2013; Moster, Lie, & Markestad, 2008; Quigley et al., 2012; Wolke, Strauss, et al., 2015). One possible explanation for the association between gestational age, IQ and other aspects of cognition may be that the immature brain is extremely vulnerable to endogenous and exogenous injury (Volpe 2009). Gestational age has in fact been linearly associated with a higher prevalence of focal and widespread structural brain alterations that are also thought to underlie cognitive performance (Ball et al., 2013; Nosarti et al., 2014). Furthermore, weeks 24–32 of gestation are critical for the development of thalamocortical connections, which are crucial for behavioral flexibility (Makinson & Huguenard, 2015), and executive functions (Eisenberg & Berman, 2010). Therefore, the implication of the current findings is that every additional week of gestation has important consequences for individuals' life-long general intellectual skills.

Our results did not find any improvement in IQ with time in very preterm born individuals, as previously reported (Mai Luu et al., 2011). However, the literature on this topic remains inconclusive, as the majority of studies to date have examined

participants who were substantially younger than those currently investigated (C. S. Aarnoudse-Moens, Smidts, et al., 2009; Lohaugen et al., 2010; Nosarti et al., 2002). A meta-analysis examining IQ changes in very preterm individuals between childhood and adolescence also did not find evidence of an IQ improvement over time (Kerr-Wilson et al., 2012). Moreover, an extension of this study found stability in IQ scores, but reported that the influence of perinatal factors on cognitive outcomes diminished with time (Kormos et al., 2014), suggesting that study participants' age may, in part, explain the inconsistent results. Recent studies examining very preterm individuals of comparable age to the current sample (26 years old), also did not report IQ improvement over time (Breeman et al., 2015; Madzwamuse et al., 2015).

We further found that, while Full-scale IQ remained stable from childhood to adult life, IQ subtypes changed over the lifespan, suggesting that in very preterm individuals gestational age exerts a greater effect on Performance IQ compared to Verbal IQ. 34% of participants displayed a specific IQ deficit indicated by a large difference (15 points; Blackburn et al, 2007) between verbal and performance subtests. This finding has been previously demonstrated in very preterm children (Gabrielson et al., 2002), in autism (Bucaille et al., 2016), epilepsy (Blackburn et al, 2007), and traumatic brain injury (Gao, Jiang, Wang, & Chen, 2000), but is novel in adults who were born very preterm. Large IQ discrepancies are rarely found in healthy populations; it has been postulated that when they occur, they may represent cerebral alterations (Kim et al, 2003).

However, considering that there are only a few existing longitudinal studies examining IQ subtest trajectories in the very preterm literature, it is difficult to draw firm conclusions on the precise mechanisms that may be driving specific developmental trajectories. Changes in specific IQ subtests are thought to correlate with changes in brain development (Ramsden et al., 2011), underlying the fact that even if an

individual's overall IQ remains stable, fluctuations in specific skills may change over time (Baxendale, 2011).

Considering that the very preterm brain often follows an atypical developmental trajectory (Nam, Castellanos, Simmons, Froudish Walsh, et al., 2015), examination of the neural correlates of IQ subtype is needed to clarify how atypical development can influence cognition.

The findings presented here indicate that it may be insufficient to solely rely on Full-scale IQ scores when examining cognition in very preterm populations. Furthermore, we noticed that IQ subtype significantly interacted with time, with the greatest discrepancies between verbal and performance IQ occurring in childhood and disappearing by adult life; and that socio-economic factors particularly influenced Verbal IQ both in childhood and in adult life. Such findings could help to identify the role that potentially protective environmental factors may play in shaping intellectual abilities, and to isolate critical periods during which cognition-enhancing interventions may be most beneficial (Jolles & Crone, 2012).

This study has several limitations. Throughout the years, different cognitive measures were administered; this was necessary for age-specific testing. However, this limitation should not have a significant impact on data quality because we were primarily interested in delineating the cognitive trajectories of a heterogeneous group of very preterm individuals; any test bias would have affected all trajectories in a similar manner. Finally, as rates of attrition are common in longitudinal studies, with evidence that those most vulnerable do not return (Wolke et al., 2009), the findings presented may be more relevant for well-functioning individuals who were born very preterm.

3.4.1 Conclusion

Our study shows that every full gestational week contributes to a higher IQ in individuals who were born very preterm. IQ is thought to predict important life outcomes, such as educational achievement, employability, and life satisfaction (Staff et al, 2014; Bourne et al, 2006). What is most important is that IQ can be improved. Future efforts

Chapter 4: Real-Life Impact of Executive Function Impairments in Adults who were Born Very Preterm

Research Questions: 1. Will preterm born adults show a global or specific cognitive deficit? 2. Do executive function abilities in adulthood impact social and occupational outcomes?

4.1 Introduction

Executive functions (EF) are widely accepted as fundamental components of human cognition, enabling individuals to engage in complex reasoning, and goal-oriented and adaptive behaviours. These abilities include the maintenance and manipulation of information, temporal organization, set shifting, self-monitoring, concept formation, verbal fluency, inhibition, motivation, organization and planning (Wechsler, 1981) and allow the individual to override automatic responses (Diamond & Doar, 1989). Indeed, it is thought that executive function and cognitive control regulate perceptions, thoughts and behaviours through the activation and inhibition of other brain regions (Shallice, 2002).

What exactly constitutes EF is still debatable and several models of executive function have been proposed. There are largely two disparate models in the EF literature: the unitary model (Baddeley, 1992; Norman & Shallice, 1986), that considers EF as one construct that regulates various subprocesses and the componential view that emphasises the dissociable EF subprocesses (Diamond, 1991; Pennington, 1997). Recent work has shifted towards an integrated framework of the two models that proposes three primary processes: working memory, set shifting and response inhibition (Miyake et al., 2000) that are mediated by attentional control (Rueda, Posner, & Rothbart, 2005). Simple cognitive skills are the foundation for the EF components to

be built upon (Fischer, 1995) and early disruptions, especially to attentional networks may compromise the development of EF abilities (Garon, Bryson, & Smith, 2008). Moreover, EF are 'higher-order' cognitive functions that integrate the input and output from lower-order modalities, such that alterations in these connections may result in wide spread cognitive and social disruptions.

Although core executive functions can be localised to the lateral prefrontal cortex, other typical 'executive' brain regions include the anterior cingulate gyrus, the medial prefrontal and posterior cortices in addition to the basal ganglia and the thalamus (Cole & Schneider, 2007). Moreover, the lateral prefrontal cortex is densely connected with the sensory, cortical and subcortical motor systems, and with the limbic system which is involved in emotion, reward and memory (Morton, 2010). The prefrontal cortex is among the slowest developing brain region and its connections may continue to develop until adulthood (Benes, 2001). The underdeveloped prefrontal cortex in children results in similar behavioural patterns on executive function tasks as those seen in adults with frontal lobe impairments (Huizinga, Dolan, & van der Molen, 2006). Such findings may be even truer for children who follow atypical developmental trajectories. While there is robust evidence of an EF deficit in preterm born children and adolescents, we cannot be certain whether these deficits will persist in adulthood or whether these deficits signify a delay in cognitive development.

4.1.1 Executive Function in Preterm Individuals

In the preterm literature, difficulties in executive function are one of the most consistent findings (Aarnoudse-Moens, Smidts, et al., 2009; Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, et al., 2013; Mulder, Pitchford, Hagger, & Marlow, 2009) and can persist after accounting for the lower IQ in these populations (Ment, Allan, Schneider, & Vohr, 2011; Nosarti et al., 2007). Preterm individuals tend to show

deficits across the spectrum of EF abilities. These include inhibition, planning abilities, verbal fluency, spatial organization and working memory (Aarnoudse-Moens et al., 2012; Anderson & Doyle, 2004; Breeman et al., 2015). These findings suggest a global cognitive impairment in higher-order cognitive processing that is likely mediated by cerebral alterations. Indeed, while some evidence points to a linear relationship between gestational age or birth weight and EF performance (Bhutta et al., 2002) other studies found this association to be modest (Anderson & Doyle, 2004), indicating that other factors may be involved.

Although cerebral alterations may play a crucial role in the development of EF abilities (Bolisetty et al., 2014); even in their absence, and when excluding participants with neurosensory or neurological deficits, EF abilities remain compromised (Thuy Mai Luu et al., 2011). Although the mechanisms linking the two are not fully understood (Blencowe, Lee, et al., 2013), they are likely to include alterations in whole brain connectivity, preferentially affecting corticostriatal and thalamocortical connections, which could affect an efficient integration between brain regions underpinning different aspects of information processing, with long-term implications for cognitive outcomes (Ball et al., 2015; Fische-Gomez et al., 2014). Evidence of alterations in several functional and structural networks may also explain the general cognitive deficits often reported in preterm populations and evidence that in addition to deficits in EF abilities, intellectual capacity is also reduced. This may also reflect the complexity of assessing cognition and the need to consider multiple sub-process that when altered may lead to impairments across a number of cognitive domains.

Findings of a recent meta-analysis concluded that alterations detected by MRI around term equivalent age in preterm infants is limited in predicting neurocognitive outcomes (Van't Hooft et al., 2015) indicating the importance of environmental factors in cognitive development. Similar to IQ, environmental factors such as maternal education,

parental IQ and socio-economic status are strong predictors of EF abilities in preterm children (Vohr, et al., 2011). In addition, attentional capacity is thought to be an underlying mechanism of EF abilities and may constitute a foundation for the development of later EF skills (Miyake et al., 2000). EF scores in preterm populations are approximately 0.25-0.8 SD below those seen in full-term controls (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009), whereas attention appears to also be affected with similar effect sizes in the range of 0.3-0.7 (Anderson & Reidy, 2012; Mulder et al., 2009).

Alterations in attentional networks and subsequent attention development and impairment appear to increase with age in preterm children (van de Weijer-Bergsma et al., 2008). However, the exact nature and severity of the cognitive deficits observed in preterm populations is uncertain due to methodological differences between studies (Anderson, 2002) and the fact that the majority of studies have focused on only one attentional network rather than the interaction between attentional networks and EF (van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008).

Considering the extensive findings of EF dysfunction in younger preterm cohorts, it remains unclear whether preterm adults will demonstrate similar deficits to those described in younger populations although initial evidence suggests cognitive performance does remain stable in adulthood (Breeman et al., 2015). Preterm individuals in their early 20's have been shown to have impairments in several aspects of EF abilities such as verbal fluency, attentional performance and working memory (Nosarti et al., 2007; Nosarti et al., 2011) which is thought to be mediated by a distinctive neural trajectory including alterations in white and grey matter (Nosarti et al., 2014).

At present, the need to examine the precise nature and severity of EF deficits in preterm individuals, and in particular in adults born preterm, is crucial as it may inform

cognitive remediation. In the general population the initial evidence indicates that remediation programmes may not only improve EF abilities, but that this improvement may influence other cognitive and behavioural domains including reducing learning deficits associated with preterm birth (Grunewaldt, Lohaugen, Austeng, Brubakk, & Skranes, 2013; Lohaugen et al., 2011). Moreover, even subtle cognitive deficits may lead to disproportionate adverse outcomes and further work is required to understand how EF deficits may manifest into daily life.

4.1.2 Do cognitive deficits affect social functioning and achievement?

In adult survivors of preterm birth, no study has explored cross-sectional associations between neurocognitive deficits and levels of achievement, despite evidence demonstrating that these individuals compare unfavourably with term-born controls in a variety of achievement measures including: socioeconomic status, marital status and biological parenthood (Basten, Jaekel, Johnson, Gilmore, & Wolke, 2015; Hack et al., 2009; Heinonen et al., 2013; Moster, Lie, & Markestad, 2008). In very preterm children and adolescents executive function deficits have been suggested to underlie academic underachievement, as well as social and behavioural problems (Aarnoudse-Moens, Smidts, et al., 2009; Anderson & Doyle, 2004; Delobel-Ayoub et al., 2009). However, there is a paucity of studies investigating if and how specific aspects of cognition affect real-life achievements. One such study, demonstrated a direct association between mathematical abilities in childhood and wealth in adulthood (Basten, Jaekel, Johnson, Gilmore, & Wolke, 2015). Moreover, individuals who were born very preterm continue to be susceptible to experiencing a range of subtle deficits in young adulthood, ranging from cognitive impairments to behavioural difficulties (Lindstrom, Lindblad, & Hjern, 2009; Nosarti et al., 2007; Nosarti, Murray, et al., 2012; Van Lieshout, Boyle, Saigal, Morrison, & Schmidt, 2015), which can result in a substantial burden to both families

and society (Joseph et al, 2016; Heinonen et al, 2013; Lindstrom et al, 2007). In adulthood, they also have worse life satisfaction, decreased academic qualifications, a lower net income and are less likely to establish a family compared to their full-term born counterparts (Basten et al., 2015; Lindstrom, Winbladh, Haglund, & Hjern, 2007; Moster et al., 2008; Saigal et al., 2016). Whereas most published studies have explored the association between perinatal variables (e.g., gestational age and birth weight) and a variety of outcomes, such as academic and educational performance in school-aged children and adolescents (Anderson & Doyle, 2003; Cheong et al., 2013), no study to date has investigated how cognitive difficulties experienced by very preterm individuals may be associated with the way they function in adult life. These social difficulties are thought to lie on a causal pathway to developing a psychiatric disorder and may be mediated by neurocognitive factors. Considering the social difficulties reported in the literature in preterm children and adolescence, it may be that the increased risk of psychiatric outcomes is linked to cognitive deficits that underlie social behaviours. Here, we attempted to extend current knowledge by studying whether executive function deficits in adults who were born very preterm are associated with a range of real-life achievements, including educational attainment, income, personal relationships and social adjustment.

4.2 Methods

4.2.1. Study Participants

From the full cohort described in Chapter 2, 122 very preterm individuals with a mean age of 31.2 years (range of 28-34 years) were recruited. 79 term-born controls were also studied (please see Chapter 2 for details of inclusion and exclusion criteria). The current assessment period started in 2012 and lasted approximately 3.5 years. Very preterm individuals who were assessed did not differ from those who were not

assessed in terms of birth weight (assessed at 31: 1306.70g, ranging from 552g -2309g, not assessed at 31: 1371.75 g, $t=-1.73$, $df=447$, $p=.084$); however, those who were assessed were born at a slightly younger gestational age than those who were not (assessed at 31: mean gestational age=29.21 weeks, not assessed at 31: mean gestational age=29.67, $t=-2.05$, $df=447$, $p=.040$). In the returning cohort males were overrepresented compared to females (assessed at 31: 62% male, not assessed at 31: 48% male, $\chi^2=7.06$, $df=1$, $p<0.01$).

4.2.2 Materials

Socio-demographic data were collected for each participant including: years in full-time education, employment status (employed vs. unemployed), income, relationship status, biological parenthood and SES using a standardized tool which provides a 6 tier ordinal scale ranking professions as: 1 – Professional; 2 – Intermediate; 3 – Skilled non-manual; 4 – Skilled Manual; 5 – Semi-skilled and 6 – Unskilled Manual (HMSO, 1991).

Testing lasted between 3.5 to 4 hours with the tests administered in a quasi-random order, with refreshment breaks when required. In addition, each participant completed a comprehensive neurocognitive assessment covering a variety of domains, but with a focus on executive function.

IQ was assessed using the *Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999).

Executive Function was assessed with the following:

The *Hayling Sentence Completion Test* (HSCT; Burgess & Shallice, 1997) assesses initiation and suppression responses. Participants are asked to provide a semantically related or unrelated word to complete a sentence. The overall scaled score is based on time to initiate response and errors made.

The *Controlled Oral Word Association Test* (COWAT; Benton & Hamsher, 1976) a

measure of verbal fluency; the mean of the total words produced for each of the three letters F, A and S provides a measure of phonetic fluency.

Two subtests from the *Cambridge Neuropsychological Test Automated Battery* (CANTAB; Fray, Robbins, & Sahakian, 1996) were included. The *Stockings of Cambridge* (SOC) a task that assesses spatial planning. Participants are required to plan and execute a set of moves by shifting coloured circles between different locations. A 'Problems Solved in Minimum Moves' score is then calculated. The *Intra-Extra Dimensional Set Shift* (IED) is a task involving maintaining attention to a reinforced stimulus and then shifting attention to a previously irrelevant stimulus. A 'Total Errors Adjusted' scores is then calculated, which provides a measure of rule acquisition and reversal.

The *Trail Making Test* (TMT-B; Tombaugh, 2004) a measure of visual attention, set shifting and cognitive flexibility. Participants are asked to connect numbers and letters, alternating between the two sequences. The time in seconds for completion of Part B is used as summary score.

The *Continuous Performance Test - Errors of Commission* (CCPT-EC; Conners, 2000) is a computerised task of attention and response inhibition. The 'Errors of Commission' are incorrect responses to non-targets or stop-stimuli (such as the letter x).

Real-life Achievement was assessed with the following:

The *Role Functioning Scale* (RFS; Goodman, Sewell, Cooley, & Leavitt, 1993) is an interviewer-rated assessment of functioning in work and in social domains. The 'Global Role Functioning Index' (GRFI) is the sum of four subscales: 'Working Productivity', 'Independent Living and Self Care', 'Immediate Social Network Relationships' and 'Extended Social Network Relationships'.

The *Social Adjustment Scale Self-Report* (SAS-SR; Weissman & Bothwell, 1976) is a self-rated measure. The SAS-SR yields an 'Overall Score' that provides a measure of an individual's satisfaction with his/her social situation.

4.2.3 Statistical analysis

SPSS 22.0 (IBM, Armonk, NY) and Matlab 13b (Mathworks Inc) were used for the analyses. 5.7% of the very preterm sample had cerebral palsy and 2.5% had another neurosensory disability. Analyses were repeated excluding individuals with disabilities. This, and other reasons such as fatigue, resulted in 8.9% of data missing including individuals with disabilities and 6.4% of data missing after excluding individuals with disabilities. This was dealt with by multiple imputations using the 'MNAR' procedure implemented in SPSS. All measures were transformed for normality except the IQ measures. Group differences in neurocognitive and socio-demographic measures were initially examined using independent *t*-test, Chi-Square or Fisher's exact test, with significance set at $p < 0.05$. Analysis of covariance (ANCOVA) was then performed to explore group differences when controlling for age and sex. Mean performance differences are presented as standardized scores (mean=0; SD=1), and discussed in terms of effect size, using Cohen's *d* (.20=small, .50=moderate, .80=large; (Cohen, 1992). Principal Component Analysis (PCA) with Direct Oblimin rotation was performed on the executive function tests. Components were extracted based on examination of scree plots and the criterion of having eigenvalues > 1 . Factor scores from extracted components were then used in further analyses.

Multiple regressions were run to examine whether real-life achievements were associated with executive function. In order to assess the contribution of executive function to real-life achievements, independently from IQ, and of IQ, independently from executive function, a ZCA-whitening transformation of IQ and executive function scores was performed (e.g., Brown et al., 2012). Transformed scores have several useful properties: a) they are orthogonal (i.e., de-correlated), allowing to make inferences

about the contribution of one factor to the outcome independently of the other; b) they show maximal covariance with the un-transformed scores (i.e. remain as similar as possible to the original data); c) their standard deviation is equal to 1, implying that estimated regression coefficients can be treated as estimates of the effect size. We ran a regression analysis examining the independent contribution of IQ and executive function and their interaction with group membership to lifetime achievement. Group and sex were included as nuisance covariates. Logistic regression was used to fit 'Work Status' scores (unemployed vs. employed) and linear regression was used to fit 'Global Role Functioning Index', 'Years in Education' and 'Social Adjustment Scores'.

4.3 Results

Demographic and neonatal risk variables (for the very preterm group only) are presented in Table 5. The very preterm group contained significantly more men than the term-born group ($\chi^2=4.76$, $df=1$, $p=.029$).

Table 5: Participants' Neonatal and Demographic Variables

Demographic and Neonatal risk variables	Term (n=79)	Very Preterm (n=122)
Gestational age (weeks)	-	29.24 ($\pm$ 2.16)
Birth weight (grams)	-	1306.70 ($\pm$ 356.94)
Neonatal Cranial Ultrasound Classification (% no-PVH/PVH/PVH+DIL)	-	47/24/29
Sex (N (% male))	42(47)	76(62)*
Ethnicity (% Caucasian, African, Afro-Caribbean, Indian-Subcontinent, Other)	75/8/5/3/9	81/2/4/6/7
Age at current assessment (years)	30.18($\pm$ 5.23)	30.54($\pm$ 2.35)

Means and standard deviations ($\pm$) are presented, unless otherwise specified. * $p<0.05$ using Student's t-test, Pearson Chi-Square or Fisher's exact test as appropriate.

Ultrasound Classification: no-PVH: normal neonatal cranial ultrasound, PVH: uncomplicated

periventricular haemorrhage without ventricular dilatation, PVH+DIL: periventricular haemorrhage with ventricular dilatation.

4.3.1 Neurocognitive test performance

The very preterm group performed worse than controls on the majority of neurocognitive tests (Table 6). After adjusting for age and sex, differences at conventional thresholds of significance were observed for the following individual executive function tests: the HSCT, COWAT, IED and TMT-B. PCA results conducted on all 6 executive function tests indicated that the best model involved just one component, including the HSCT, COWAT, SOC, IED and TMT-B tests. The Kaiser-Meyer-Olkin measure of sampling adequacy was .73, Bartlett's test of sphericity was significant (χ^2 (10, $N = 211$) = 139.90, $p < .01$) and all communalities were above .3. This single component accounted for 43% of the variance in test performance. Factor scores for this component are also detailed in Table 6, with the very preterm group displaying significantly lower scores than controls.

Table 6: Participants' Neurocognitive Test Scores

Neurocognitive domain/measure	Term Mean (SD)	Very preterm Mean (SD)	Adjusted Mean Difference (95% CI)	<i>d</i>	<i>d</i> ^a
General Intelligence					
Full-scale IQ	112.15(12.19)	103.57(13.75)	-.66 (-.40 to -.92)***	-.71	-.67
Verbal IQ	109.64(12.80)	101.99(14.78)	-.56 (-.30 to -.82)***	-.60	-.59
Performance IQ	112.76(12.22)	104.49(14.68)	-.62(-.35 to -.88)***	-.65	-.61
Executive Function					
HSCT	6.31(.96)	5.57(1.41)	-.63 (-.36 to -.89)***	-.66	-.62
COWAT	14.25(3.76)	12.71(4.56)	-.39 (-.11 to -.66)**	-.39	-.38
SOC	9.49(1.70)	9.0(1.97)	-.28(-.01 to .55)	-.29	-.23
IED ^a	17.82(14.57)	24.97(18.64)	-.50(-.24 to -.77)***	-.52	-.49
TMT-B ^a	77.31(34.71)	95.18(53.48)	-.42(-.15 to -.69)**	-.42	-.38
CCPT-EC ^a	11.75(5.74)	12.47(6.79)	-.11(-.17 to .39)	-.18	-.14
Executive Function Factor Score	.36(.88)	-.26(1.0)	-.66(-.40 to -.92)***	-.68	-.65

Raw scores are presented as means and standard deviations. Mean differences are all standardized scores (mean=0; SD=1). Effect sizes are calculated with Cohen's *d*. Results are adjusted for age and sex.

^aHigher scores indicate better performance except where indicated; * $p \leq 0.05$ ** $p \leq 0.01$ *** $p \leq 0.001$

^a Effect sizes, excluding participants with cerebral palsy or a neurosensory disability, are calculated with Cohen's *d*. Results are adjusted for age and sex. HSCT: Hayling Sentence Completion Test, COWAT: Controlled Oral Word Association Test, SOC: Stockings of Cambridge, IED: Intra-Extra Dimensional Shift, TMT-B: Trail Making Test Part B, CCPT-EC: Conner's Continuous Performance Test – Errors of Commission, Executive Function.

4.3.2 Achievement measures

Real life achievement measures are detailed in Table 7. The very preterm group was significantly less educated ($t=6.13$, $df=192.63$, $p<.01$), had a lower employment rate ($\chi^2=5.80$, $df = 1$, $p=.016$) and had worse GRFI scores ($t=2.54$, $df = 173.68$, $p = .012$) compared to controls. A higher proportion of very preterm adults had become biological parents ($\chi^2=6.05$, $df= 1$, $p=.014$).

Table 7: Participants' Achievement Variables

Achievement variables	Term (n=79)	Very preterm (n=122)
Years in full-time education	16.51($\pm$ 2.37)	14.47($\pm$ 2.43)***
Work status (% employed)	96	85*
Income (% in bands 'a' (£0-£9,999) through 'f' (£50,000+))	10/10/38/25/1 0/7	3/24/22/25/9/17
Socio-economic status (% subject)		
I-II (Professional & Intermediate)	58	60
III (Skilled manual & Non-manual)	40	33
IV-V (Semi-skilled & Unskilled manual)	2	7
Relationship status (% in relationship)	57	57
Biological parenthood (% with ≥ 1 child)	15	30*
Global Role Functioning Index (0-28) ^a	25.39($\pm$ 1.77)	24.32($\pm$ 4.17)*
Social Adjustment Scale ^b	1.72($\pm$ 0.37)	1.71($\pm$ 0.48)

Means and standard deviations ($\pm$) are presented, unless otherwise specified. Results are adjusted for sex.

* $p \leq 0.05$ *** $p \leq 0.001$ using Student's t-test, Pearson Chi-Square or Fisher's exact test as appropriate.

^aCohen's $d = -0.33$; ^bCohen's $d = 0.03$

4.3.3 Association between neurocognitive test scores and life achievement measures

Results of the regression analyses revealed a differential association between executive function score, adjusted for IQ, and measures of real-life achievement in the two groups. Specifically, executive function was significantly associated with scores on the Role Functioning Scale ($\beta=.49$, $t=3.52$, $df = 169$, $p<.01$), years of education ($\beta=.24$, $t=2.06$, $df = 205$, $p = .04$), scores on the Social Adjustment Scale ($\beta = -.46$, $t= -3.27$, $df = 205$, $p<.01$), and participants' work status ($\beta= -1.97$, $t= -3.09$, $df = 177$, $p<.01$) in the whole sample. Statistically significant interaction effects, adjusted for sex, between executive function and group were evident and are detailed in Figure 7. Results show that executive function score in the very preterm group had a stronger positive association with real-life achievement measures than in the control group. There was a significant association between IQ and years in education, independently of executive function, in the whole sample ($\beta= .47$, $t= 5.24$, $df = 205$, $p<.01$).

Figure 7: Association between Executive Function and Real-Life Achievement

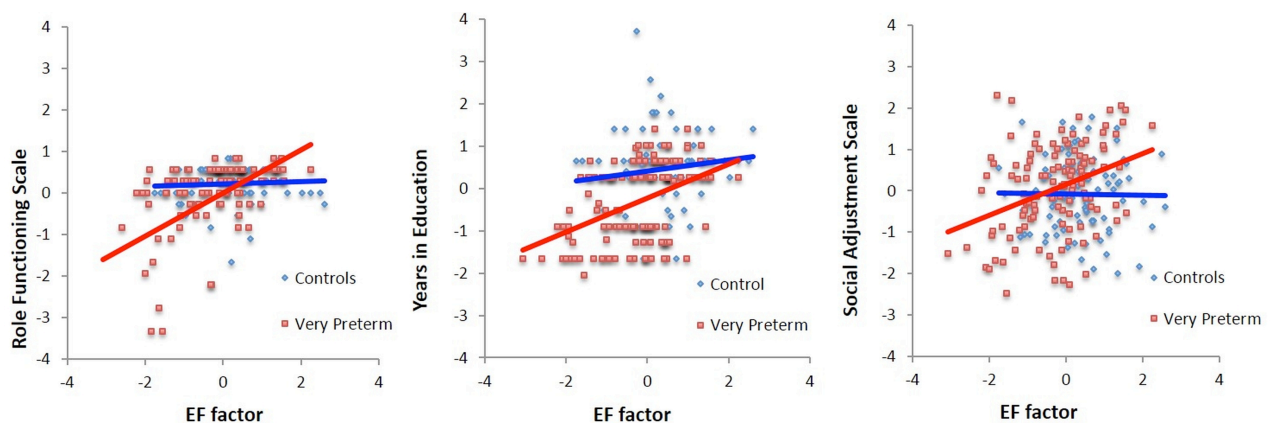


Figure 7: The relationship between Executive Function factor score and achievement measures including years in education, the Role Functioning Scale - Global Role Functioning Index and the Social Adjustment Scale in the two groups. Significant interactions between group and all three measures are shown.

Neurocognitive performance in the very preterm group after removal of cases with cerebral palsy and other neurosensory impairments

Results remained unchanged after excluding very preterm individuals who had cerebral palsy or another neurosensory disability.

4.4 Discussion

Very preterm adults performed worse than full-term controls on measures of executive function and IQ with moderate to large effect sizes. Similarly, they also showed poorer real-life achievements than controls: they were significantly less educated, had poorer overall social and occupational functioning and had a lower employment rate. Executive function performance in the preterm group was found to explain the variance in real-life achievements, independently of IQ, indicating how crucial these skills are for everyday functioning.

The current results are similar to previously reported findings, which indicated that individuals who were born very preterm performed worse than full-term controls on neurocognitive measures in childhood, adolescence and young adulthood (26 y/o) (Burnett, Scratch, & Anderson, 2013; Eryigit Madzwamuse et al., 2015). However, executive function abilities, which are subserved by the frontal lobe, are believed to continue to develop until the third decade of life (De Luca et al., 2003, Petanjek et al., 2011), hence it has been difficult to ascertain whether the impairments described in younger very preterm populations persist into adulthood or ameliorate with time (Luu, Ment, Allan, Schneider, & Vohr, 2011). Here we found that adults over the age of 30 who

were born very preterm continue to demonstrate lower neurocognitive scores compared to full-term controls. These include lower scores on both IQ subtests (Verbal IQ and Performance IQ) and on several executive function tasks, which may imply a global, rather than a specific, cognitive problem (Lohaugen et al., 2010; Wolke & Meyer, 1999). Despite evidence of a global impairment, very preterm adults appeared to experience difficulties in specific executive function domains, such as response initiation and suppression, verbal fluency, visual attention and set shifting. These findings extend previous work demonstrating similar difficulties (Aarnoudse-Moens, Smidts, et al., 2009; Anderson & Doyle, 2003; Mulder et al., 2009) including in the current sample when participants were in their early twenties (Nosarti et al., 2007; Nosarti et al., 2014), suggesting a developmental stability into adulthood (Breeman et al., 2015), although longitudinal studies are required to ascertain this. There were no statistically significant group differences in measures of rule acquisition and reversal and in a task involving spatial planning. Further work is required to understand whether these findings may suggest a very preterm profile in which only some aspects of executive function are affected (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012) or whether this variance may be attributed to methodology (i.e. tasks chosen) (Mulder et al., 2009).

Although further studies are required, there is evidence to suggest that a global executive function impairment is related to neonatal brain injury such as white matter alterations, which can affect up to a fifth of preterm individuals (Cheong et al., 2009; Woodward, Clark, Bora, & Inder, 2012). Similarly, two recent studies undertaken with subsamples of this cohort, demonstrated significant associations between EF ability and alterations in cortical maturation between mid- to late-adolescence in temporal, occipital and parietal cortices (Froudish-Walsh et al., 2015; Nam, Castellanos, Simmons, Froudish-Walsh, et al., 2015) and in basal ganglia connectivity at age 30 (Karolis et al.,

2016). It therefore seems plausible that the neurocognitive deficits seen here may be at least partly explained by underlying neurodevelopmental alterations.

Considering the importance of executive function abilities for real-world functioning (Salthouse, 2012) our finding of a significant relationship between executive function and adult achievement are perhaps unsurprising. Executive function deficits are associated with worse school functioning including poorer attention and math skills (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, et al., 2013) which have direct consequences on adult achievements (Basten et al., 2015). Hence, the findings presented here may be a result of a cascade of effects that include executive function deficits and worse academic performance that may each contribute to social opportunities and achievement in adulthood. Moreover, the stronger association between executive function and achievement detected in the very preterm group may emphasize the importance of executive function for everyday life (Burnett et al., 2013) thus, even subtle impairments may have a disproportionate impact on real-life functioning.

Indeed, our results showed that very preterm individuals had spent less time in education (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Burnett et al., 2013) and had lower rates of employment, a finding that has, however, not been commonly reported (Hack et al., 2009; Saigal et al., 2006). We also found lower interviewer-rated scores on a measure of adult functioning in areas such as work productivity and quality of social relationships, but not in self-rated social adjustment (SAS-SR). One possible explanation for this discrepancy may be a self-reported bias whereby very preterm individuals perceive themselves as functioning better than others do (Saigal et al., 1996). Despite this, those very preterm individuals who were employed did not earn less than their full-term counterparts and a similar proportion of very preterm adults and term-born controls were in relationships; findings contrary to

the literature (Lindstrom et al., 2007; Moster et al., 2008; Swamy, Ostbye, & Skjaerven, 2008; Winstanley, Lamb, Ellis-Davies, & Rentfrow, 2015). The very preterm group also had higher rates of biological parenthood, which may reflect the fact that very preterm individuals are likely to have children at a slightly earlier age than their term born counterparts (Mathiasen, Hansen, Nybo Anderson, & Greisen, 2009). Early biological parenthood may be related to poorer achievement such as fewer years of education and lower work status (Cooke 2004), but also to findings that very preterm adults display reduced risk-taking behaviours including having multiple partners (Cooke, 2004; Saigal et al., 2016), and that they rate the quality of their existing relationships as being highly satisfying (Hallin, Hellström-Westas, & Stjernqvist, 2010; Winstanley et al., 2015).

Our result of a stronger association between executive function deficits and poorer real-life achievements in very preterm adults compared to controls enhances the current understanding of the mediating factors underlying the social and economic risk following very preterm birth. Whilst acknowledging that no single factor is likely to be a sole predictor of overall life achievement, the fact that executive function scores proved so crucial in the current analysis may have important implications. Executive function abilities could represent ideal targets for intervention as they are potentially malleable (Dahlin, Nyberg, Backman, & Neely, 2008; Hsu, Novick, & Jaeggi, 2014), relying on brain regions such as the prefrontal cortex, which show protracted developmental change compared to other brain regions, (Froudish-Walsh et al., 2015; Petanjek et al., 2011) thus leaving a longer window of opportunity for improvement (Nosarti & Froudish-Walsh, 2016). Therefore, the most immediate implication of our study is the requirement for research to investigate the efficacy of targeting executive function in very preterm individuals with appropriate strategies (*i.e.* cognitive training) and the concomitant effects of this on broader indices of achievement and function. Recent findings indicate that training has led to an improvement in working memory in very

preterm samples (Grunewaldt et al., 2013; Lohaugen et al., 2011) although the potential benefits of cognitive training for real-life functioning are yet to be investigated.

Limitations of this study include the fact that the very preterm individuals we studied were born in the late 1970's and may have displayed deficits in adulthood that are not representative of very preterm cohorts born in more recent years (Basten et al., 2015), due to advances in neonatal care. Similar to other longitudinal studies, attrition is a critical limitation; participants studied here are a subset of the original cohort. However, participants in the current study did not differ from those who did not attend in terms of birth weight and were born at only a slightly younger gestational age. A further limitation is that the current very preterm participants are relatively 'high-functioning' as they had mean IQ scores within the average range, while being lower than those obtained by controls, in line with results of other studies (Allen, Cristofalo, & Kim, 2010). Hence, we examined the associations between executive function score, independently of IQ, and measures of real-life achievement. The current preterm participants were recruited from a major teaching hospital in central London, which encompassed several 'wealthy' geographical catchment areas. Previous studies examining the current preterm cohort have found no differences in parental SES compared to controls (Nosarti et al., 2007), which supports the notion that executive functions may have a unique role in determining life achievement. Lastly, the examiners were not blind to the participants' group membership, which may have biased some results. However, the majority of tasks are completed independently of the assessor or administered using a script (such as the IQ assessment).

4.4.1 Conclusion

The main hypothesis of this study was supported; cognitive deficits are evident in adulthood and may be partly accountable for the lower levels of real-life achievement

seen in very preterm survivors. These results highlight the need to investigate the multifactorial underpinnings of achievement in very preterm populations and further studies are required to ascertain how specific factors may influence outcomes. Our findings emphasize the need for cognitive remediation programmes to be delivered to vulnerable groups, which thus far have targeted specific executive function components (e.g. working memory, cognitive control), and may one day show generalizable benefits for a successful overall life adjustment.

Chapter 5: Elevated Psychiatric Symptomatology in Very Preterm Born Adults

Do very preterm adults present with elevated psychiatric symptomatology compared to controls? What are the specific symptoms that characterise their profile?

5.1 Introduction

Population-based studies have confirmed an increased prevalence of psychiatric diagnoses in very preterm adults compared to term-born controls; with higher prevalence rates associated with decreasing gestational ages (Doyle & Anderson, 2010; Nosarti, Reichenberg, et al., 2012; Walshe et al., 2008). Overall, a 2- to 7.4-fold increase in risk of receiving a psychiatric diagnosis is evident in those born very preterm, (Johnson & Wolke, 2013; Nosarti, Reichenberg, et al., 2012; Treyvaud et al., 2013) which remains even after adjusting for genetic risk (Wiles, Peters, Leon, & Lewis, 2005); suggesting a role for prematurity in psychiatric disorders. In children and adolescence, diagnostic studies often report a higher prevalence of attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) (Johnson & Marlow, 2011; Treyvaud et al., 2013). In addition to neurodevelopmental disorders, emotional disorders such as depression and anxiety may also be elevated in those born preterm. It has been reported that preterm populations show a specific risk for anxiety disorders in childhood with a 4- to 6-fold increase in odds described in very low birth weight children (Botting, Powls, Cooke, & Marlow, 1997; Indredavik et al., 2004; Johnson & Marlow, 2011). Results from samples of extremely preterm children show a 9%

prevalence of emotional disorders (mainly anxiety) compared to 2% in term controls (Johnson et al., 2010). Anxiety and behavioural difficulties in early life may be a precursor for adult-onset psychiatric illnesses such as depression and psychotic disorders (Dobson, Schmidt, Saigal, Boyle, & Van Lieshout, 2016).

Our knowledge of adult outcomes is limited, few cohort based studies have followed-up their samples into adulthood and the majority of our knowledge stems from Scandinavian register studies. Despite some inconsistent results, these studies report an increased risk of adulthood onset disorders such as bipolar affective disorder, non-affective psychosis, depression, and anxiety (D'Onofrio et al., 2013; Moster et al., 2008; Nosarti, Murray, et al., 2012). Emotional instability and addictive disorders are also reported in addition to childhood onset disorders such as an increased risk of autism spectrum disorder in adults born preterm (Lindstrom et al., 2009; Moster et al., 2008).

Although epidemiological studies have been extremely useful in identifying the incidence of psychiatric illness, it is likely that the clinical presentation of very preterm individuals will extend across the standard diagnostic boundaries (Johnson & Marlow, 2014); hence these papers may underestimate the real prevalence of psychiatric problems in these samples. Moreover, up to half of individuals with a mental disorder may go untreated and may remain unidentifiable in these studies. In addition, psychiatric morbidity is increasingly being understood in terms of a continuous phenotype, measurable in both healthy and ill individuals (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009), and it can therefore be hypothesized that accompanying the increased incidence of clinically significant psychiatric problems in preterm survivors, there would be an overall higher incidence of subclinical psychiatric symptomatology in in this population as well, although this has yet to be demonstrated in the adult literature.

5.1.1 Preterm Behavioural Phenotype

Qualitative differences in the clinical presentation of those born very preterm are commonly reported suggesting that prematurity may represent a differential aetiological risk and that the profile of symptoms may differ from the general population. Approximately 10% of children born preterm are diagnosed with ADHD, for example, and their clinical profile differs substantially from those seen in their full-term counterparts. Firstly, there is little evidence for an increase in hyperactivity; rather the problems experienced by preterm children appear in the attention domain (Hack et al., 2009). Secondly, in contrast to the general population, there is not a male predominance (Elgen, Sommerfelt, & Markestad, 2002; Indredavik et al., 2010). Thirdly, preterm born children with ADHD are less likely to be diagnosed with comorbid conduct disorder (Johnson et al., 2010). These findings, together with evidence of a increased neurological complications in those diagnosed with ADHD, has suggested that this form of the disorder may be a 'purer' or more 'biological' form compared to the general population (Johnson & Marlow, 2011). Similar descriptions have been reported in preterm participants with ASD-like symptoms.

In anxiety disorders, there is a lack of gender differences and this may also be associated with more biological mechanisms, i.e., brain alterations and with cognitive difficulties, such as inattention (Elgen et al., 2002; Hille et al., 2001). Emotional and behavioural problems have also been reported in preterm populations. The terms 'emotional' and 'behavioural' define a wide spectrum of difficulties in behavioural self-regulation, attention, eating and sensory sensitivity, problems with peer, anxiety and depression. Such problems result in increased rates of subclinical symptomatology that,

at the furthest end of the distribution, meet clinical criteria (Elgen, Sommerfelt, & Markestad, 2002; Johnson & Marlow, 2011).

Similar patterns of symptoms have been observed in very preterm children in different countries, despite cultural differences and disparities in perinatal care, indicating a universality to the traits associated with preterm birth (Bhutta et al., 2002). Hence, the preterm “behavioural phenotype” has been described in children and adolescents (further details are provided in Chapter 1; Johnson & Marlow, 2011) and it is likely that this will extend into adulthood (Hack et al., 2004). Although a similar profile may be delineated from findings in adulthood, the expression and nature of the symptomatology is likely to appear different, reflecting natural age-related developmental changes. Indeed, in adulthood higher prevalence of anxiety problems is often reported; in addition to lower self-esteem, inattention and more social withdrawal symptoms (Hack et al., 2004; Rickards et al., 1987). Since there is a paucity of adult studies it remains unknown how these symptoms may appear in adulthood; however, these qualitative differences may indicate the need to implement a symptom-based approach to assessing psychopathology in the preterm population.

5.1.2 Theories linking preterm birth and psychopathology

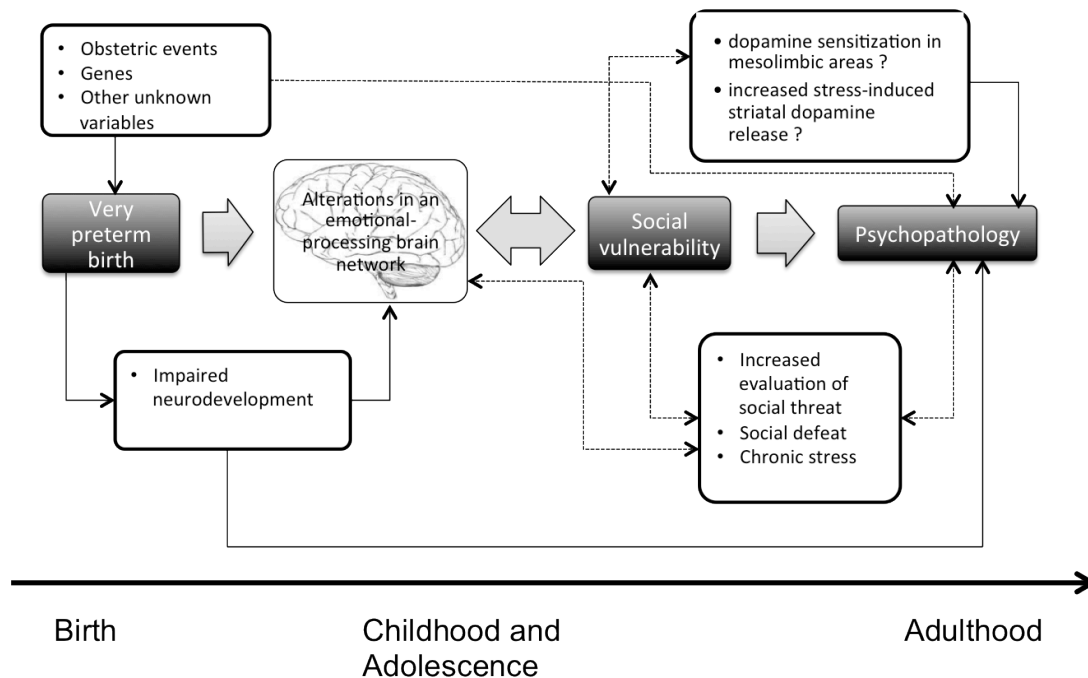
The casual pathway between very preterm birth and higher risk of psychiatric impairments is not fully understood. Since a linear relationship exists between gestational age and higher incidence of psychiatric illness it may be that this link is mediated by alterations in neurodevelopment. Brain injury such as PVH, occurs near key areas in the brain linked with symptomatology such as the striatum and the hippocampus (Aanes et al., 2015; Thompson et al., 2014). A recent study on the current cohort (Froudish-Walsh et al., 2017), examined striatal dopamine synthesis capacity and found decreased presynaptic dopamine release. This study found alterations in the

dopaminergic system only in individuals with a history of PVH but not in those without, thus indicating a possible role for brain injury in psychopathology. As described, in neurodevelopmental disorders a possible cognitive aetiology has been proposed that is mediated by neurological alterations. This theory is strengthened by evidence, that in contrast to the general population, emotional disorders in very preterm children seem to be associated with cognitive impairments (Johnson et al., 2010; Johnson & Marlow, 2011). Studies examining psychiatric problems have described a comorbid profile of mental health problems and neurosensory or cognitive impairments (Woodward et al., 2009). Cognitive impairments have also been studied extensively in relation to psychotic-like features and in schizophrenia and are thought to be central to the manifestation of symptomatology (Fusar-Poli et al., 2012). If preterm birth confers a risk to cognitive dysfunction even in early childhood (Anderson & Doyle, 2004) then it may be that the risk for developing symptomatology is mediated by early cognitive development. A unique framework for understanding psychiatric function in preterm individuals is therefore required, one that will consider the unique biological and environmental factors associated with preterm birth. Although the majority of studies have examined psychiatric disorders in preterm samples, it is clear that the majority of children without a psychiatric disorder may suffer from elevated symptomatology.

The traditional view of mental illness as a categorical entity has been challenged for epidemiological, experimental and theoretical reasons indicating that symptoms might in fact be distributed along a continuum. Indeed, psychiatric morbidity is increasingly being understood in terms of a continuous phenotype, measurable in both healthy and ill individuals (van Os et al., 2009) and has been investigated in several 'high-risk' populations (Demjaha, Valmaggia, Stahl, Byrne, & McGuire, 2012). However, no study to

date, has utilised a dimensional approach to examining psychopathology in adults born very preterm.

Figure 8: A developmental socio-biological vulnerability model linking preterm birth, social vulnerability and psychopathology (from Healy et al., 2013)



Based on existing evidence suggesting that very preterm individuals have an increased risk of both sub-threshold psychiatric symptomatology and clinical disorders, the aim of this study was to utilise a dimensional approach to examine whether adults who were born very preterm would demonstrate elevated levels of psychopathology compared to controls, and secondly, to explore the specific characteristics of their symptom profile.

5.2 Materials and Methods

5.2.1 Study population

Very preterm individuals who were assessed at the current follow-up did not differ significantly from those who were not assessed in terms of their birth weight (Assessed at 30: 1305.83 grams, Not assessed at 30: 1371.75 grams, $t=-1.78$, $df=450$, $p=.075$),

however, those who were assessed were born at a slightly younger gestational age than those who were not (Assessed at 30: mean gestational age = 29.18 weeks, Not assessed at 30: mean gestational age=29.67, $t=-2.23$, $df=451$, $p=.026$) and there was a higher proportion of males in the returning cohort (Assessed at 30: 62% male, Not assessed at 30: 48% male, $X^2=7.19$, $df=1$, $p<0.01$).

The term-born control group consisted of 96 individuals recruited from advertisements in the local community.

5.2.2 Socio-demographic, cognitive and behavioural assessment

Participants' socio-economic status (SES) was assessed with Her Majesty's Stationary Office Standard Occupational Classification Information (Her Majesty's Stationary Office, 1991). IQ was examined using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

Psychiatric symptomatology was assessed with the 'Comprehensive Assessment of At-Risk Mental States' (CAARMS; Yung et al., 2005). The CAARMS is an interviewer-rated, semi-structured tool, measuring current rates of psychopathology on the following subscales: positive and negative symptoms, cognitive problems, emotional disturbance, behavioural changes, motor/physical changes and general psychopathology. General psychopathology included depression, anxiety, mania, and mood swings. Each scale is rated on a 0-6 severity scale ('0 - Never/absent' to '6 - Extreme'). Inter-rater reliability was assessed by comparing ratings for all subscales for three very preterm individuals who were assessed by both study raters and a 'gold-standard' rater (an experienced psychiatrist). Intra-class Correlation Coefficients were 0.89 between study raters PJB and JK and .90 and .86 between raters PJB and JK and the gold-standard rater respectively. These values represent 'Almost Perfect' agreement (Landis & Koch, 1977).

5.2.3 Statistical analysis

Matlab, version R2016a (Mathworks, MA, USA) and SPSS for Macintosh, version 22.0 (IBM, Armonk, NY), were used for the statistical analyses. Group differences in socio-demographic measures were examined using independent *t*-test or Chi-Square test, with significance set at $p < 0.05$.

Part 1: Group differences in symptomatology

Between-group differences on each of the CAARMS subscales were explored using the Mann-Whitney U-test. Spearman correlation was used to examine the association between IQ and Total Psychopathology.

To further examine between-group differences, a previously described cut-off was used to define individuals born very preterm that are at risk of clinically significant problems, defined as a CAARMS score greater than or equal to the 90th percentile score of controls (Healy et al., 2013; Rickards, Kelly, Doyle, & Callanan, 2001). This group will be referred to as 'high-risk' in the text.

In order to quantify this risk on each CAARMS scale, Fisher's Exact Test was performed and summarized as Odds Ratio. Motor symptoms were excluded from the analyses as very few controls scored above zero on this measure. Multiple comparison correction was performed using false discovery rate (FDR) correction (Benjamini & Hochberg, 1995).

Part 2: Specificity of symptom profile

A principal component analysis (PCA) was performed on the CAARMS scales to provide a dimensional overview of the pattern of psychiatric symptoms. A skree plot was used to identify the number of components that parsimoniously described the variance in the psychopathology data. Once the ideal number of principal components was found, k-means clustering was performed, in order to group individuals according to their symptom distribution. In order to analyse whether very preterm born individuals were more likely to experience a certain cluster of symptoms compared to controls, a Chi-square test was used. Pairwise Fisher's Exact Test was performed to compare participants' symptoms distribution in each cluster to that in the low psychopathology cluster.

5.3 Results

Neonatal, socio-demographic, cognitive variables and psychiatric history are presented in Table 8. There were more men than women in the very preterm group compared to controls. Very preterm individuals had a significantly lower IQ and were more likely to report a lifetime psychiatric history compared to controls.

Table 8: Participants' Neonatal, Socio-Demographic, Cognitive and Psychiatric

	Term (n=96)	Very preterm (n=152)	Statistics
Gestational age (weeks)	-	29.28 (SD 2.09)	-
Birth weight (grams)	-	1312.45 (SD 349.92)	-
Neonatal Cranial Ultrasound Classification (% no-PVH/PVH/PVH+DIL)	-	49/22/28	-

Age (years)	30.64 (5.24)	31.46 (2.33)	N.S.
Gender (% male)	46	59	$X^2_{(1)} = 4.24; p = .04$
Full-scale IQ	111.62 (13.15)	102.40(15.27)	$t = 4.42 p = .000$
Self-reported psychiatric history	10 (11.4)	40 (26.5)	$X^2_{(1)} = 7.69; p=.006$

no-PVH: normal neonatal cranial ultrasound, PVH: uncomplicated periventricular haemorrhage without ventricular dilatation, PVH+DIL: periventricular haemorrhage with ventricular dilatation. Means and standard deviations (SD) are presented, unless specified.

5.3.1 CAARMS results

Very preterm participants had significantly elevated levels of emotional disturbances, positive, negative, cognitive, negative and motor symptoms compared to controls (Table 9), and all results survived FDR correction. However, there were no significant between-group differences in emotional disturbance, while differences in general psychopathology reached borderline levels of significance.

Table 9: CAARMS scores for very preterm and term-born participants

CAARMS measures Mean	Term	VPT	Mann-Whitney U	p
Total Psychopathology	7.57	15.39	4179	.001
Positive Symptoms	.056	1.74	4448	.002
Cognitive Symptoms	1.02	2.04	4376	.003
Emotional Disturbances	0.77	1.21	5265	.414
Negative Symptoms	0.93	1.96	4717.5	.020
Behavioural Changes	1.21	2.56	4825	.042
General Psychopathology	2.89	4.89	4799.5	.051

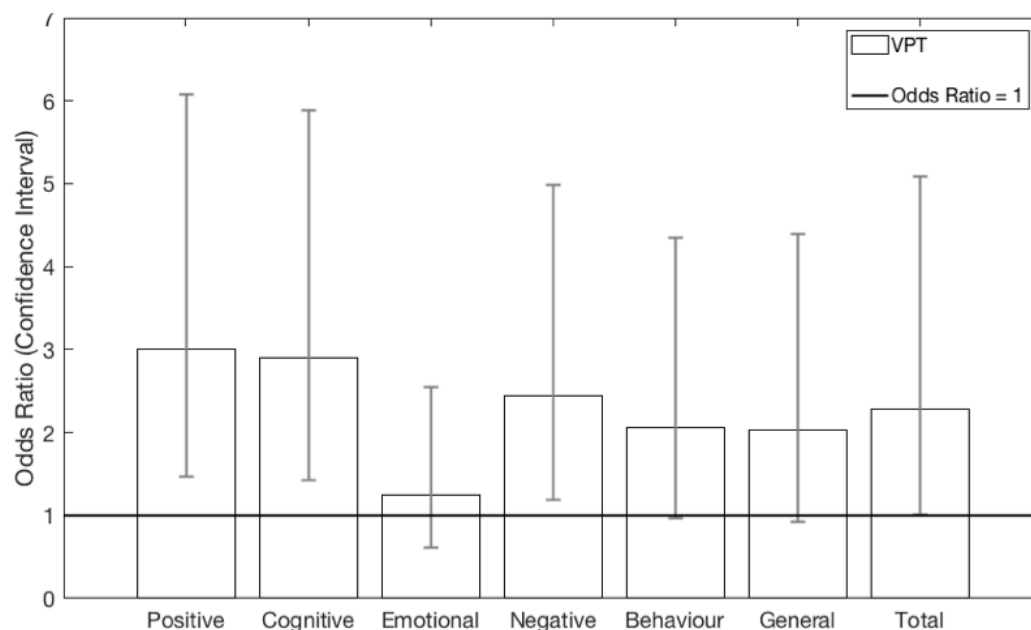
CAARMS: Comprehensive Assessment of At-risk Mental States. Total psychopathology score is the sum of all subscales.

In the whole sample, higher Total Psychopathology scores were significantly associated with lower full-scale IQ (Spearman's $r = -.268$, $p = .000$); however within group analyses showed that this association was significant in the very preterm group ($r = -.259$; $p = .003$), but not in controls ($r = -.187$; $p = .114$). The difference between these two correlation coefficients was not statistically significant (Fisher's $z = -0.51$, $p > 0.05$).

5.3.2 Group and 'high-risk' symptomatology

Very preterm individuals were significantly more likely than controls to score above the 'high-risk' threshold for total symptomatology ($p = 0.044$), as well as for the positive ($p = 0.002$), cognitive ($p = 0.002$) and negative ($p = 0.014$) scales. There were no significant differences between the groups on the emotional disturbance ($p = 0.596$), behavioural ($p = 0.057$), or general psychopathology ($p = 0.101$) scales as described in Figure 9. After FDR correction significant between group results remained on the positive, cognitive and negative scales.

Figure 9: Odds ratio for being at 'high-risk' in adults born very preterm



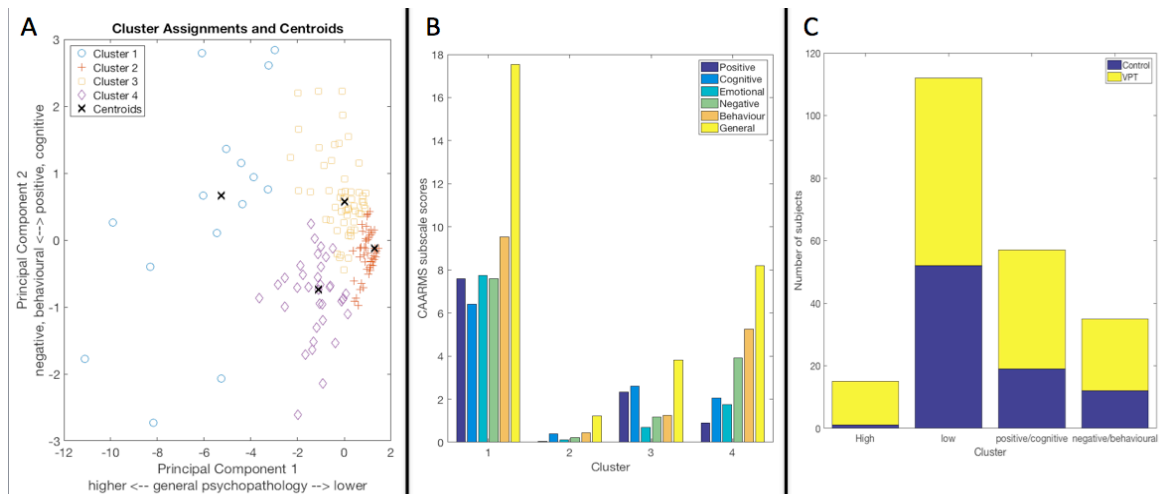
Adults born very preterm were more likely than controls to belong to the 'high-risk' category, on the basis of total symptoms, as well as positive, negative and cognitive symptoms.

5.3.3 Symptom clustering

Principal components analysis revealed two components that explained 77.44% of the variance in the CAARMS scales (principal component 1 (PC1) = 67.08%, principal component 2 (PC2) = 10.36%). PC1 had negative weights of a similar size (between -0.38 and -0.43) for each CAARMS subscale, indicating a non-specific psychopathology dimension. PC2 had large positive weightings on positive and cognitive subscales (0.57, 0.56) and relatively large negative weightings on the negative and behavioural subscales (-0.32, -0.45), indicating a variance in symptomatology along a positive-to-negative symptom axis.

In order to investigate if very preterm birth was likely to be a risk factor for a specific psychiatric dimension, we used K-means clusters ($k=4$) to separate the study sample into clusters that differed on their loadings on both the non-specific psychopathology axis, and the positive-to-negative symptom axis. Specifically, Cluster 1 contained individuals who scored high on non-specific psychopathology. Cluster 2 contained individuals who scored low on non-specific psychopathology. Clusters 2 and 3 both exhibited only mild overall symptoms, but were separated on the positive-to-negative axis, with individuals in Cluster 2 tending to have more positive and cognitive symptoms, and individuals in Cluster 3 tending to have more negative and behavioural symptoms (Figure 10).

Figure 10: Symptom clustering



A) Principal Components Analysis revealed two major components. The first component separated individuals with high and low non-specific psychopathology. The second component accounted for variance along a positive/cognitive to negative/behaviour symptom axis. K-means clustering of participants' loadings on these two components identified four psychopathology clusters. B) CAARMS sub-scores by clusters: Cluster 1: high non-specific psychopathology; Cluster 2: low non-specific psychopathology; Cluster 3: high positive and cognitive symptoms; Cluster 4: high negative and behavioural symptoms. C) Group composition by cluster.

The distribution of the groups within each cluster is shown in Table 9 and Figure 10. A Chi-square test indicated significant between group differences in their distribution into clusters ($X^2 = 10.31$, $p = .016$). In order to further probe whether study participants were more likely to belong to a particular psychopathology cluster than chance, we performed a series of Fisher's Exact Tests to study whether the prevalence of very preterm participants in the high non-specific psychopathology, positive/cognitive and negative/behavioural clusters was greater than their prevalence in the low general psychopathology cluster. Results indicated that preterm individuals were more likely to belong to the high non-specific psychopathology cluster than controls, but this was not found for the positive/cognitive or the negative/behavioural cluster (Table 9).

Table 11: Distribution of Participants within Psychopathology Clusters

Cluster	Control N (%)	VPT N (%)	Odds Ratio [95% Confidence Interval]	p
1. Low non-specific psychopathology	52 (61.9%)	60 (44.4%)	–	–
2. High non-specific psychopathology	1 (1.2%)	14 (10.4%)	12.13 [1.54, 95.43]	0.0039
3. High positive/cognitive symptoms	19 (22.6%)	38 (28.2%)	1.73 [0.89, 3.37]	0.137
4. High negative/behavioural symptoms	12 (14.3%)	23 (17.0%)	1.66 [0.75, 3.66]	0.244

5.4 Discussion

The current study found that adults who were born very preterm demonstrated elevated psychiatric symptomatology compared to controls. As well as displaying increased total psychopathology, they showed increased positive, cognitive and negative symptoms. Individuals who were born very preterm were also between one- to three-fold more likely than controls to belong to a ‘high-risk’ group (defined by CAARMS scores above the 90th percentile of control scores) on several symptom scales.

These results are in line with previous research, indicating higher rates of psychiatric symptomatology in very preterm children, adolescents and in young adults (Hack et al., 2004; Healy et al., 2013; Johnson et al., 2010). Although the instrument we used, the CAARMS, was designed to explore subclinical psychopathology believed to indicate an imminent development of first-episode psychosis, it covers wider psychopathological domains and in this respect our results could be comparable with population-linkage studies that reported a significant association between very preterm birth and a number of psychiatric disorders such as depression, anxiety, schizophrenia and bipolar affective disorder (Johnson & Marlow, 2011; Nosarti, Reichenberg, et al., 2012; Nosarti,

Murray, et al., 2012; Crump, Winkleby, Sundquist, & Sundquist, 2010). Hence, the findings presented here suggest the existence of a major, yet poorly appreciated, psychiatric burden in adults who were born very preterm.

5.4.1 Participants' Clinical Profile

In the current assessment very preterm individuals scored higher on the majority of CAARMS sub-scales compared to controls, which may suggest a non-specific risk (Nosarti, Reichenberg, et al., 2012). Nonetheless, several of the symptoms that have been previously described as characterising a 'preterm behavioural phenotype' in childhood (Johnson & Marlow, 2011) and that are included in the CAARMS continued to be prevalent in our very preterm sample in adult life and these included attention and concentration difficulties, social withdrawal, cognitive changes, alogia, anhedonia, a decreased ability to perform adult roles, apathy, and depression/anxiety. In this sense, such symptom profile may transcend current diagnostic boundaries.

One challenge in understanding the psychiatric profile of adults who were born very preterm, is to disentangle the commonly described cognitive deficits, such as IQ and executive function deficits, which are thought to underlie social and behavioural problems (Aarnoudse-Moens, Smidts, et al., 2009; Anderson & Doyle, 2004; Delobel-Ayoub et al., 2009). Considering the significant association between IQ and psychiatric symptomatology, we are tempted to speculate that preterm adults may represent an aetiologically and prognostically distinct subgroup characterised by cognitive impairments (Fusar-Poli et al., 2012). Moreover, prospective studies indicate that in populations at risk of developing psychiatric disorders, deficits in social cognition and executive function, along with emotional and behavioural disturbances, may arise in childhood (van Os & Kapur, 2009) and continue into adulthood, when symptom

expression may change in magnitude and character to reflect age-related changes (Hudziak, Achenbach, Althoff, & Pine, 2007).

Indeed, a study conducted in a partially overlapping subsample of the current cohort in mid-adolescence, reported elevated scores on the ‘Social Problems’ scale of the parent-rated Child Behaviour Checklist (CBCL; Healy et al., 2013), with items such as “does not get along with peers”, “gets teased” and “too dependent”. Similarly, at age 18, this cohort was found to have increased levels of psychiatric ‘caseness’ according to the Clinical Interview Schedule – Revised (Walshe et al., 2008) with the most common diagnoses being mood and anxiety disorders. It may be, therefore, that these results represent a continuum of psychiatric risk from mid-adolescence through to adulthood, albeit highlighted with different instruments.

5.4.2 Neurodevelopmental Origin of Psychiatric Risk

The current findings support the notion of a neurodevelopmental origin of psychiatric disorders (Howes & Murray, 2014). According to the neurodevelopmental hypothesis, early brain lesions interact with the developing brain to increase vulnerability to psychopathology in adolescence and in adulthood (Murray, Lappin, & Di Forti, 2008). This hypothesis is supported by results from animal studies which have shown that a lesion may remain relatively silent until the neuronal system affected reaches a degree of maturity at which point abnormal behaviour manifests (Sams-Dodd, Lipska, & Weinberger, 1997). In humans, complications in pregnancy, abnormal fetal growth and complications in delivery have been linked to psychosis (Cannon, Jones, & Murray, 2002); however, determining causality is difficult and the precise pathway linking very preterm birth and psychopathology remains unclear. It has previously been proposed that a theoretical framework needs to be considered which incorporates both biological and environmental contributions (Montagna & Nosarti, 2016). According to this model,

very preterm birth leads to long-lasting structural and functional brain alterations in socio-emotional and cognitive networks (Fischi-Gomez et al., 2014; Papini et al., 2016; Reininghaus et al., 2016). These may increase an individual's vulnerability to psychopathology, including enhanced stress sensitivity and aberrant salience (Reininghaus et al., 2016). Furthermore, very preterm individuals may be particularly susceptible to bullying, social defeat and internalising symptoms, which have also been studied as risk factors for psychopathology (Johnson & Marlow, 2011; Montagna & Nosarti, 2016; Valmaggia et al., 2015; Wolke, Baumann, Strauss, Johnson, & Marlow, 2015). Within this theoretical framework, psychiatric disorder may represent the endpoint of a risk pathway that begins at birth (Dutta et al., 2007). Hence our findings highlight the importance of collecting perinatal data as part of routine psychiatric assessments, of monitoring possible antecedents to psychiatric disorder in preterm born individuals and of developing preventative interventions early in life. Moreover, further studies are required to examine the generalizability of the current results to other high-risk populations, such as those with obstetric complications other than very preterm birth and those at genetic risk for psychopathology.

5.4.3 Limitations

The current study had a number of limitations. Our study participants were born in the late 1970's and early 1980's and, due to advances in neonatal care, may have displayed mental health symptoms in adulthood, which are not representative of very preterm cohorts born in more recent years. Similar to other longitudinal studies, attrition is a critical limitation; participants studied here were a subset of the original cohort. A previous study found a bias in selective dropout where those with the worst outcomes did not return for assessments; however, this would decrease the prevalence of self-

reported psychiatric history, indicating our results may be an underestimation of participants' current psychiatric profile (Wolke et al., 2009).

We further acknowledge that a major limitation of this study is the use of one assessment tool, which was originally designed to evaluate attenuated symptomatology in individuals at risk of psychosis. Considering the overlap between these symptoms and other disorders (Prata et al., 2009) the findings presented here may be secondary in nature to the neurocognitive and behavioural difficulties often described in preterm populations.

5.4.4 Conclusion

Our findings highlight the impact of very preterm birth on mental health, lending support to the notion of a neurodevelopmental origin of psychopathology. These results further suggest that very preterm birth is a risk factor across a number of symptom domains and may not be limited to standard diagnostic boundaries. Further studies should focus on the investigation of known antecedents of psychopathology in very preterm children, such as emotion regulation problems (Treyvaud et al., 2012). These results further suggest that early preventative interventions should extend to target individuals born very preterm.

Chapter 6: Salience Processing and Psychopathology In Very Preterm Adults

Does salience processing mediate psychiatric symptomology in preterm born adults?

6.1 Introduction

Very preterm individuals not only show elevated sub-clinical psychiatric symptomatology, but their symptom profile may transcend current diagnostic boundaries (Johnson & Wolke, 2013), similar to findings in populations at high genetic risk (van Os & Linscott, 2012). As previously mentioned, qualitative differences in the clinical presentation of those born very preterm are commonly reported and may be mediated by cognitive deficits. Indeed, the importance of cognitive symptoms in relation to psychopathology is increasingly being recognised (Owen, O'Donovan, Thapar, & Craddock, 2011). Even disorders that share a genetic overlap such as schizophrenia and bipolar affective disorder may be mediated by specific cognitive pathways (Demjaha, Maccabe, & Murray, 2011). Similar to preterm born individuals, those with a diagnosis of schizophrenia often exhibit lower executive function scores and IQ, whereas there is little or no evidence for this in bipolar disorder (Zanelli et al., 2010). Indeed, over the last decades there has been increasing emphasis on identifying cognitive risk factors as early as in childhood, which may predict adult psychopathology. Indeed premorbid cognitive function may not only predict psychotic symptoms (Cannon, Caspi, et al., 2002), but can be considered a casual risk factor for symptomatology (Reichenberg, 2005). These cognitive impairments, evidenced in childhood and adolescence may share a genetic overlap with neurodevelopmental disorders (Rutter, Kim-Cohen, & Maughan, 2006), commonly reported in premature populations. Furthermore, cognitive performance may not only be a precursor to psychopathology but may directly be

associated with socio-emotional difficulties (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, Oosterlaan, et al., 2013) including in the current cohort (Kroll et al., 2017).

Difficulties in learning, especially in motivated reward learning, have been studied as precursors to psychiatric symptoms (Kapur, 2003), but this is yet to be investigated in preterm born individuals. Findings of a positive association between dopamine, salience processing and psychiatric symptomatology have been demonstrated in healthy controls (Boehme et al., 2015) and in individuals at high-risk of psychosis (Roiser et al., 2009). Considering this, and the evidence of an increased incidence of psychiatric symptomatology in preterm populations, it can be hypothesised that preterm adults may also demonstrate increased aberrant salience that may underlie their clinical profile.

6.1.1 Salience Processing

Salience refers to a stimulus that stands out and grabs our attention; it can be a feature contrast (a red circle amongst hundreds of green ones) or novelty (a burning candle in a dark room) (Schmidt & Roiser, 2009). Attribution or motivational salience refers to the way in which a stimulus drives our attention and motivation and is related to whether we associate a reward or punishment with that stimulus. Motivational salience can be adaptive, when a neutral stimuli is conditioned into an attractive representation (Berridge & Robinson, 1998). In contrast, aberrant motivational salience refers to stimuli that are not reinforced, but come to grab our attention and capture our thoughts (Jensen & Kapur, 2009). This is often not a conscious process, it is conditioned within our personal experiences of learning and memory and neurobiological factors, such as the dopaminergic state of the mesocorticolimbic system (Berridge, 2012). Despite some shared neurobiology with reinforcement learning (Boehme et al., 2015), the salience

hypothesis posits that attributional salience may be considered a direct risk factor underlying psychopathology (Kapur, 2003; Schmidt & Roiser, 2009).

Dopamine plays a key role reward learning, and in particular in motivational salience in healthy individuals and patients with schizophrenia (Berridge & Robinson, 1998). Phasic firing of dopamine neurons in the midbrain are associated with rewarding stimuli, but not with neutral ones (Schultz, Dayan, & Montague, 1997) . Moreover, dopamine mediated networks such as the fronto-parietal network; which in addition to the insula, cingulate, striatum and the hippocampus is implicated in adaptive and aberrant salience processing (Murray et al., 2008). Adaptive reward learning is associated with the midbrain, medial dorsal thalamus, and ventral striatum mediated by dopamine release (Berridge & Robinson, 1998). The thalamus projects input from the ventral striatum and sends projections to the prefrontal cortex; the ventral prefrontal cortex projects back to the ventral striatum; thus creating the cortico-striatal-thalamic circuit (Roiser 2010). Aberrant salience is likely modulated by dopaminergic transmission in the ventral striatum in both individuals with a psychiatric diagnosis and controls (Boehme et al., 2015; Murray et al., 2008; Wyvell & Berridge, 2000).

Midbrain dopamine neurons that extend to the striatum are part of a 'learning system' (Schultz et al., 1997) hence, disruption to the dopamine system is associated with erroneous attribution of incentive salience or reward learning. Aberrant salience may underlie psychotic symptoms by chaotic dopamine firing that can be attenuated with the administration of antipsychotic medications. According to this model, antipsychotics will not only decrease dopamine levels, but they will also decrease levels of motivational salience. Since preterm born individuals are at risk of demonstrating decreased striatal dopamine (Froudish-Walsh et al., 2017), it can be hypothesised that they will also demonstrate decreased motivational salience.

6.1.2 Salience Processing and Psychiatric Symptoms

6.1.2.1 Positive Symptoms

Kapur (2004), within a phenomenological framework, combined disparate lines of research, and proposed a salience model of schizophrenia. According to this model, psychosis may be conceptualised as a process in which hyperdopaminergic transmission leads to aberrant experiences and perception; the individual, in an attempt to ‘make sense’ of these experiences creates a distorted reality, resulting in delusions and perceptual abnormalities. Aberrant experiences may occur when there is a dissonance between prediction and reward (Heinz & Schlagenhauf, 2010). At the extreme end of the spectrum, psychosis may be associated with reduced attribution to relevant stimuli and increased attribution to irrelevant stimuli. Increased dopamine release occurs when a reward supersedes expectation and is inhibited when a punishment is worse than expected. When there is no dissonance between prediction and outcome, dopamine release will no longer occur (Schultz et al., 1997). This has been demonstrated in psychosis and high-risk populations where there is an increased incentive or motivational salience to *irrelevant cues* (Roiser, Howes, Chaddock, Joyce, & McGuire, 2013; Roiser et al., 2009). Delusional thoughts are inferred on these irrelevant cues in order to explain their salient qualities. In contrast, a decrease in motivational salience towards *relevant cues* has been described in patients receiving antipsychotic medication, resulting in a dampening of dopaminergic transmission (Abboud et al., 2016), and in controls with high schizotypy traits (Schmidt & Roiser, 2009). Symptom severity is thought to positively correlate with increased aberrant salience in patients and healthy controls (Corlett et al., 2007).

6.1.2.2 Negative Symptoms

The salience hypothesis of schizophrenia provides a heuristic framework for the conception of psychosis in schizophrenia. However, negative symptoms may also be explained as a result of aberrant salience processing. Indeed, dysfunction in reward learning and goal-directed behaviour may drive negative symptoms such as motivation and emotional expression. A mismatch between expectations and outcomes, aberrant salience, can create negative experiences within the individual who is unable to predict reward or punishment. Negative symptoms such as anhedonia may be explained by an anticipation of a reward that is not received (Gold, Waltz, Prentice, Morris, & Heerey, 2008); which can also lead to a vicious cycle of undermining motivation to seek further rewards. The relationship between reward learning and negative symptoms is likely to be complex. Waltz et al (2007) found individuals with schizophrenia were worse at predicting unexpected rewards compared to controls (i.e., reward-based learning), but they were not worse at negative predictions or punishments (i.e., punishment-based learning).

Behaviourally, patients with schizophrenia often report experiencing a reward as satisfactory as controls; however, neuroimaging findings seem to contradict this. Differences in the neural response to positive stimuli have been reported (Plailly, d'Amato, Saoud, & Royet, 2006), in addition to reduced insula and striatal volumes, key components of the reward system. Moreover, the discrepancy between behavioural and neuroimaging results may, at least in part, explain the negative symptoms observed in schizophrenia and in other disorders characterised by similar symptoms. Reduced grey matter in areas associated with reward learning has also been described in very preterm populations, although the impact of this on behaviour has yet to be investigated.

6.1.3 Aberrant Salience as a Non-Specific Risk Factor for Psychiatric Disorder

Whilst the majority of evidence for the salience model is for psychotic disorders or for those individuals at high risk of psychosis (Bloomfield et al., 2016; Roiser et al., 2009), increasingly aberrant salience processing is being implicated in other neuropsychiatric disorders, such as autism and fronto-temporal dementia (Uddin, 2015), indicating that it may be a non-specific risk factor for psychopathology. Similarly, following acute cannabis administration, healthy volunteers showed an immediate impairment in salience processing (Wijayendran, O'Neill, & Bhattacharyya, 2016), whereas this was not the case in long-term users (Bloomfield et al., 2016). Further research needs to examine whether salience processing may underlie cognitive biases and subsequent symptomology in other high-risk populations such as those born very preterm.

To date, no study has assessed salience attribution in adults who were born very preterm, despite their increased vulnerability to psychiatric risk. Hence, we hypothesise that adults born very preterm will demonstrate impairments in salience processing compared to full-term controls. We further predict that increased aberrant salience will be associated with psychiatric symptomatology.

6.2 Materials and Methods

6.2.1 Study population

For the current study, 67 very preterm adults and 38 term-born controls participated, recruited from the cohorts described in Chapter 2.

6.2.2 Perinatal and Socio-demographic Assessment

Each participant completed a comprehensive neurocognitive examination covering a variety of domains including IQ using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Sustained attention was assessed using the Conners' Continuous Performance Test (Conners, 2000). Participants' socio-economic status (SES) was assessed with Her Majesty's Stationary Office Standard Occupational Classification Information (Her Majesty's Stationary Office, 1991).

6.2.3 Salience Attribution Task

All participants completed the Salience Attribution Test (SAT; Roiser et al., 2009), which measures aberrant and adaptive salience processing. Implicit salience is measured by reaction time to a cue that appears. This can vary across two dimensions: colour (red or blue) and form (animal or object) as shown in Figure 11. The SAT examines how participants respond to task-relevant and task-irrelevant cue features. A monetary reward (5-100 pence) is offered for faster responses to task-relevant dimensions. Each stimulus features a reward related cue – for example, blue objects provide a reward 87.5% and red objects 12.5% of the time). The second dimension carries no predictive information about the reward and is therefore irrelevant (50% reward for animal and household object). Thus there is a task relevant: colour (blue stimuli - 87.5% reward; red stimuli – 12.5% reward) and task irrelevant: form (animal and household objects – 50% reward) component. Participants are asked to respond to the onset of a probe following the appearance of these objects in order to 'win' money. Faster responses yield higher rewards when money is available. A message of 'Sorry – no money available' appears in the task irrelevant dimensions. When money is available faster reaction times provide more money and a message displays 'Hit – good: 10 pence' or

‘Quick – very good: 78 pence’. The maximum reward is one pound. Implicit aberrant salience was measured by the participant’s RT and calculated by subtracting the RT of the low reward stimuli from the RT of the high reward stimuli. Participants perform this task twice in two blocks of 64 trials each following two practice sessions. Explicit adaptive (relevant) and aberrant (irrelevant) motivational salience is measured on a visual analogue scale (VAS; Figure 12). The VAS is used to provide a subjective probability rating of reward measure. At the end of each block participants are asked to estimate how often each of the four stimuli provided a reward, from 0 – 100.

Figure 11: Implicit Salience - Salience Attribution Test

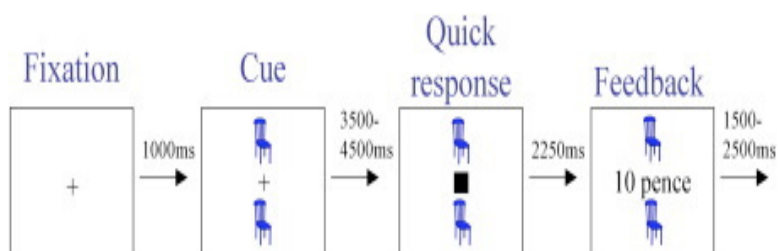
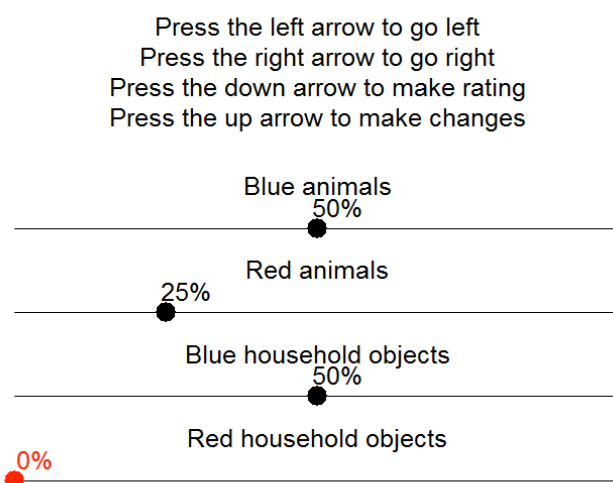


Figure 12: Explicit Salience - Visual Analogue Scale



6.2.4 Psychopathology Assessment

Psychiatric symptomatology was assessed with the 'Comprehensive Assessment of At-Risk Mental States' (CAARMS; Yung et al., 2005). The CAARMS is an interviewer-rated, semi-structured tool, measuring current rates of psychopathology on the following scales: positive and negative symptoms, cognitive problems, emotional disturbance, behavioural changes, motor/physical changes and general psychopathology. Since the salience hypothesis proposes that aberrant salience processing may drive positive and negative symptoms we examined these two CAARMS scales. In addition, to a total positive and negative scale we were interested in looking at specific symptoms within each scale. Hence, we included three subscales that comprise the positive symptoms and three subscales that comprise the negative symptom scale. Each subscale is rated on a 0-6 severity scale ('0 – Never/absent' to '6 – Extreme').

6.2.5 Statistical analysis

SPSS 22.0 (IBM, Armonk, NY) was used for the analyses. Neonatal risk variables included: birth weight, gestational age and severity of perinatal brain injury, based on the results of neonatal cranial ultrasound classification. (Nosarti et al., 2011). Group differences in socio-demographic measures were examined using independent *t*-test or Chi-Square test, with significance set at $p < 0.05$. Analysis of covariance (ANCOVA) was then performed to explore group differences in salience processing when controlling for sustained attention. Between-group differences on the CAARMS subscales were explored using the Mann-Whitney U-test. Spearman correlation was used to examine the association between salience and positive and negative scales.

6.3 Results

Perinatal and socio-demographic risk variables are presented in Table 11. The very preterm group contained significantly more men than the term-born group ($\chi^2=4.92$, $df=1$, $p=.027$).

Table 11: Participants' Neonatal and Demographic Variables

Demographic and Neonatal risk variables	Term (n=38)	Very Preterm (n=67)
Gestational age (weeks)	-	29.96 ($\pm$ 3.41)
Birth weight (grams)	-	1439.67 ($\pm$ 636.57)
Neonatal Cranial Ultrasound Classification (% no-PVH/PVH/PVH+DIL)	-	47/21/28
Sex (N (% male))	19 (50)	48 (71)*
Age at current assessment (years)	31.97($\pm$ 6.76)	31.49 ($\pm$ 2.21)
CPT	408.73 (52.52)	421.52 (68.28)
IQ	110.08 (14.06)	104.43. ($\pm$ 1.96)*

Means and standard deviations ($\pm$) are presented, unless otherwise specified. * $p<0.05$ using Student's t-test, Pearson Chi-Square or Fisher's exact test as appropriate.

Ultrasound Classification: no-PVH: normal neonatal cranial ultrasound, PVH: uncomplicated periventricular haemorrhage without ventricular dilatation, PVH+DIL: periventricular haemorrhage with ventricular dilatation.

As presented in Table 12, very preterm participants showed poorer performance than controls on the adaptive explicit salience trials. However, there were no significant between group differences in adaptive implicit and aberrant explicit or implicit salience.

Table 12: Salience Processing Variables

Salience measures Mean (SD)	Term	VPT	Adjusted Mean Difference (95% CI)	<i>p</i>
Adaptive Implicit	6.64 (6.93)	4.27 (8.9)	1.90 (-.95 to 5.69)	0.258
Aberrant Implicit	4.51 (3.28)	5.86 (5.08)	3.46 (-3.17 to .47)	0.066
Adaptive Explicit	45.78 (24.93)	33.32 (28.93)	7.49 (1.25 to 23.66)	0.008
Aberrant Explicit	6.72 (7.31)	9.37 (10.29)	3.34 (-6.44 to 1.15)	0.071

Salience Attribution Test: the four scales are presented. Raw scores are presented as Means and Standard Deviations. Results are adjusted for sustained attention.

Implicit salience relies on reaction time to a conditioned stimuli. Implicit adaptive salience is calculated as the speeding of responses on high- vs. low-probability trials. Implicit aberrant salience is defined as the absolute difference in reaction time to the task-irrelevant dimension. Explicit salience was derived from a Visual Analogue Scale (VAS). Adaptive explicit salience was calculated as a rating of high-probability relative to low-probability stimuli. Aberrant explicit salience was derived as the absolute difference in VAS rating between the two levels of the task-irrelevant dimensions. Higher values on the Adaptive scales reflect better performance, while higher values on the Aberrant scales reflect worse performance.

Table 13: Positive and Negative Symptoms

CAARMS	Term	VPT	Mann-Whitney U	<i>p</i>
Positive	.56	1.74	825	.029
Thought Content	.12	.70	937	.087
Perceptual Abnormalities	.14	.33	918	.022
Disorganised Speech	.30	.71	906	.110
Negative Symptoms	.93	1.96	4716	.020
Alogia	.07	.34	5022	.017
Avolition	.52	.99	4886.5	.040
Anhedonia	.33	.63	5103.5	.076

Salience Attribution Test: the four scales are presented

The very preterm participants displayed significantly higher positive and negative symptoms as described in Table 13. Upon further explorations of these scales, results showed that very preterm participants had significantly higher rates of perceptual abnormalities, alogia and avolition compared to controls. However, there were no group differences in thought content, disorganised speech and anhedonia.

Table 14: Associations between Salience and CAARMS

Spearman coefficients (p-values)	Adaptive Implicit	Aberrant Implicit	Adaptive Explicit	Aberrant Explicit
<i>Positive Symptoms</i>	.075(.56)	.136(.287)	-.155(.224)	.191(.133)
Thought Content	.092(.471)	-.004(.978)	-.062(.63)	.282 (.025)
Perceptual Abnormalities	-.023(.857)	.263(.038)	.087(.499)	.037(.774)
Disorganised Speech	-.059 (.647)	.216(.089)	-.304(.015)	.156(.221)
<i>Negative Symptoms</i>	.082(.523)	-.131(.307)	-.205(.107)	.133(.298)
Alogia	.247(.051)	-.172(.178)	-.05(.677)	.185(.146)
Avolition	-.007(.955)	-.068(.594)	-.249(.05)	.157(.22)
Anhedonia	.111(.386)	-.073(.571)	-.035(.786)	-.063(.625)

Spearman correlation analysis of salience processing and Positive and Negative Symptoms for the preterm group. Please see significant associations in bold. No statistically significant associations were detected in the control group.

In order to examine the relationship between salience attribution subscales and positive and negative symptoms, Spearman correlations were performed in the preterm and control group separately. There were no significant associations between any salience subscale and psychopathology in the control group. In the preterm group, as presented in Table 14, aberrant implicit salience was significantly associated with perceptual abnormalities, adaptive explicit with avolition and aberrant explicit with

thought content. A trend towards significance was detected in the association between adaptive implicit and alogia.

6.4 Discussion

This is the first study to explore salience processing in adults born very preterm. Preterm born participants performed worse than controls on adaptive explicit salience trials, which reflect a diminished capacity to learn correctly (“adaptive salience” refers to responding more quickly after predictive images rather than irrelevant ones). Similarly, they had increased negative and positive symptoms compared to full-term controls. Significant associations were found between salience processing and psychiatric symptomatology in the preterm group only and not in controls. Aberrant salience processing, which reflects assigning predictive meaning to irrelevant cues, was associated with positive symptoms: aberrant implicit salience with perceptual abnormalities, aberrant explicit salience with thought content. Adaptive salience processing was associated with negative symptoms: adaptive implicit salience with alogia, adaptive explicit salience with avolition. This indicates a specific pattern of associations between psychiatric symptomatology and salience, namely aberrant salience and positive symptoms, adaptive salience and negative symptoms, which is in line with the salience model of psychosis (Kapur, 2003; Smieskova et al., 2015).

Our results, showing worse performance on adaptive salience trials in preterm participants, are in line with findings in psychotic patients receiving antipsychotic medication (Roiser et al, 2009) and in individuals with an at-risk mental state (Smieskova et al, 2015). These results indicate that very preterm participants may not be able to distinguish between high- and low- probability stimuli features. Deficits in explicit salience processing also rely on several cognitive processes such as sustained attention, working memory, maintaining stimulus information, processing and decision

making (Roiser et al., 2009) which have been demonstrated to be worse in preterm individuals (Anderson & Doyle, 2004; Kroll et al., 2017).

One explanation for this finding may be that preterm individuals have worse decision making skills and acquired learning compared to their full-term counterparts (Strang-Karlsson et al., 2010) and this may extend to findings that preterm individuals are less likely to make 'risky' decisions compared to controls (Saigal et al., 2016). Estimating that a stimulus may offer a high reward involves taking a risk. Similar to findings in the schizophrenia literature, this finding may also be interpreted as a negative bias, whereas patients can identify punishment more than reward. Further work is required to evaluate whether a deficit in adaptive salience processing represents a cognitive impairment that may extend to the negative symptoms described or whether preterm individuals may behaviourally favour making 'low-risk' decisions.

Smieskova et al (2015) found that reduced adaptive salience was associated with the volume of the secondary somatosensory cortex, the insula and the prefrontal cortex; which are brain regions which have been implicated in cognitive psychotic-like experiences (Fuser-Poli et al, 2012). Alterations in these areas have previously been described in preterm populations (C. Nosarti et al., 2014b; Ullman et al., 2015; White et al., 2014) and are in line with Palaniappan & Liddle's (2013) conceptualisation of psychosis that proposes that the salience network and behavioural correlates play a central role in the development of psychotic symptoms (Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013).

Interestingly, there were no statistically significant group differences in aberrant salience, although it was associated with perceptual abnormalities in very preterm participants. Considering that very preterm individuals performed worse than controls on adaptive explicit salience trials, coupled with the evidence that they have increased perceptual abnormalities that are associated with aberrant salience performance, leads

me to speculate that very preterm individual may be a distinct subgroup of individuals experiencing negative/ cognitive –associated psychotic-like experiences (Demjaha et al., 2012).

The relationship between salience processing and dopamine release may also be altered in individuals with a psychiatric diagnosis compared to healthy controls. Bloomfield et al (2016) found that increased striatal dopamine capacity was associated with aberrant salience in individuals with cannabis-induced psychotic symptoms. However, in healthy controls there was a positive relationship between dopamine synthesis capacity and adaptive salience and a negative association between aberrant salience and striatal dopamine; similar findings have been reported by other groups (Boehme et al., 2015; Roiser et al., 2013). This is in contrast to findings examining patient or high-risk groups and to the salience hypothesis of schizophrenia. However, Roiser et al (2013) proposes that in healthy controls, high dopamine synthesis capacity may aid motivational salience since the dopamine baseline levels are relatively low. We demonstrated that striatal dopamine synthesis capacity was decreased in adults born very preterm who sustained perinatal brain injury (S. Froudish-Walsh, Bloomfield, M., Veronese, M., Kroll, J., Karolis, V., Jauhar, J., Bonoldi, I., McGuire, P.K., Kapur, S., Murray, R.M., Nosarti, C., Howes, O. , 2017). If higher dopamine synthesis capacity predicts increased adaptive salience then the results shown here may reflect the opposite effect. Decreased dopamine synthesis capacity can be associated with decreased adaptive reward prediction. In the near future I plan to examine the associations between dopamine synthesis capacity and salience processing in adults born very preterm.

6.4.1 Limitations

Impaired cognitive abilities may confound the ability to accurately complete the SAT, as this task demands a high cognitive workload for optimised performance. However, I

controlled for sustained attention when assessing group differences in salience processing. In addition, the fact that only some of the salience subscales were significantly different between the groups may indicate that the results presented are not secondary to other cognitive processes. Similar to other longitudinal studies, I had a high attrition rate, which is a common problem in longitudinal designs, with evidence that those individuals most vulnerable to neurodevelopmental sequelae do not return for follow-up (Wolke et al, 2009). Hence, the findings presented here may be an underestimation of the actual problems experienced by preterm adults. Despite this, I was able to demonstrate a significant association between premature birth and higher psychopathology and salience processing. Further cross-sectional studies are required to examine the magnitude of these findings and their clinical implications.

6.4.2 Conclusion

Although our very preterm participants did not display increased psychotic-like symptoms compared to controls, they showed a significant association between a known mediator of psychopathology, aberrant salience processing and positive symptoms, which is line with observations from clinical samples and individuals with an at risk mental state. I interpret these results as highlighting a possible mechanism underlying an increased psychiatric risk in very preterm individuals. Further research is required to ascertain the specificity of this risk and transition rates in very preterm populations.

Chapter 7: General Discussion

This thesis investigated the outcomes of adults who were born preterm. Its broad aim was to understand whether differences in cognitive and psychiatric outcomes could be detected in adults as has previously been described in preterm children and adolescence. This study also attempted to elucidate the characteristics of the cognitive and psychiatric profile of this population.

Hence, this thesis attempted to explore whether adults born preterm continue to demonstrate deficits similar to those described in childhood and to characterise the nature of these deficits.

In the following sections the main findings will be summarised in relation to the specific research question proposed:

1. *What is the course of IQ trajectories from childhood to adulthood in individuals born very preterm?*

The results of Chapter 3 confirmed that IQ trajectories in very preterm individuals remain stable between the ages of 8 until adulthood (age 31). However, my results highlighted the usefulness of examining IQ subtypes, as these appear to fluctuate over time. Only two other studies to date have examined IQ subtypes in preterm born children, hence these initial results warrant further investigation. Although Performance IQ appeared more vulnerable to the effects of preterm birth, Verbal IQ appeared more resilient. Similar to findings in other populations, SES and sex played an important role in intellectual outcomes. Although, preterm children with low SES were at a higher risk of worse IQ performance compared to preterm children with high SES, one also needs to consider that high SES may be a protective factor for cognitive development in children born preterm. These findings give rise to hope that environmental factors may be more easily mediated than neurological ones and

could result in protecting vulnerable individuals from biological risks by intervening appropriately (Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014).

2. *Will preterm born adults show a global or specific cognitive deficit? Do executive function abilities in adulthood impact social and occupational outcomes?*

In this cross-sectional study, presented in Chapter 4, EF abilities were compromised in adults born preterm in their fourth decade of life compared to the full-term controls. Similarly, adults born preterm also showed poorer real-life achievement and social functioning compared to controls. EF performance, independently of IQ, had a stronger association with real-life achievement variables in the preterm group. An important implication of this study is that efforts must focus on improving EF abilities in preterm populations. Recent studies have obtained encouraging results (Lohaugen et al., 2011). A hopeful conclusion from this study is that appropriate interventions aimed at younger preterm populations may one day also have effects on their achievement or social functioning.

Lastly, an important consideration that is easy to overlook is the differences between objective and subjective achievement measures. The interviewer-rated scales indicated that preterm adults had lower levels of social functioning and achievement compared to full-term controls, which is consistent with the current literature (Saigal et al., 2016). However, when participants were asked to self-rate their achievement and functioning, there were no significant between-group differences. Although this is consistent with previous reports that preterm individuals may rate themselves higher or 'better functioning' than people who are close to them do (Saigal et al., 1996), it may also serve as a protective factor.

In a sense, it can be argued that the subjective experience may be more powerful or important to the individual than the interview-rated one (Diener, 2012).

3. *Do very preterm adults present with elevated psychiatric symptomatology compared to controls? What symptoms characterise their profile?*

Preterm adults demonstrated increased psychiatric symptomatology compared to the control group. They were more likely to belong to a 'high-risk' group defined by symptoms above the 90th percentile of the control scores. The risk appeared non-specific as preterm adults fell into a general psychopathology profile. On the one hand, a non-specific psychiatric risk may be more difficult to address in terms of therapeutic interventions, and it could require a new aetiological framework for theory, research and clinical practice. The high association between IQ and psychiatric symptomatology may also shed light on the cognitive variance seen within a psychopathology profile. If preterm adults represent a group characterised by underlying cognitive symptoms it may be that cognitive interventions, especially in early childhood, could have a beneficial effect on symptom reduction in later life. Of course, further work is required to assess the validity of this argument, but similar work is now being conducted in clinical high-risk populations and in schizophrenia (Linke, Jankowski, Wichniak, Jarema, & Wykes, 2017).

4. *Does salience processing mediate psychiatric symptomatology in preterm born adults?*

Chapter 6 demonstrated that preterm adults performed worse than controls on adaptive explicit salience trials, which reflect a diminished capacity to learn correctly. A relationship between perceptual abnormalities and aberrant salience

processing (e.g., assigning predictive meaning to irrelevant cues) was also demonstrated in the preterm group. It is attractive to speculate that these findings lend support to notion that the preterm group's psychiatric symptomatology may be mediated by cognitive, and perhaps social factors, while this may not be the case in controls. It is important to emphasise the existence of psychiatric symptoms in the general population (van Os & Reininghaus, 2016; Verdoux & van Os, 2002) and that these are not necessarily mediated by salience but may involve other processes (Jensen et al., 2008), although further work is required to understand this. Considering the cognitive and social deficits that are widely described in the preterm literature, it is perhaps unsurprising that salience, which is a cognitive and social construct, may underlie the psychiatric outcomes previously described. Very few studies to date have explored the relationship between social, cognitive and psychiatric symptoms in preterm populations. Since several studies have now demonstrated an increased rate of mental disorders in preterm samples and I have previously shown that psychiatric symptoms exist at sub-clinical levels, the obvious next step to is to examine mediating factors. Salience processing may be an outcome in itself of a lifetime of altered cognitive abilities, coupled with social difficulties, which may result in attenuated symptomology that may be overlooked in diagnostic outcome studies. Hence, here I have only been able to open the dialogue between cognition and symptoms in preterm populations and I hope this will be the focus of future studies.

7.2 Limitations

Limitations of each study were presented in each chapter. Beyond study specific limitations there exist more general difficulties in studying survivors of preterm birth and in particular preterm adults.

Longitudinal studies: A major limitation of the studies presented here is attrition rate. Perhaps most worrying is evidence that those individual lost to follow-up are often those at greatest risk and worse psychosocial disadvantage (Saigal, 2000; Wolke et al., 2009). Despite this there were minimal statistical differences between the cohorts that were examined and those who did not attend.

Exclusion Criteria: A variety of exclusion criteria implemented by different studies could influence the generalisability of findings. This may include the exclusion of children with neonatal cranial ultrasound abnormalities or neurodevelopmental disabilities or with an IQ<70. Here I decided to include the whole sample because I was interested in providing a true reflection of the preterm profile. More consensus in research studies would help to generalise findings and their clinical implications.

Age of the sample: With improvements in perinatal medical care, increased survival rates of very preterm infants were observed in the past decades and this decreased mortality was mainly observed in the most immature, tiniest and sickest infants who are at higher risk for later adverse outcomes. Cautious interpretations are therefore needed when comparing outcomes of children born in the mid-2000 to the outcome of children born in the late 1970's, as it is likely that mid-2000 samples include a higher proportion of high-risk infants. However, the rate of cognitive and behavioural difficulties observed in older populations appears to be similar to those found in younger populations (P. Anderson & Doyle, 2003; Emsley, Wardle, Sims, Chiswick, & D'Souza, 1998).

7.2 Future Directions

There are several promising lines of future research:

1. A growing consensus regarding the appropriate methodology in examining preterm born participants may aid the creation of new innovative strategies for interventions. This includes more follow-up studies into adolescence and adulthood, increased consistency regarding the design and reporting of these studies, the use of validated measures and the inclusion of participants with disabilities in order to determine the precise nature and prevalence of specific outcomes associated with preterm birth. Considering these recent efforts, it is hopeful to think that these new strategies will help inform innovative and preventive interventions.
2. Cognitive remediation programmes: In terms of cognitive functioning, recent cognitive remediation programmes have obtained some promising results in preterm samples (Lohaugen et al., 2011; Spittle, Orton, Anderson, Boyd, & Doyle, 2012). These primarily focused on improving executive functions such as working memory or attention. If indeed we view the preterm profile as a multi-faceted system the hope is that improvements in one specific domain will have effects on the whole system. Despite efforts for early screening and interventions, prevention remains a major challenge. The findings presented here may be beneficial for future developments of preventive interventions.
3. Increased awareness of specific and general difficulties experienced by preterm born children may aid parents and teachers in the daily care of these children, in addition to providing information for clinicians. Poor awareness of the needs of preterm children have previously been described by teachers (Johnson, Gilmore, Gallimore, Jaekel, & Wolke, 2015), despite increased efforts to raise awareness to the wider community. Taking into account the robust evidence of the influence of

the home, parent and school environments on cognitive and emotional functioning, interventions may focus on strengthening parent/infant interactions. Initial results suggest that targeted interventions involving the family may have promising results on future developmental trajectories (Spittle, Orton, Anderson, Boyd, & Doyle, 2015; Spittle & Treyvaud, 2016). In addition, the need for researchers to collaborate with clinicians and with the wider public may increase the awareness of the preterm phenotype in the general population.

4. Medical advances in neuroimaging may be able to identify those at highest risk and intervene appropriately. Beyond identification of alterations, currently neuroscience-based treatments such as neurofeedback have provided some promising results in treating other populations (Ruiz et al., 2013) and may one day be adapted to meet the needs of preterm populations. Finally, the integration of multimodal imaging modalities and neuropsychological assessments may enhance our understanding of the neural correlates of the preterm phenotype.

7.3 Linking Cognitive, Social and Psychiatric Outcomes in Preterm Adults

This thesis sought to integrate disparate lines of research and characterise an adult cognitive and behavioural profile associated with very preterm birth, in line with descriptions of preterm phenotypes in childhood and adolescence (Johnson & Marlow, 2011). Despite evidence indicating a strong association between prematurity and risk of cognitive and behavioural problems that are described in previous work and in this thesis, only a few studies to date have attempted to integrate these domains. Exploring the cognitive and behavioural correlates of preterm birth and determining whether preterm born individuals are susceptible to a unique profile of risk factors is imperative for early interventions.

Here, it was shown that IQ deficits following very preterm birth are not only evident in adulthood but that the trajectory of IQ between childhood and adulthood remains stable, while it tends to increase in typically developing individuals (Salthouse, 2015). While an improvement in full-scale IQ over time was not demonstrated in this sample, IQ domains such as Verbal and Performance fluctuated over the considered time-frame and should be the focus of future studies. Consistent with previous findings, the present work showed that specific risk factors, such as lower gestational age and lower SES, may put certain individuals at a disproportionately higher risk of lower IQ.

This risk was quantified in Chapter 4 by comparing cognitive outcomes in preterm and full-term control participants. Results showed that preterm born adults had both lower IQ and executive function compared to full-term controls. Executive function independently of IQ was associated with lower educational attainment and worse adult social functioning. These findings supported the research hypotheses of the study and emphasised the importance of cognitive performance, namely executive function abilities, on a range of real-life outcomes.

Despite previous research linking emotional difficulties, social functioning and cognitive outcomes, this area of research has received little attention in the preterm literature. Hence, the study described in Chapter 5 sought to investigate whether adults born prematurely had increased psychiatric symptomatology compared to full-term controls, and whether IQ was significantly associated with psychiatric symptomatology. As summarised in the main text of this thesis, the majority of our knowledge regarding psychiatric outcomes in preterm adults stems from population-based studies (Nosarti, Reichenberg, et al., 2012), which demonstrated that preterm birth is associated with a range of psychiatric disorders. While such studies are informative, they do not allow us to describe the clinical profile of these individuals and examine whether they display a unique type of psychiatric symptomatology. Results of clustering analysis indicated that

preterm individuals had an increased risk of a range of psychiatric symptoms and particularly positive, negative and cognitive symptoms, which are regarded as reflecting psychotic-like experiences. These symptoms were significantly associated with IQ in the preterm group only, which is in line with findings from the at-risk mental state and schizophrenia population (Woodberry, Giuliano, & Seidman, 2008). To better understand this association, Chapter 6 focused on salience processing, a cognitive and social construct that has been proposed to underlie symptomatology (Kapur, 2004). Results showed that salience processing was significantly associated with both positive and negative symptoms in the preterm group only. This may indicate that the underlying mechanisms in preterm born individuals may differ from full-term controls. Specifically, there is evidence that aberrant salience processing is associated with alterations in striatal dopamine transmission and cognitive impairments (Roiser et al., 2013), which have also been described in preterm populations (Froudish-Walsh et al., 2017). Similar to other high-risk groups, the pathway to increased symptomatology in preterm adults may include a complex interplay of several factors that result in a state of aberrant salience processing and subsequent symptomatology.

The studies presented here support the hypothesis of a preterm behavioural phenotype that is characterised by a pattern of both cognitive and behavioural factors and their complex interactions. On the basis of the current findings it could be speculated that the widespread deficits in cognitive performance may lead to socio-emotional impairments in preterm samples (Johnson & Marlow, 2011). Simultaneously, cognitive impairments may also lead to chronic psychosocial stress and subsequently act as a risk factor for psychiatric disorders (Cannon et al., 1997). Individuals with atypical social and cognitive development, poor social competence and high levels of anxiety are at greater risk of developing psychiatric symptomatology in adulthood compared to those with typical functions (Cannon et al., 2000; van Os, Kenis, & Rutten, 2010). Although causality

cannot be determined, the interaction between adverse cognitive and social factors may manifest in higher rates psychiatric symptomatology (Ziv, Leiser, & Levine, 2011). Salience may bridge the gap between social and cognitive factors, as it can be considered a construct embedded within our social world and within our cognitive abilities and may underlie psychopathology symptoms (Roiser et al., 2009). It is also possible that psychiatric symptoms may precede cognitive functions and may be linked to abnormal dopaminergic transmission that is associated with perinatal brain injury (Froudish-Walsh et al., 2017). One conclusion to draw from reviewing the literature may be that the model required to conceptualise the preterm adult profile is complex and multi-factorial. We can identify this population as being at high-risk in several domains and respond with the limited resources we currently have, while an increased understanding of the relations between risk factors will enable us to inform new effective preventative interventions.

Searching for prognostic factors in preterm born individuals is a new focus of research (Linsell et al., 2016) and further studies are required to highlight interventional approaches and their effectiveness. While the results of this thesis are in line with previous studies (Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015) when explored collectively they have yet to be replicated in other preterm adult samples. Early identification of those at risk for cognitive and psychiatric disorders would facilitate intervention programmes which thus far have focused on cognitive factors such as working memory (Lohaugen et al., 2011), but that may have subsequent influence on socio-emotional difficulties as well.

Chapter 8: References

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Appendix A - Study Information

A.1. Ethics - Risk Checklist

Research Ethics – Risk Checklist

- Complete the checklist ticking yes to any of the sections relevant to your study.

Name:	Chiara Nosarti
Review Committee:	KCL - PNM RESC
Title of Study:	Structural and functional fronto-hippocampal maturation and neurodevelopmental outcome following very preterm birth in adulthood

		Yes	No
A	Does the study involve participants who are particularly vulnerable or unable to give informed consent or in a dependent position (e.g. vulnerable children, your own students, over-researched groups, people with learning difficulties, people with mental health problems, young offenders, people in care facilities, including prisons)? If you have ticked yes to this section, will financial incentives (other than expenses) be offered to participants? YES ☐ NO ☐ If yes, please state how much.	☐	x
B	Will participants be asked to take part in the study without their consent or knowledge at the time or will deception of any sort be involved (e.g. covert observation of people in non-public places)?	☐	x
C	Is there a risk that the highly sensitive nature of the research topic might lead to disclosures from the participant concerning their own involvement in illegal activities or other activities that represent a threat to themselves or others (e.g. sexual activity, drug use, or professional misconduct)?	☐	x
D	Could the study induce psychological stress or anxiety , or produce humiliation or cause harm or negative consequences beyond the risks encountered in normal life?	☐	x
E	Does the study involve imaging techniques such as MRI scans or ultrasound?	x	☐
F	Does the study involve sources of non-ionising radiation (e.g. lasers)? (see Appendix B)	☐	x
G	Does the study involve physically intrusive procedures? If yes, continue below and ensure you have also completed the Section B form:	☐	x ☐
i	Does the study involve only moderately intrusive procedures (<i>taking less than 40ml blood, collecting bodily waste, cheek swabs</i>)?	☐	☐
ii	Are substances to be administered (such as food substances) which are not classified as 'medicinal products' by the MHRA? (see Section B guidelines for more details)	☐	☐
iii	Are substances which are classified as ' medicinal products ' by the MHRA to be administered? (see Section B guidelines for more details)	☐	☐

iv	Does the study involve DNA or RNA analysis of any kind? (see Appendix D)	☐	☐
v	Are invasive, intrusive or potentially harmful procedures not already covered by items i, ii, iii & iv to be used in this study?	☐	☐



For office use only:

REC Protocol No

Date rec'd:

APPLICATION FOR ETHICAL APPROVAL

Please tick the Subcommittee or Panel you are applying to:

Research Ethics Subcommittees (RESCs)

PNM RESC ☒

(Psychiatry, Nursing & Midwifery)

SSHL RESC ☐

(Social Sciences, Humanities & Law)

(High Risk)

BDM RESC (Health) ☐

(Biomedical Sciences, Dentistry, Medicine
and Natural & Mathematical Sciences)

Research Ethics Panels (REPs)

For SSPP, Humanities and Law (non-high risk only)

E&M REP ☐

(Education & Management)

GSSHM REP ☐

(Geography, Social Science, Health &
Medicine)

Humanities REP ☐

War Studies Group REP ☐

Law REP ☐

(Law & Department
of Political Economy)

Notes for all applicants

- Please read the guidelines before filling out the application form and refer to the specific guidelines about each section when filling in the form.
(<http://www.kcl.ac.uk/innovation/research/support/ethics/applications/apply.aspx>)
- Refer to the Guidelines for the submission deadlines for your Subcommittee and the number of copies to submit (including electronic versions if applicable).
- All applications should be submitted **by 5pm on the deadline day**.
- All Subcommittee applications should be submitted to the Research Ethics Office, 5.11 Franklin Wilkins Building, (Waterloo Bridge Wing), Waterloo Campus, King's College London, Stamford Street, London SE1 9NH.
- All Research Ethics Panel applications should be submitted to SSPP Ethics Administrator, K0.58 Ground Floor Strand Building, King's College London, The Strand, London WC2R 2LS.

SECTION A – TO BE COMPLETED BY ALL APPLICANTS

1. APPLICANT DETAILS
1.1 RESEARCHER
Researcher's Name: Chiara Nosarti Researcher's Department & School: Department of Psychosis Studies, Institute of Psychiatry Status: ☐ Undergraduate ☐ Taught Postgraduate ☐ MPhil / PhD/ Specialist Doctorate ☒ Staff Research If Student: Name of course/qualification: If Staff: Researcher's Post: Senior Lecturer in Mental Health Studies and Neuroimaging
1.2 CONTACT DETAILS
Email: (Please use your KCL email address where possible) chiara.nosarti@kcl.ac.uk Telephone number: 0207 848 0133 Address: Department of Psychosis Studies, PO63, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF
1.3 SUPERVISOR - COMPLETE FOR ALL STUDENT PROJECTS (Including PhD)
Name of Supervisor: Supervisor's Post: Supervisor's Department (if different to student):

Supervisor's email address:

1.4 OTHER INVESTIGATORS, COLLABORATORS, ORGANISATIONS

List any other investigators/collaborators involved with the study, and ensure that their role (e.g. collaborator, gatekeeper) and responsibilities within the project are explained. You should include any draft/preliminary approach letters to gatekeeper organisations and confirm that you will have permission letters available for inspection if requested for audit purposes.

NB: For other investigators/collaborators clarify if their employer is not King's College London.

Dr Muriel Walshe, Lecturer, Department of Psychosis Studies, Institute of Psychiatry. Role: Advice on participants' recruitment for follow-up. Help with database administration.

Dr Matt Allin, Clinical Senior Lecturer, Department of Psychosis Studies, Institute of Psychiatry. Role: MRI analysis. Advice on integration of current data and those collected at previous time-points. Analysis.

Prof Robin Murray, Professor of Psychiatric Research, Department of Psychosis Studies, Institute of Psychiatry. Role: Supervision of overall study and advice on data integration and analysis.

Prof Seven Williams, Professor of Neuroimaging, Department of Neuroimaging Sciences, Institute of Psychiatry. Role: Supervision of neuroimaging component of the study and advice on data integration and analysis.

Three research workers to be recruited. Their names will be communicated as soon as they are in post.

2. PROJECT DETAILS

2.1 Project Title	Structural and functional fronto-hippocampal maturation and neurodevelopmental outcome following very preterm birth in adulthood
2.2 Projected Start Date of Project This should be when you intend to start work with participants.	1/10/2012
2.3 Expected Completion Date of Project Please note: Ethical approval must cover the duration of the study, up to the end of data collection. See the guidelines for further details.	30/9/2015
2.4 Sponsoring Organisation Your sponsor will be assumed to be King's College London unless stated otherwise. NB: Do not put 'N/A'.	KCL
2.5 Funder (e.g. self-funded, King's College London, ESRC, AHRB, EU)	MRC (ref: MR/K004867/1)

2.6 DOES THE STUDY INVOLVE HUMAN PARTICIPANTS OR FOR OTHER REASONS REQUIRE ETHICAL APPROVAL?

NB: It may be the case that research does not involve human participants yet raises other ethical issues with potential social or environmental implications. In this case you should still apply. Please consult with the Research Ethics Office (rec@kcl.ac.uk) if in doubt.

☒ **X Yes** ☐ **No**

2.7 OTHER INFORMATION RELATING TO RISK

Will the study place the researcher at any risk greater than that encountered in his/her daily life? (e.g. interviewing alone or in dangerous circumstances, or data collection outside the UK).

Yes ☐ **No** ☒ **X**

If applicable:

Does the study involve the using a Medical Device outside of the CE mark approved method of use? (see guidelines) If you are using a medical device 'off label' (outside of the approved method of use) then a risk assessment needs to be completed. For further information on medical devices see the Medicines and Healthcare Products Regulatory Agency web pages: <http://www.mhra.gov.uk/Publications/Regulatoryguidance/Devices/index.htm> and

<http://www.mhra.gov.uk/Publications/Regulatoryguidance/Devices/GuidanceontheECMedicalDevicesDirectives/index.htm>

Yes ☒ No ☐

If you have ticked yes to either of the above:

X Yes, and I have completed a risk assessment which has been co-signed by the Head of Department/ I have discussed the risks involved with my supervisor or Head of Department and agreed a strategy for minimising these risks.

2.8 OTHER PERMISSIONS, ETHICAL APPROVALS & CRIMINAL RECORDS BUREAU CLEARANCE REQUIRED

ANOTHER REVIEWING BODY/PERMISSIONS - Are any other approvals by another reviewing body (including other ethics committees, gatekeepers and peer review) required? If yes, give details and say when these will be obtained. In cases where ethical or legal permissions are required from local organisations or gatekeepers, it is the researchers responsibility to ensure that these have been obtained prior to commencing the study. If they have already been obtained you should provide a copy of the approval with the application otherwise you will need to supply it when ready.

YES ☐ NO ☒

CRIMINAL RECORDS BUREAU – If you think Criminal Records Bureau clearance might be necessary for your project, ensure you have contacted the Criminal Records Bureau directly to confirm whether or not this is the case. You will need to ensure you have the appropriate and necessary Criminal Records Bureau clearance for your study prior to commencing recruitment or data collection. You may wish to consult with the relevant 'gatekeeper' organisation in which you are undertaking the study with respect to this issue.

If Criminal Records Bureau clearance is required for your study, please confirm that clearance will be sought before commencement of the project. YES ☐ N/A ☒

2.9 Research involving human volunteers

Please consult the following page of the King's College London website to see if your study falls under the exclusion criteria with respect to the College's insurance arrangements:

(<http://kcl.ac.uk/about/structure/admin/finance/staff/insurance/trials.html>)

If your study **does** fall under these exclusions, confirm that prior to undertaking the study you will ensure you have gained confirmation from the Finance department that the study is covered by the College's insurers, as per the procedure outlined on the aforementioned web page: YES ☐ NO ☒ (the study does NOT fall under the exclusion criteria with respect to the College's insurance arrangements)

3. AIMS, OBJECTIVES & NATURE OF STUDY

Provide the academic/scientific justification of the study as well as detailing and explaining the principal research question, objectives and hypotheses to be tested.

Applications to the BDM and PNM RESC should include a full list of references/citations to back up the academic/scientific justification of the study. Note that sufficient information must be provided to allow the Committee to locate any sources to which you refer.

Scientific Justification:

Studies on the health and psychological well-being of individuals who were born very preterm beyond the age of 20 years are scarce and although the majority of preterm young adults conduct normal lives, they are less likely to graduate from university, are at increased risk of experiencing medical and social disabilities, a variety of cognitive deficits, and neurological abnormalities. We will now study for the first time longitudinal dynamic processes of brain development from mid-adolescence to adulthood using several different neuroimaging techniques to examine the structure, composition and function of frontal cortex and hippocampus / medial temporal lobe in unprecedented detail in relation to cognitive and behavioural outcome. The age of the cohort we propose to investigate, 28 to 33 years, is particularly

important for the study of psychiatric outcome, as it represents the peak period of onset for adult psychiatric disorders.

The main aim of this project is to further the understanding of the structural dynamic brain maturational patterns from mid-adolescence to adulthood following very preterm birth and to study how these patterns affect adult cognitive and behavioural function. Thus, the results of this project could aid the early detection of those individuals at risk of developing cognitive and behavioural problems and inform the delivery of appropriate targeted interventions aimed at alleviating such problems. Some of these cognitive training interventions in vulnerable children and adolescents have demonstrated to produce medium-to-large beneficial effects on outcome.

Primary Research Question:

Are there differences in the dynamic sequences of structural brain maturation from mid-adolescence (14-15 years) to adulthood (28-33 years) in frontal cortex and hippocampus / medial temporal lobe between individuals who were born very preterm and controls?

Secondary Research Questions:

Can we use dynamic sequences of brain maturation from mid-adolescence to adulthood in fronto-temporal cortices to predict cognitive and behavioural outcomes in adulthood? If so, do these associations differ between individuals who were born very preterm and controls?

Which specific structural brain maturational patterns are associated with neurodevelopmental risk and which ones are associated with neurodevelopmental resilience?

4. STUDY DESIGN/METHODOLOGY, DATA COLLECTION & ANALYSIS

Provide a brief outline of the step-by-step procedure of your proposed study in lay language, in no more than 1 page where possible. (For applications to the BDM and PNM RESCs it is strongly recommended that you provide the Committee with a flowchart diagram demonstrating step by step the process of the study. An example of a flow chart that can be used is in the Guidelines.)

Design: This is a longitudinal case-control study, and is a follow-up of individuals who have already been assessed (at age 15 and 19 years).

Participants: This study builds on a longitudinal study of brain development in term and preterm born individuals, in collaboration with the UCLH Department of Neonatal Paediatrics. Assessments of neurological, neuropsychological and behavioural functioning of VPT individuals were carried out at 1, 4, 8, 15 and 19 years. This wealth of data is a major strength of this cohort.

Very preterm (VP) group. We will now study **153 VP individuals** who have had MRI at age 14-15 years and who will be recruited from this larger sample, along with **89 term-born individuals (control group)** recruited from the longitudinal control group. The age range of participants will be 25 to 36 years. Contact has been maintained with the potential participants through a newsletter sent out by our group.

Clinical and neuropsychological measures

All participants will be assessed at the time of imaging using standardized and validated ratings scales, comprising the following instruments:

Socio-demographic information, occupational status, history of substance use and ethnicity of all participants will be recorded. A battery of standardized ratings scales will be administered.

The assessments we will use are:

1. **Psychiatric and Behavioural assessment:** Comprehensive Assessment of At Risk Mental State (CAARMS)^(Yung et al., 1998), which include assessment of attenuated psychotic symptoms, schizotypal personality disorder and family history of psychiatric disorder; General Health Questionnaire^(Goldberg et al., 1997), which measures current anxiety and depression, Lancashire Quality of Life Profile^(Huxley, Bridges, & Mohamad, 1996), and a measure of personal and social skills, the Vineland Adaptive Behavior Scales: second edition^(Sparrow, 2005).

Total duration of this battery: 1.5 hour

2. **Neuropsychological assessment:** Wechsler Adult Intelligence Scale^(Wechsler, 1998), which estimates intelligence quotient (IQ); Controlled Oral Word Association Test^(A. L. Benton & K. deS Hamsher, 1976), assessing verbal fluency; Hayling Sentence Completion Test^(Burgess & Shallice, 1997), assessing executive function; California Verbal Learning Test^(Eiwood, 1995) and Wechsler Memory Scale^(Wechsler, 1997) assessing various aspects of memory function and the Trail Making Test Part B^(Reitan & Wolfson, 1985).

measuring cognitive flexibility and control. We will further include three tests taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (CANTABeclipse version, 2003): Paired Associates Learning, Stockings of Cambridge, Intra-/extra-dimensional shift, assessing various aspects of executive function.

Total duration of this battery: 2 hour

References for these assessments are:

1. Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, et al. (1998): Prediction of psychosis. A step towards indicated prevention of schizophrenia. *BrJ Psychiatry Suppl.* 172:14-20.
2. Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, et al. (1997): The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med.* 27:191-197.
3. Oliver J, Huxley P, Bridges K, Mohamad H (1996): *Quality of life and mental health services*. London: Routledge.
4. Sparrow SSC, D.V.; Balla,D.A.; (2005): *Vineland Adaptive Behavior Scales, Second Edition. A measure of adaptive behavior from birth to adulthood*. Livonia, Michigan, USA: Pearson Assessments.
5. Wechsler D (1998): *The Wechsler Adult Intelligence Scale*. San Antonio, Texas: Psychological Corporation (Harcourt).
6. Benton AL, Hamsher Kd (1976): *Multilingual Aphasia Examination*. Iowa City: University of Iowa.
7. Burgess PW, Shallice T (1997): *The Hayling and Brixton Tests*. Bury St. Edmunds: Thames Valley Test Company.
8. Elwood RW (1995): The California Verbal Learning Test: psychometric characteristics and clinical application. *NeuropsycholRev.* 5:173-201.
9. Wechsler D (1997): *Wechsler Memory Scale - Third Edition*. San Antonio, TX: The Psychological Corporation.
10. Reitan RM, Wolfson D (1985): *The Halstead-Reitan neuropsychological test battery*. Tucson, AZ: Neuropsychology Press.

Neuroimaging data

We will use a combination of neuroimaging sequences acquired on a 1.5 and a 3.0 Tesla MR scanner (General Electric, Milwaukee WI, USA) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London. Total scanning time will be **up to 90 minutes** per person.

(1) **Diffusion Tensor MRI (DT-MRI)**: This allows white matter tract anatomy to reconstructed in detail. DT-MRI provides good information about the coherence and connectivity of white matter, but provides less information about its myelin content.

(2) **Driven equilibrium single pulse observation of T1 and T2 (DESPOT1 and DESPOT2)**: These sequences provide high-resolution 3D structural images with improved resolution of grey and white matter, and of deep grey matter structures. T1/T2 fast and slow relaxation times (multicomponent DESPOT) can also be used to identify microstructural characteristics of tissue – particularly the myelin fraction.

(3) High-resolution 3D **structural MRI (sMRI)** sequences will also be acquired, to assess brain structure in detail.

(4) **Functional MRI (fMRI)**: There will be three 'tasks': *a.* resting state functional connectivity MRI (fcMRI) during which participants will be asked to look at a fixation cross displayed in the middle of a computer screen. *b.* A memory task involving the explicit encoding and recognition of abstract pictures will also be completed, which engages the prefrontal cortex and the hippocampus. *c.* A working memory n-back task will be administered with three difficulty levels (1-back, 2-back, 3-back). In order to ensure successful on-line performance, participants will be asked to practice these tasks 'off-line', prior to scanning. In addition, all participants will have the opportunity to use a mock scanner in the Centre to familiarize with the scanner environment.

MRI analysis strategy: We will focus on two broad areas: i) longitudinal analyses of structural MRI and DT-MRI; and ii) cross-sectional analyses of structural and functional data acquired at the present time-point.

We will use a combination of whole-brain group mapping, region of interest and DT-MRI tractography approaches. The combination of tractography with myelination information from the DESPOT sequences will allow us to examine the anatomy and the composition white matter *in vivo* at a level of detail that has previously been impossible. Comparisons with previous longitudinal sMRI and DT-MRI will be performed.

Whole-brain analyses will be performed using Statistical Parametric Mapping (SPM version 8). Region-of-interest analyses will be determined using MultiTracer and Measure software. fMRI data will be analysed with FSL (www.fmrib.ox.ac.uk/fsl) and XBAM (www.brainmap.it).

Statistical analysis

Longitudinal MRI measures will be compared between groups using repeated-measures Analyses of Covariance, correcting for likely confounding variables (principally, age and socioeconomic status). Group differences at a single time-point will be compared using chi-square tests (for categorical information) and analyses of variance (for continuous variables). Voxel-wise linear regressions will be used to model the relationship between brain growth rates and outcome measures.

MEASURES TO BE USED – Confirm that any measures (such as tests/questionnaires) employed in the research study will be used in accordance with any copyright or licensing conditions that apply. **YES** X **NA** ☐

Further, confirm that the researcher administering these measures is qualified to do so (for example, in cases where only registered practitioners are able to administer such a measure). **YES** X **NA** ☐

5. PARTICIPANTS TO BE STUDIED

5.1 PROJECTED NUMBER OF PARTICIPANTS

Number: 153 very preterm-born individuals and 89 controls. **If applicable:** How many will be male and female. We plan to study 121 males and 121 females – the numbers may slightly change depending on participants' availability.

Justification for the sample size: Based on our experience at previous follow-up points, we conservatively estimate that approximately 70% of individuals who were assessed at age 15 years (218 preterm-born individuals and 127 controls) will take part in further follow-up.

Statistical Power: We performed a power calculation using G*Power 3.1 based on differences between preterm individuals and controls in corpus callosum growth between mid- and late adolescence. With the proposed sample size we will have 97% power (1- β error probability), $p=0.05$ (two-tailed), effect size $d=0.52$, to detect significant differences in regional brain changes between the two groups.

The lower age limit will be assumed to be 16 years of age unless specified otherwise. If an upper age limit is needed you must provide a justification.

All very preterm-born participants were born between 1979 and 1985. Control subjects will also be of this age.

Upper Age Limit: 36

Lower age limit: 25

5.2 SELECTION CRITERIA

This study builds on a longitudinal study of brain development in term and VP individuals, in collaboration with the UCLH Department of Neonatal Paediatrics. Assessments of neurological, neuropsychological and behavioural functioning of VP individuals were carried out at 1, 4, 8, 15 and 19 years. All participants will be over 25 years of age. Participants will be identified from the preterm research group database, at the Institute of Psychiatry. All very-preterm born participants for the proposed study ($n=153$) were assessed at age 15 years.

Eighty-nine age matched right-handed controls matched for sex and born in 1979-1985 will be also studied. Inclusion criteria will be full-term birth (38-42 weeks) and birth weight >2500 grams. Exclusion criteria will include any history of neurological conditions including meningitis, head injury and cerebral infections. Controls will be identified from our research group database. Controls will be a group of individuals who had been enrolled to act as controls for previous assessments made on the VP cohort described above. We will not contact any potential participant who has expressed the wish not to be contacted again when last assessed.

5.3 RECRUITMENT

Describe how participants will be (i) identified and (ii) approached.

(i) Participants will be identified from the preterm research group database, at the Institute of Psychiatry, as related above.

(ii) Individuals will be approached by letter or email [King's College Letterhead; King's College email address]. The text of this will ask potential participants to indicate whether they are willing to be contacted about the research study. An information sheet about the study will be included. Participants who are willing to be contacted about the study will be contacted by telephone, email or letter (according to their preference) to discuss the study further. All the potential participants will speak English as their first language.

5.4 LOCATION

State where the work will be carried out e.g. public place, in researcher's office, in private office at organisation.

The research will be carried out at the Institute of Psychiatry, at the Centre for Neuroimaging Sciences (scanners and assessment rooms) and at Denmark Hill Campus (main building – assessment rooms).

6. ETHICAL CONSIDERATIONS

6.1 INFORMED CONSENT

Describe the process you will use to ensure your participants are freely giving fully informed consent to participate. This will **always** include the provision of an information sheet and will normally require a consent form unless it is a purely self-completion questionnaire based study or there is a justification for not doing so (this must be clearly stated). Templates for these are at the end of this document and they should be filled in and modified where necessary.

Potential participants will be given written information and verbal information, and given an opportunity to discuss this with an investigator. The information sheet and consent form proposed are included with this application. It will be made clear that participants have the right to participate or not as they choose. They will be given time to consider this. Participants will be asked to sign a consent form indicating their agreement. Informed consent will be taken before the study commences, on the same day as the MRI scan and other assessments. It will be made clear that future access to clinical care in no way depends on participation, and that participation is entirely voluntary.

6.2 RIGHT OF WITHDRAWAL

(Participants should be able to withdraw from the research process at any time and also should be able to withdraw their data if it is identifiable as theirs and should be told when this will no longer be possible (e.g. once it has been included in the final report). Please describe the exact arrangements for withdrawal from participation and withdrawal of data depending on your study design).

All data collected will not be identifiable except by the study researchers.

6.3 RISK CHECKLIST

Where you have ticked '**Yes**' on the risk checklist, provide details of relevant qualifications and experience **with reference to those sections**. This **must** include the researcher and/or supervisor as well as other collaborators (if applicable) involved in those sections marked as presenting risk. (Do not submit a c.v.)

I have extensive experience working with MRI scans, and am familiar with the risks involved. The scans will be carried out at the Institute of Psychiatry, where the radiographers are expert and highly experienced in MRI, and in preparing participants to have a scan. All new researchers on the study will undertake the IoP training session on scanner safety before supervising participants in the scanner. The actual running of the scanner is the responsibility of the radiography staff and the MRI department, headed by Professor Steven Williams. The study will be conducted in strict accordance with professional codes of conduct.

You must also specifically address the ethical issues raised from those sections here.

(1) MRI scanning: This does not carry any risk of exposure to radiation. Ferromagnetic materials are strictly prohibited in the scanner, and could potentially cause injury if present. All participants will be asked to remove any metallic items from their person before scanning. They will be asked about the possibility of such material being in their body (a result of e.g.

surgery, or trauma). If such items are present, the participant will be excluded from the study. Furthermore, MRI scanners can evoke claustrophobia in persons who are susceptible to this. Participants will be asked about this possibility in advance. Female participants who are or may be pregnant will be excluded from the scanning part of the study. All participants will be in communication with radiography staff throughout the scan, and will be able to stop the scan at any time should they feel uncomfortable.

Individuals participating will already have had previous scans at 15 and some of them at 19 years of age. Adverse events are therefore unlikely. However, each participant will be asked about any medical procedures or operations they may have had in the intervening time, and about any circumstance where metal may have been introduced into their body. This would be a contraindication to MRI scanning.

(3) There is a potential for MRI to reveal previously unsuspected clinical findings which may be of significance. All MRIs are assessed by a clinical radiologist and suspicious findings will be reported to the participant's general practitioner.

(4) Likewise, there is a potential to discover abnormalities of brain structure which are "incidental" i.e. are not thought to be associated with any illness or impairment. There is a risk that individuals may suffer distress and worry when informed of such scan appearances. In this case, all the participants will have already been scanned at least once, so that "incidental" findings of this kind are likely to be already known. As stated above, all scans will be clinically assessed, and significant findings will be communicated to GPs.

NB:

If you ticked yes to point F of the checklist, you must also complete and submit the Appendix B form relating to use of radiation.

If you ticked yes to any point in G i - v of the checklist, you must also complete and submit the Section B application form.

6.4 OTHER ETHICAL ISSUES

Please consider whether there are other ethical issues you should be covering here. **Please note that all research projects have some ethical considerations, even if this only relates to how confidentiality will be maintained. DO NOT LEAVE THIS SECTION BLANK.**

Further, **if applicable**, please also add the professional code of conduct you intend to follow in your research.

<http://www.kcl.ac.uk/innovation/research/support/ethics/training/codes.aspx>

1. Recruitment of participants. The proposed study is a follow up of a longitudinal cohort of people born prematurely and a group of people who were born at term ("controls"). They last participated in this research programme at age 15 or 19 years. They are now in their mid twenties-early thirties. We propose to contact potential participants by letter inviting them to take part again. Ethical issues to consider here are those of contacting individuals at an interval of several years after their last assessment in the study. There is a slight risk of causing distress by doing this, but this seems unlikely to be severe. Participants who indicate that they no longer wish to be included will not be contacted further.

2. Potential burden of participation: (i) travel to the Institute of Psychiatry; (ii) possible need to take time off work. The majority of the proposed participants are residing in the London area, which means that travel should be relatively straightforward. We will reimburse travel expenses. To minimise disruption to participants' work/education we will offer assessment slots at the weekends as well as during the week.

3. Clinical interview: This has the potential to ask about subjects or events that may be uncomfortable to the participant and even (in extreme cases) to cause distress. This will be minimised by having a trained researcher conduct the interviews. If required, support and signposts to further professional help will be provided. It is not anticipated that this will occur commonly.

6.5 BENEFITS & RISKS

Please describe any expected benefits and risks to the research participant.

Potential Risks:

Cognitive and psychiatric assessment

Cognitive, psychiatric and socio-demographic information will be collected using standardized research instruments comprising structured interviews, symptom rating scales, questionnaires and computerized and 'pencil and paper' neuropsychological measures.

The psychiatric assessments will take about 1.5 hours. They will cover personal information concerning the volunteer's health. This raises issues about confidentiality (see below) and the possible effect of a clinical assessment on a volunteer. Clinical assessments may potentially be perceived as intrusive or distressing by subjects. As this is not a "clinical" sample, this risk is low. We will minimize the risk of distress in a number of ways. The assessments will be conducted by a trained assessor with experience in assessing people with mental illness. Subjects will be able to terminate the assessment at any point should they wish without giving a reason, and the assessor will be careful to ensure that he/she explains all aspects of the clinical assessment in advance. An experienced psychiatrist will be available to counsel any subject who is distressed by the clinical assessment, or wishes to discuss any issues raised further.

Individuals will also be asked to complete neuropsychological testing which will take around 2 hours. There is a risk of participants becoming fatigued, and to address this they will be offered frequent breaks. Similar cognitive assessments would have been completed by all participants during previous assessment visits, therefore we do not envisage any significant burden or risk.

Potential benefits:

- (1) This study has the potential to benefit people born very preterm by determining if trajectories of brain maturation are linked to the development of psychiatric illness and related cognitive and social impairments - with important implications for the development of targeted and preventive interventions which may reduce the risk of developing long term problems.
- (2) Individuals who take part in the research may have an interest in the outcome. We aim to keep participants informed through a newsletter which will communicate findings of interest in an accessible and comprehensible format.
- (3) People born very prematurely have at the moment no access to information or resources about what to expect, and what help they may need, as they grow and mature. This project is a small step towards providing that information.
- (4) People who may be suffering mental or physical distress might be benefited by the opportunity to discuss their problems with mental health professionals, and receive advice about appropriate resources.
- (5) Similarly, the appropriate authorities would be informed if it were discovered that any individual was under serious threat of abuse.

6.6 CRIMINAL OR OTHER DISCLOSURES REQUIRING ACTION

Is it possible that criminal or other disclosures requiring action (e.g. evidence of professional misconduct) could be made during this study?

YES ☐ NO ☒

If yes, detail what procedures will be put in place to deal with these issues. The Information Sheet should make it clear under which circumstances action may be taken by the researcher.

7 FINANCIAL INCENTIVES, EXPENSES AND COMPENSATION

7.1 Will travelling expenses be given? If yes, this should be stated on the Information Sheet

YES X NO ☐

7.2 Is any reward, apart from travelling expenses to be given to participants? If yes, please provide details and a justification for this. It is recommended that participants are informed of the compensation on the information sheet.

YES X NO ☐

On the basis of previous studies, participants will be paid £60 for the visit and £10 will be provided towards refreshments. This is to acknowledge the inconvenience involved in adult subjects (many of whom will be working) taking time out to participate. It will partly mitigate loss of participant income should they have to take time out of work. It is likely to increase the response rate of the study.

7.3 Is the study in collaboration with a pharmaceutical company or an equipment or medical device manufacturer? If yes, please give the name of the company and indicate what arrangements exist for compensating patients or healthy volunteers for adverse effects resulting from their participation in the study (in most cases, the Committee will only approve protocols if the pharmaceutical company involved confirms that it abides by APBI (The Association of the British Pharmaceutical Industry) guidelines. A copy of the indemnification form (Appendix C) should be submitted with the application.

YES ☐ NO ☒

7.4 No fault compensation scheme If your study is based in the UK you **must** offer the No-fault compensation scheme to participants unless there is a clear justification for not doing so (if this is the case this must be stated and you should bear in mind that the Sub-Committee reserves the right to make this a condition of approval).

YES, I am making the scheme available to participants ☒

NO, the study is based outside the UK and so the scheme is not applicable ☐

NO, the study is within the UK but the No-fault compensation scheme is not offered for the following reason:

8. DATA PROTECTION, CONFIDENTIALITY, AND DATA AND RECORDS MANAGEMENT

8.a. Confirm that all processing of personal information related to the study will be in full compliance with the Data Protection Act 1998 (DPA) including the Data Protection Principles).

If you are processing any personal information outside of the European Economic Area you **must** explain how compliance with the DPA will be ensured. See the following page of the Governance section of the website for guidance on the DPA: <http://www.kcl.ac.uk/aboutkings/governance/dataprotection/guidance.aspx>

YES ☒ NO ☐

8b. What steps will be taken to ensure the confidentiality of personal information? Give details of anonymisation procedures and of physical and technical security measures. Please note to make data truly anonymous **all information** that could potentially identify a participant needs to be removed in addition to names. **NB: Personal data held on mobile devices must be encrypted** : <http://www.kcl.ac.uk/college/policyzone/index.php?id=222>

Electronic transfer of data by magnetic or optical media, email or computer networks: no personal data will be transferred electronically except from the neuroimaging images which have an identifying unique number, known only to the researchers and the neuroradiographers (who assign it).

All data will be anonymised and the code kept securely in a separate locked filing cabinet. Access will be restricted to members of the research team. Personal identifiers will be removed from the database used by researchers.

Participants will be fully informed about the use of their personal information. The researchers will have proper regard to participants' expectations of confidence and privacy. Personal data will not be used freely for further research if this research is beyond the scope of participants' original consent. Data will be kept securely in a Microsoft Access database. This will be encrypted. Data will not be transferred outside the European Economic Area.

8c. Who will have access to personal information relating to this study? Confirm that any necessary wider disclosures of personal information (for instance to colleagues beyond the study team, translators, transcribers auditors etc) have been properly explained to study participants. Further guidance on the above issues can be found at the following link: <http://www.kcl.ac.uk/innovation/research/support/ethics/training/feedback.aspx>

The named investigators only. Data will be also accessible for the purposes of research governance i.e. audit.

8d. Data and records management responsibilities during the study. The 'Principal Investigator' is the named researcher for staff projects and the supervisor for student projects.

I confirm that the Principal Investigator will take full responsibility for ensuring appropriate storage and security for all study information including research data, consent forms and administrative records and that, where appropriate, the necessary arrangements will be made in order to process copyright material lawfully.

YES ☒ NO ☐

Further, provide a **specific location** at which research data will be stored **during** the study.

Pencil and paper assessments will be kept in securely locked cabinets located on the 5th floor, Department of Psychosis Studies, Institute of Psychiatry. Computerised/electronic data will be kept (password protected, anonymised and encrypted whenever possible) on computer at the Institute of Psychiatry.

8e. Data management responsibilities after the study.

State **how long** study information including research data, consent forms and administrative records will be retained, **what format(s)** the information will be kept in and **where** the data will be stored. For example, where

within King's College London? See the Information Management pages of the website for further guidance:
<http://www.kcl.ac.uk/library/info-management/index.aspx> and
<http://www.kcl.ac.uk/library/info-management/guidance/guide.aspx>

We propose to keep study information for 10 years. As this is a longitudinal study, current data will be used in predicting participants' outcome at further follow-up. They will be further used as outcome data to be studied in relation to data collected at previous time points. Hard copies of participants' assessments will be assigned an identifying number by the study researchers, and only members of the Preterm research team will be able to use personal identifiers. This will be necessary in order to link the data collected at current assessment with those collected since birth at various time points. Computerised/electronic data will be password protected, encrypted and anonymised.

Data will be stored within locked cabinets on the 5th floor, Department of Psychosis Studies, Institute of Psychiatry, and on password protected computers, accessible only by the study team.

NB: Any personally identifiable data that is held on any mobile device should be encrypted. This includes data stored on USB keys, laptop/netbooks, desktop computers, smart phones, workgroup servers and relevant emails.

In addition, confirm whether the storage arrangements comply with the Data Protection Act 1998 and the College guidelines.

YES ☒ NO ☐

Will data be archived for use by other researchers?

NO ☐

YES (in anonymised form) ☒ If you intend to share anonymised data with other researchers, you must make this clear on the information sheet. This is part of the MRI consent sheet, which we are enclosing.

YES (in identifiable form following the guidance below) ☐

Will any personal information related to this study be retained and shared in unanonymised form? If you tick yes you must ensure that these arrangements are detailed in the Information Sheet and that participant consent will be in place.

YES ☐ NO ☒

9. AUTHORISING SIGNATURES

9.1 RESEARCHER/APPLICANT

I undertake to abide by accepted ethical principles and appropriate code(s) of practice in carrying out this study. The information supplied above is to the best of my knowledge accurate. I have read the Application Guidelines and clearly understand my obligations and the rights of participants, particularly in so far as to obtaining valid consent. I understand that I must not commence research with human participants until I have received full approval from the ethics committee.

Signature Date.....23rd August 2012.....

9.2 SUPERVISOR AUTHORISATION FOR STUDENT PROJECTS (including PhD)

I confirm that I have read this application and will be acting as the student researcher's supervisor for this project. The proposal is viable and the student has appropriate skills to undertake the research. The Information Sheet and recruitment procedures for obtaining informed consent are appropriate and the ethical issues arising from the project have been addressed in the application. I understand that research with human participants must not commence without full approval from the ethics committee.

If applicable:

The student has read an appropriate professional code of ethical practice ☐

The student has completed a risk assessment form ☐

Name of Supervisor:

Signature

Date.....

9.3 MEDICAL SUPERVISION (if appropriate – see the Guidelines)

Name of Medical Supervisor:

Medical Supervisor's MDU/MPS (or other insurance provider) number:

.....

Signature of Medical Supervisor:

.....

Date.....

10. INFORMATION SHEET AND CONSENT FORM

Remember to submit your information sheets for participants and consent form (if necessary) with your application. Failure to do so will cause delays to your applications.

The information sheet for participants should be composed according to the guidelines. **The text in red should be deleted or modified as appropriate. If the language in the template is not suitable for your intended participant group it can be modified.** There is also a template consent form that can be used. Please refer to the guidelines for further information on how these documents should be used.

Submission Checklist	Tick box (where applicable)
Section A Application Form	X
Section B Application Form (where applicable)	
Information Sheet	X
Consent Form (where applicable)	X
Recruitment Documents (eg recruitment email, posters, flyers or advertisements)	X
Measures to be used (eg questionnaires, surveys, interview topic guides/schedules as appropriate)	References are provided in section A
Approach letters to 'gatekeeper' organisations (where applicable)	n/a
Evidence of any other approvals or permissions (where applicable)	n/a

A.3 Ethics - Approval

Dr Chiara Nosarti
Department of Psychosis Studies
Psychological Medicine and Psychiatry
PO63 Institute of Psychiatry
King's College London
De Crespigny Park
London SE5 8AF

19 October 2012

Dear Dr Nosarti

PNM/12/13-10 Structural and functional fronto-hippocampal maturation and neurodevelopmental outcome following very preterm birth in adulthood.

Review Outcome: Full Approval

Thank you for sending in the amendments/clarifications requested to the above project. I am pleased to inform you that these meet the requirements of the PNM RESC and therefore that full approval is now granted with the following provisos:

1. Information Sheet and Letter to participants: Please state the full name of the PNM RESC, at present you have missed out the words 'Research Ethics Subcommittee'. The sentence should read 'This study has been approved/reviewed by King's College London Psychiatry, Nursing and Midwifery Research Ethics Subcommittee'.
2. Information Sheet: At the end of the Sheet include your departmental address.
3. Consent Form:
 - I. Insert the KCL logo which can be found here:
<http://www.kcl.ac.uk/about/structure/admin/extrel/staff/depts/design/>
 - II. State 'All data so stored will comply with the provisions of the Data Protection Act 1998'. At present the year is missing.

Note that you do not need to submit a response to the above provisos, however it is a condition of the approval granted by the PNM RESC that the provisos are carried out prior to the study commencing. If the provisos are not adhered to, the approval granted by the PNM RESC would no longer be valid. Should you have any queries on this please do not hesitate to contact the Research Ethics Office.

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (<http://www.kcl.ac.uk/college/policyzone/index.php?id=247>).

For your information ethical approval is granted until **19 October 2015**. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the duration of the research study, up to the conclusion of the research. The conclusion of the research is defined as the final date or event detailed in the study description section of your approved application form (usually the end of data collection when all work with human participants will have been completed), not the completion of data analysis or publication of the results. For projects that only involve the further analysis of pre-existing data, approval must cover any period during which the researcher will be accessing or evaluating individual sensitive and/or un-anonymised records. Note that after the point at which ethical approval for your study is no longer required due to the study being complete (as per the above definitions), you will still need to ensure all research data/records management and storage procedures agreed to as part of your application are adhered to and carried out accordingly.

If you do not start the project within three months of this letter please contact the Research Ethics Office.

Should you wish to make a modification to the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications:

<http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx>

The circumstances where modification requests are required include the addition/removal of participant groups, additions/removal/changes to research methods, asking for additional data from participants, extensions to the ethical approval period. Any proposed modifications should only be carried out once full approval for the modification request has been granted.

Any unforeseen ethical problems arising during the course of the project should be reported to the approving committee/panel. In the event of an untoward event or an adverse reaction a full report must be made to the Chair of the approving committee/review panel within one week of the incident.

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance

(<http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx>). We wish you every success with this work.

With best wishes

Yours sincerely

Catherine Fieulleateau

Senior Research Ethics Officer

Appendix B - Participant Information

B.1. Participant Information Sheet & Consent Form

INFORMATION SHEET FOR PARTICIPANTS



Title: Brain development in adults born preterm

Introduction

We would like to invite you to participate in this original research project. This study has been reviewed by the Psychiatry, Nursing and Midwifery at King's College London (PNM 12/13-10). You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Background

The human brain grows and changes throughout our lives. This may allow us to adapt to changing circumstances as we grow up and face new challenges. At the moment, not much information is available on these important changes in adulthood. A crucial aspect of brain development is the relationship between the structure and function of specific regions of the brain.

Purpose of the study

The aim of the research is to investigate how the brain grows and changes as we enter adult life. We plan to compare how the brain grows and changes in adults. We will do this by comparing a new brain scan with scans that many of you had when you took part in this research study before (around age 15, or age 19 years). We will also use a new scans that will look at the structure and function of the brain in greater detail than was possible before. The benefits of this research will be in enhanced understanding of how the brain grows and changes to meet the demands of adult life, and how this may be altered by premature birth.

We are recruiting two groups of people: (1) people who were born prematurely at University College Hospital, London. This is an extension of the UCLH/King's College follow up study of premature birth, which you may have been involved in previously; (2) people who were born at "term", many of whom also took part in this study previously.

The research project

If you do decide to take part, you will be asked to come to the Institute of Psychiatry (De Crespigny Park, London, SE5 8AF). Transport can be arranged for you if that would be easier. We will refund your travel expenses.

There will be one visit, which will take around 6- hours. There are three parts to it:

(1) MRI scans

MRI (Magnetic Resonance Imaging) scans use a powerful magnet, so if you have metal in your body you may not be able to take part. Examples of this include: heart pacemaker; brain aneurysm clips; ear implants; eye injury involving metal fragments; operations leaving metal in the body (plates, joint replacements). If you are in any doubt about this, please speak to the researcher. The first MRI scan will

be very similar to the scan you had before. It will last up to a maximum of 1 hour and 30 minutes, during which you will need to lie still. For part of the scan, you will be asked to perform two memory tasks, which will be displayed to you on a computer screen. During one of the tasks you will be asked to remember a series of pictures, which you may later be asked to recall. During the second task you will be presented with a series of letters, and you will have to keep track of the order in which they appear.

(2) An interview with a researcher

One of the investigators will ask you some questions about your health and well-being. These will be in the form of two assisted questionnaires, asking about physical and mental health. This will take around 45 minutes

(3) Psychological testing

You will be asked to do some tests of your thinking and reasoning abilities. This will involve a test of general intelligence (known as IQ) and some tests of specific abilities – in particular, memory and verbal fluency. The IQ test is called the Wechsler Abbreviated Scale of Intelligence (WASI). In this test you will be asked to do 4 groups of tasks. Two of these are about language abilities, and take the form of word games (for example, describing the similarities in pairs of words). The other 2 tests are tests of non-language abilities. One involves guessing the next symbol in a sequence; the other involves making geometric shapes out of a collection of blocks. You will also be asked to complete some tests of rule-learning and memory on a touch screen computer. This set of tests are included in the Cambridge Neuropsychological Tests Automated Battery (CANTAB).

Risks

You are unlikely to be put at risk of harm by this study. MRI scans are safe, and do not involve radiation (unlike X-rays). Some people feel claustrophobic in the scanner. If you do feel distressed, please remember that you can ask to stop the scan at any time. MRI scanners use very powerful magnets to acquire their images and therefore some people, with certain metal implants, are not suitable for MRI scanning. This especially applies to people with cardiac pacemakers, electrical devices or pumps inserted in their body, those who have had surgery to their head or chest or abdomen (belly), or those who might have metal fragments in their eyes. MRI scans are also not routinely carried out on pregnant women.

MRI scans may discover problems that were unexpected. A limited assessment of the MRI scans will be performed by a neuroradiologist and identification of a major abnormality that requires action will be reported to the doctor you specify on your MRI consent form.

It is possible for difficult issues to be raised by the interview with the doctor. If this should happen, please feel free to discuss it, either at the time or at a later time that suits you. The lead researcher can be contacted using the details below.

Will your taking part in this study be kept confidential?

Yes. All information about you will be kept confidential. The information that you give will be anonymised and digitised and stored confidentially on computer memory at the Institute of Psychiatry in accordance with the Data Protection Act 1998. Only employees of King's College London who are working on this study will have access to it. MRI scans will also be stored in electronic form on the computer system at the Institute of Psychiatry. In both cases, information will be stored for 10 years, and you will be able to ask at any time to have your information removed from the record. Participants' anonymised data will be shared with other researchers working on related studies.

To take part in this study you will need to give your agreement (consent) in writing. It is up to you to decide whether to take part in this research project or not. If you decide to take part you are still free to

withdraw at any time and without giving a reason. You are also free to withdraw information that you have given from the study at any time, without giving a reason.

If this study has harmed you in any way you can contact King's College London using the details below for further advice and information:

Chiara Nosarti

Telephone: 0207 848 0133

email: chiara.nosarti@kcl.ac.uk

B.2 Participant Consent Form

Participant Consent Form:

Title of project:

Brain development in adults born preterm (PNM 12/13-10)

The participant should complete the whole of this sheet him or herself.

(please tick each statement if it applies to you)

I have read the Information Sheet.

☐

I have been given the opportunity to ask questions and discuss this study.

☐

I have received satisfactory answers to all my questions.

☐

I have received enough information about the study.

☐

I give permission for the researchers to view my medical records,
and I understand that the information will be kept confidential.

☐

I give permission for my doctor to be informed if any of the tests done
as part of the research are important for my health

☐

I understand that I will not benefit financially if the research leads to
the development of commercial products.

☐

I agree that data collected in this study is made available for future studies
approved by the ethics committee.

☐

I understand that data collected during my participation in this study
may be stored electronically on a research database. I understand such data
will be anonymised so that I cannot be identified on the database. All data so
stored will comply with the provisions of the Data Protection Act.

☐

The study has been explained to me by: Prof/Dr/Mr/Mrs/Ms _____

I understand that I am free to withdraw from the study at any time,
without having to give a reason for withdrawing and without affecting
my future medical care.

☐

I agree to take part in this study.

☐

Signed.....Date.....

(NAME IN BLOCK CAPITALS).....

Investigator's signature.....Date:

(NAME IN BLOCK CAPITALS).....

B.3 Advertisement for Control Volunteers

During the current assessment, approximately 87% answered an advertisement placed in the local press (see below) and agreed to take part in the current assessment. An additional 13% of control participants were recruited through a university circular e-mail describing the current study.

**Institute of
Psychiatry**

at The Maudsley

KING'S
College
LONDON
Founded 1829

University of London

Research Study Healthy Volunteers Needed

Are you aged between 28-35?

Do you want to participate in a study about preterm birth and brain function?

You will be reimbursed for your time and your travel expenses will be refunded.

For more information please contact us:

Email: jasmin.kroll@kcl.ac.uk

Appendix C - Study Population

C.1 Longitudinal Assessment Description

Recruitment at Birth

A prospective study was started in 1979 at University College Hospital London (UCHL) of all infants born before 33 weeks who entered the Neonatal Unit within 5 days of birth. Between 1979 and 1982, 223 infants survived to discharge and were enrolled in follow-up. Extensive simultaneous data were collected concerning the pregnancy, labour, delivery, and early neonatal period and a cranial ultrasound was performed repeatedly on all the infants from the first hours of life until they were discharged. Neonatal variables collected at birth included: birth weight, gestational age, social class and severity of perinatal brain injury, based on neonatal cranial ultrasound classification, summarized as a) normal, no-periventricular haemorrhage (no-PVH), b) uncomplicated periventricular haemorrhage without ventricular dilatation (PVH), and c) periventricular haemorrhage with ventricular dilatation (PVH+DIL) for exact classification details please refer to (Nosarti et al., 2011a). Further information obtained included mode of delivery, Apgar score, occipitofrontal head circumference at birth and discharge, time to spontaneous respiration, and endotracheal mechanical ventilation data.

In 1983, the capacity of the neonatal unit in UCHL increased. Between 1983 and 1984 332 infants survived to discharge and were enrolled in follow-up; 80 died before one year, and the remaining 252 were enrolled for long term follow-up. The total cohort of participants born between 1979 and 1984 known as the University College London Hospital cohort included 473 participants who were reassessed periodically

throughout their lives (Nam, Castellanos, Simmons, Froudish-Walsh, et al., 2015; Stewart et al., 1989a).

Childhood Assessments

In childhood, prospective assessments of the neurological and cognitive status of these children were conducted at ages 1, 4, and 8 (Roth et al., 1994; Stewart et al., 1989a; Vollmer et al., 2003). At age one and four, 455 participants were assessed using a range of neurodevelopmental and neurological assessments and a physical examination. At age eight, the neurodevelopmental assessment was expanded and included a wide range of tools such as an IQ assessment and behavioural questionnaires for the child's parents and teachers. In addition, physical, neurological and neuromotor assessments were conducted.

Adolescent Assessments

Age 14

In 1997, a protocol was developed for adolescent follow-up of the 1983-1984 birth cohort. Between 1997 and 2000, aged 14-16 years, cases and controls participated in neuropsychological, neurological and mental health assessments, and underwent structural brain imaging using MRI at the Institute of Psychiatry, London. Due to limited research resources, the Principal Investigator determined that it was not possible to include the entire consecutive series in follow-up at adolescence; a decision was made to include all individuals born at 28 completed weeks gestation or less (extremely preterm n=78), as well as an SPSS-generated random sample of 40% of those born between 29 weeks and 32 completed weeks of gestation (n=69/174). A normal gestation (38-42 weeks gestation) control group of 71 adolescents matched

for age, sex, SEC were recruited from the community through advertisements in the local and national press. Reasons for non-assessment include: 15 refusals, 12 lost to follow-up, 5 resident overseas, 2 unable to attend for medical reasons; 1 VPT-birth survivor had died.

Because of the selection bias towards lower gestational age, preterm-born adolescents who participated in the 14-16 year follow-up had lower gestational ages and significantly lower birthweight than the rest of the cohort. They were more likely to have had abnormal neonatal ultrasound status. They did not differ from the rest of the birth cohort in SEC, sex ratio, mode of delivery, condition at birth (Apgar 1 and 5), the need for mechanical ventilation, nor in neurodevelopmental status when assessed at 1 and 8 years of age. 128 matched full-term participants were recruited for the current assessment. For further details please refer to (Nosarti et al., 2008).

Age 18

At age 18, 158 very preterm participants were assessed and underwent a cognitive and psychiatric assessment (Walshe et al., 2008a). A matched control group (N = 90) were recruited and took part in the assessment battery. The assessment included a structural MRI scan and a range of neuropsychological assessments including intellectual functioning, memory, language processing and attentional abilities. Further details are provided in Figure C.1. In addition to cognitive measures, behavioural questionnaires were administered to assess psychiatric symptomatology and social functioning.

Age 23

Similar to previous assessments, at age 23, 64 preterm participants and 61 full-term controls took part in a follow-up assessment. This limited number of participants was due to the fact that this study formed the basis for a PhD conducted by a single student (Elena Giouroukou). Neuropsychological and psychiatric assessments were conducted. These included intellectual functioning, attentional abilities, personality and social functioning.

Figure C1 Assessment specific tests at each adolescent and adult follow-up. Includes neuropsychological, behavioural and MRI data.

Domain	Assessment	30 yrs	23 yrs	18 yrs	14 yrs
Neurological and neuromotor	Abnormal Involuntary Movement Scale				
	Edinburgh Handedness Inventory				
	Neurological Evaluation Scale				
	Beery Test of Visual-Motor Integration (VMI)				
	Nikokitjen Battery				
Psychiatric, Behavioural and	Premorbid Adjustment Scale (Cannon-Spoor et al 1982)				
	Social Adjustment Scale				
	Clinical Interview Schedule – Revised				
	Rutter Behavioural Scale (parent and teacher)				
	Child Behaviour Checklist				
	Youth Self-Report (Achenbach and Edelbrock 1981)				
	Comprehensive Assessment for At Risk Mental State (CAARMS)				
	Conners' Hyperkinesis Index				
	Moods and Feelings Questionnaire				
	Child and Adolescent Psychiatric Assessment (CAPA)				
	Peters Delusion Inventory				
	General Health Questionnaire (GHQ-12)				
Personality	Eysenck Personality Questionnaire (EPQ-RS)				
General Cognition	Wechsler Abbreviated Scale of Intelligence (WASI)				
	Wechsler Intelligence Scale for Children – Revised				
	National Adult Reading Test (NART)				
Executive Function	Controlled Oral Word Association Test (COWAT)				
	CANTAB (IED, PAL, SOC, MOT)				
	Hayling Sentence Completion Test				
	Test of Attentional Performance				
	Trail Making Test				
Language	Reading and spelling age				
	Spoonerisms Test				
Memory	California Verbal Learning Test				
	Logical memory subtest from the Wechsler Memory Scale				
	Rey-Osterrith Complex Figure Design				
Neuroimaging	Structural MRI (SPGR)				
	DT-MRI				
	mcDESPOT – myelin-sensitive				
	Verbal fluency				
	Response inhibition				
	Verbal paired associates				
	Visual paired associates				
	Resting state functional connectivity				

