Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Social and Educational Sciences
Department of Psychology

Ane-Kristine Øien Dyrvik

Cognitive Functioning, White Matter Pathways, and Preterm Very Low Birth Weight

Master's thesis in Psychology
Supervisor: Lars Morten Rimol
May 2022

NTNU
Norwegian University of
Science and Technology

Ane-Kristine Øien Dyrvik

Cognitive Functioning, White Matter Pathways, and Preterm Very Low Birth Weight

Master’s thesis in Psychology
Supervisor: Lars Morten Rimol
May 2022

Norwegian University of Science and Technology
Faculty of Social and Educational Sciences
Department of Psychology

NTNU
Norwegian University of
Science and Technology

Abstract

During the last trimester of gestation and early postnatal period, the brain develops rapidly. Brain weight grows by approximately 90% between 20-40 weeks of gestational age. Preterm birth (before completed 37 weeks of gestation) happens during this crucial time, exposing the neonate to harsh environments in a vulnerable state, possibly creating adverse consequences for the developing brain. The preterm VLBW brain has generally been found to differ from term-born peers. These changes result in both deviating cognitive and behavioral patterns throughout development. Resulting in a preterm "behavioral phenotype" described as being generally more anxious, inattentive, and more socially inept. The research question here is in two parts: 1. "Is there a group difference in white matter integrity of white matter pathways in VLBW adults compared with controls?" 2. "How is cognitive functioning affected by these possible white matter differences?". The data used in this thesis comes from three birthyear cohorts (1986-88) born preterm with VLBW (birth weight<1500g), and an age matched term-born control group. Cognitive measurements were gathered at 20 years of age, using the Wechsler Adult Intelligence Scale III (WAIS-III). dMRI were performed at approximately 26 years of age. The dMRI analysis and tractography was performed using the FreeSurfer 5.3.0 tool TRACULA. Demographic and clinical variables were examined using the statistical software program STATA 17. The right and left uncinate fasciculus and the forceps minor had statistically significant group differences in white matter integrity after Bonferroni correction. Furthermore, this thesis found that white matter integrity in the right uncinate fasciculus and forceps minor significantly affects cognitive functioning in VLBW adults. The VLBW group seems to be more dependent on white matter association tracts to solve cognitive tasks compared with controls. In the indices of the WAIS-III processing speed in the VLBW group were significantly affected by the right uncinate fasciculus and the forceps minor. Working memory was found to be affected by lower white matter integrity in the right uncinate fasciculus, while verbal comprehension was more affected by integrity in the forceps minor, in the VLBW group. The thesis supports the notion of preterm VLBW individuals' lower white matter integrity, and being slower to process and integrate information, and having poorer working memory functions, as well as lower general cognitive functioning.

Sammendrag

Hjernen utvikler seg raskt under siste trimesteret av svangerskapet. Hjernens vekt øker med omtrent 90% mellom uke 20-40 i gestasjonsalder. Under denne tiden starter også dannelsen av hvit substans, som fortsetter å utvikles betydelig i denne perioden. Preterm fødsel (før fullførte uke 37 av gestasjonsalder) skjer midt i denne viktige tiden, som utsetter den nyfødte for harde miljøer i en veldig sårbar periode, og dermed kan bidra til å skape flere konsekvenser for den utviklende hjernen. Hjernen til preterm fødte med veldig lav fødselsvekt (fødselsvekt<1500g) har generelt blitt funnet å divergere når de sammenlignes med term-fødte jevnaldrende. Disse forskjellene resulterer gjerne i både kognitive og atferdsmessige mønstre gjennom utviklingen. Dette mønsteret blir gjerne referert til som en preterm «atferds fenotype», beskrevet som mer angstfull/nervøs, uoppmerksom, og har større sosiale problemer sammenlignet med term-fødte kontroller. Forskningsspørsmålet her er delt i to: 1. «Er det en gruppeforskjell i integritet i hvitsubstans baner blant preterm fødte voksne sammenlignet med en kontroll gruppe?» 2. «Hvordan blir kognitiv fungering påvirket av disse mulige forskjellene i hvit substans?». Dataen brukt her er hentet fra tre fødselsårs kohorter (1986-88) som var født preterm med veldig lav fødselsvekt og en term-født kontrollgruppe på samme alder. Wechsler Adult Intelligence Scale III (WAIS-III) ble brukt for de kognitive dataene, samlet da kohortene var 20 år. dMRI målingene ble utført ved omtrent 26 års alder, analysene og traktografien ble gjort med FreeSurfer 5.3.0 verktøyet TRACULA. Demografiske og kliniske variabler, samt statistiske analyser ble undersøkt ved bruk av den statistiske programvaren STATA 17. Høyre og venstre uncinate fasciculus og forceps minor hadde statistisk signifikante gruppeforskjeller i hvit substans integritet etter en Bonferroni korreksjon. Videre ble det funnet at kognitiv fungering i preterm veldig lav fødselsvekt gruppen blir signifikant påvirket av hvit substans integritet i høyre uncinate fasciculus og forceps minor. Testgruppen virker til å være mer avhengig av hvit substans assosiasjons banene når de løser kognitive oppgaver sammenlignet med kontroll gruppen. I underkategoriene av WAIS-III så ble prosesseringshastighet i veldig lav fødselsvekt gruppa signifikant påvirket av høyre uncinate fasciculus og forceps minor. I samme gruppe så ble arbeidsminne påvirket av høyre uncinate fasciculus, mens verbal forståelse ble mer påvirket av forceps minor. Denne avhandlingen støtter tidligere funn om at preterm fødte med veldig lav fødselsvekt har lavere hvit substans integritet, og er tregere til å prosessere og integrere informasjon, samt at de har dårligere arbeidsminne evner, og generelt lavere kognitiv fungering som følge av dette.

Forord

Denne masteroppgaven har ble konseptualisert av en rekke tilfeldigheter som jeg er veldig takknemlig for at har skjedd. Med flere forsøk og en del frustrasjon for å velge tema og finne veileder, så var det ingen suksess. Da kom det plutselig en e-post om en veileder som kunne ta inn et par master studenter, og temaet var intet mindre enn nevrobiologi. Jeg vurderte lenge å ta en master i nevrovitenskap pga min lidenskap for nevrobiologisk forståelse av atferd og kognisjon. Dette var ganske perfekt, så svaret ble fort sendt og arbeidet startet. Min veileder, Lars Rimol, hadde mye data fra tidligere studier tilgjengelig, blant annet dMRI og traktografi av hvit substans baner, fra en gruppe med for tidlig fødte med veldig lav fødselsvekt og kontrollgruppen deres. I tillegg hadde han data på deres kognitive profil. Jeg hadde et stort ønske om å gjøre et «eget» studie, så etter litt frem og tilbake ble det til at jeg skulle utføre nye analyser på disse datamaterialene, og arbeidet kunne begynne. Dette har vært en lang prosess, som har vært krevende, spennende, frustrerende, og utrolig lærerik.

Denne oppgaven hadde aldri blitt ferdigstilt om det ikke var for en rekke nydelige mennesker. Først og fremst vil jeg takke Lars for all hjelp og veiledning, selv til siste minutt. Jeg vil også takke alle mine fantastiske venner, som har fått utallige snapper og hørt på lange triader der frustrasjon og fortvilelse har vært tydelig, men allikevel ALLTID er klare med oppmuntring og en fullstendig tro på at jeg klarer dette. Dere har vært helt uvurderlige. Til slutt kommer den største takken, og det er til min utrolige samboer, Lasse. Du har vært havnen i vindfulle hav, du har vært klippen i stormen, ly i regnet, solskinn i mørket, ja du forstår. Jeg setter utrolig stor pris på alt du har klart å stå i med meg dette året, fra latter, til tårer, til frustrasjon, og triader. At du ikke bare har støttet, men også grepet inn og hjulpet der det trengs, når det har buttet som mest. Og ikke minst at du ville bruke din lørdagskveld for å designe (og perfeksjonere) figurer til min oppgave, kun fordi det gir oppgaven en liten ekstra snert. Tusen takk!

Ane-Kristine Øien Dyrvik
Trondheim, Mai 2022

Table of Contents

List of Figures

List of Tables

Cognitive Functioning, White Matter Pathways, and Preterm Very Low Birth Weight

Children born before completing week 37 of gestational age are defined as being born preterm. Complications from preterm birth is one of the leading causes of death among children under 5 years of age. In 2019, 17.7% (940 000) of all reported deaths among children younger than 5 years across the globe were due to preterm birth complications (Perin et al., 2022). This number has decreased substantially from 2000 (1.339 million deaths due to prematurity), mainly due to better medications, more substantial treatments, as well as technological advances leading to improved equipment and understanding of the most common complications in premature birth leading to death (Back et al., 2007; Perin et al., 2022).

According to NHI (Norwegian Health Information) the incidence of premature birth in Norway has been stable at around 6% the last few years. In 2017, 3097 infants were registered as premature, which is 5.6% of all recorded births that year (Johannessen, 2022). Even though survival rates have improved and, because of better treatment, the prevalence of more severe brain injuries (i.e., intraventricular hemorrhages grades III and IV and cystic periventricular leukomalacia) has declined, there are still several neurological and cognitive long-term consequences that remain for this population (Back, 2014; Back et al., 2007).

During the last trimester of gestation and early postnatal period, the brain grows rapidly. A fetus is considered full-term at 39-40 weeks (Early term: 37-38 weeks, 6 days. Late term: 41-42 weeks. Post term: after 42 weeks). Brain weight grows by approximately 90% between 20-40 weeks of gestational age (Guihard-Costa & Larroche, 1990; Kinney, 2006). White matter development also starts, and progress substantially in this period, and continues to develop for several decades (Lebel & Deoni, 2018). White matter consists largely of myelinated axons in the brain and spinal cord, increasing the conduction velocity of electrical impulses, improving communication between different areas of the cortices. The myelin sheaths surrounding these axons are created and managed by glial cells. Glial cells are produced throughout life as myelination follows the development of cognitive networks, possibly in order to efficiently and correctly process, adapt, and respond to stimuli in the environment (Lebel & Deoni, 2018; Lebel et al., 2012). Being born during this crucial period of brain development (before week 37), increases the risks of disruption in myelination, synaptogenesis, and pruning, possibly leads to cortical maldevelopment (Rimol et al., 2019; Volpe, 2009).

The research literature generally shows that preterm VLBW is characterized by several cortical deviations. Including a general reduction of cortical surface area, with specific areas showing thinner or thicker cortices (Bjuland et al., 2013; Rimol et al., 2019; Sølsnes et al., 2015). Along with these cortical deviations, white matter integrity has also been found to be diminished in the preterm VLBW population (Collins et al., 2021; Eikenes et al., 2011; Loe et al., 2019; Rimol et al., 2019). Several of these areas, and the white matter tracts that connect them, are involved in cognitive functions, probably affecting cognitive and thereby also socioemotional development. Cortical morphometry and cognitive ability (in several forms) have been explored a fair amount in the research literature (Olsen et al., 2018; Sripada et al., 2018; Sølsnes et al., 2015; Zhang et al., 2015; Østgård et al., 2014).

However, literature on the possible connection between VLBW, white matter pathways, and cognitive functions is scarcer. In addition, often focus on specific abilities within cognition (i.e., processing speed, working memory, attention, etc; Loe et al., 2019; Murray et al., 2014), instead of a more general measurement of cognitive functioning. This thesis takes a broader approach by investigating white matter integrity in different tracts in VLBW and term-born controls. Additionally, it explores the correlation between white matter integrity and cognitive functions. In order to investigate these connections, one must first understand all of the components involved. In the following paragraphs a thorough description of research literature on cognitive development, white matter pathways, and findings regarding deviations in preterm VLBW will be given.

General Cognitive Functions and Development

General cognitive function is a broad term, this thesis utilizes the term mainly in reference to executive functions, problem-solving and processing speed. There has been much debate on the conceptual model of executive functions, however there is general consensus that executive functions comprise a “control system” consisting of several inter-related high-level cognitive skills and processes that regulate and execute goal-directed behavior (Anderson & Reidy, 2012; Best et al., 2011; Laureys et al., 2022). One of the more influential frameworks of executive functions, the “unity and diversity”-theory, was proposed by Miyake and colleagues (2000). This framework consists of three core factors; working memory, shifting, and inhibition (Miyake et al., 2000).

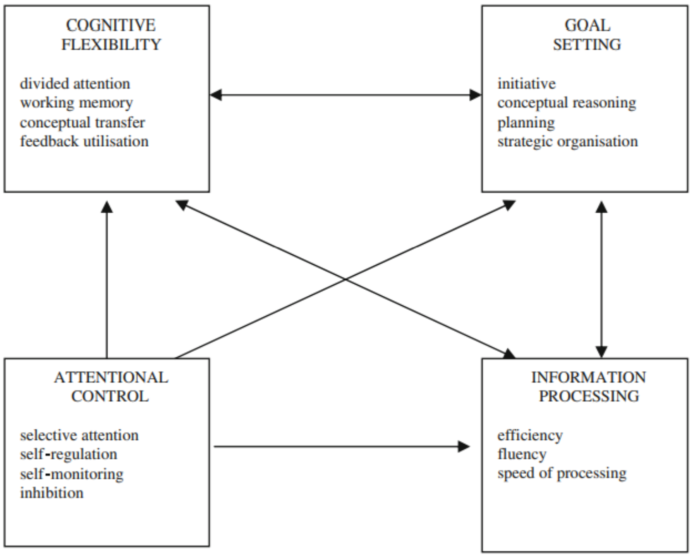
The working memory component mainly refers to the accuracy and effectiveness of updating and monitoring of relevant information and stimuli in order to successfully complete different tasks (Friedman & Miyake, 2017; Miyake et al., 2000). Shifting, the second factor, is the ability to switch between tasks, activities, and response and/or mental sets (Miyake et al., 2000). The third factor, inhibition, refers to the capacity to deliberately suppress prepotent responses. Meaning, a person's ability to stop/override dominant responses, showing intentional controlled inhibition as opposed to reactive or neural inhibition, which are autonomous (Laureys et al., 2022; Miyake et al., 2000). These three core factors have been found in several other studies as well, on both adults and teenagers, thereby giving support to this three-factor model of executive function (Friedman et al., 2016; Huizinga et al., 2006; Laureys et al., 2022; Theodoraki et al., 2020).

There are also more abstract cognitive skills that are generally considered to be executive. For example, planning is a generally accepted facet of executive function, defined as the ability to anticipate future events, conceptualize an endpoint/goal, and the steps necessary to reach that point/goal (Anderson & Reidy, 2012; Laureys et al., 2022). Although, some debate remains as to whether planning is a separate component of executive functioning or a part of working memory or inhibition (Laureys et al., 2022). Planning and several other more abstract abilities are not generally considered in models of executive functions. The executive control system, however, provides a conceptual model of several executive functions, dividing these abilities into four more abstract domains, giving a broader, and perhaps more thorough, view of "every day" executive functions (Anderson, 2008; Anderson & Reidy, 2012). Cognitive flexibility, goal setting, attentional control, and information processing are the domains in this framework (Anderson & Reidy, 2012).

According to Anderson and Reidy (2012), each of these four abstract executive functions encompass different executive abilities, including the three from the unity-diversity theory. Firstly, cognitive flexibility is comprised of working memory (as defined in unity-diversity theory), multitasking, switching between response sets, learning from mistakes and problem solve, as well as transitioning to new tasks (i.e., set shifting in unity-diversity). The second ability, goal setting, is conceptualized to contain abilities like planning, conceptual reasoning, and organization of information in order to complete goal-oriented behaviors. Information processing, the third domain in the executive control system, is comprised of processing speed, fluency, and efficiency in completing novel tasks. Lastly, attentional control is, as the name suggests, the abilities that influence attention, like inhibition, selective attention, self-regulation, and -monitoring. These four domains influence each other and cooperates to create functional behavior and responses to different cognitive tasks. According to Anderson (2008), these largely have a bidirectional effect, with the exception of attentional control. The attentional control domain influence alle the other factors in the model, however it is not necessarily affected in return, as pictured in Figure 1 (Anderson, 2008; Anderson & Reidy, 2012).

Figure 1

The Executive Control System (Anderson, 2008; Anderson & Reidy, 2012)



These cognitive abilities develop differently across the lifespan, most prominently during childhood and keeps developing throughout early adulthood (Huizinga et al., 2006; Theodoraki et al., 2020). In the general population cognitive development is fairly predictable, starting with a unified general executive function at around 7-12 years of age (Laureys et al., 2022; McKenna et al., 2017). After approximately age 12, studies find that the general trend is that this unified EF divides into three more specific skills, mainly inhibition, working memory, and planning (Laureys et al., 2022). Once late adolescence is reached (app. 17 years), a fully functioning EF system with all the abilities in place can be observed. However, the skills are not yet mature, and keeps improving into early adulthood (Albert & Steinberg, 2011; Burnett et al., 2013; Huizinga et al., 2006; Laureys et al., 2022; Miyake et al., 2000). The more abstract concepts of executive functions; planning, consequence thinking, and reasoning are some of the skills that keep developing into early adulthood (Albert & Steinberg, 2011; Burnett et al., 2013; Laureys et al., 2022). This is theorized to be a result of the abilities being dependent on neuronal development (both association, myelination, and specificity), as well as experience and practice (Anderson, 2008; Burnett et al., 2013; Laureys et al., 2022).

There are many different consequences when these cognitive abilities are diminished. This is mainly represented by behavioral or perceptual difficulties. Executive dysfunction, as it is often referred to, is frequently observable through behaviors such as impulsivity and difficulties inhibiting established behaviors, struggling with maintaining focus and attention, problems with transitions and switching between conflicting demands, as well as trouble with monitoring and regulating their own behavior and performance (Anderson & Reidy, 2012; Burnett et al., 2013). These problems often lead to poorer academic achievement, social and emotional problems, and is fairly common in diagnosis' pertaining to the central nervous system, such as attention deficit/hyperactivity disorder, autism spectrum disorder, and prematurity (Anderson & Reidy, 2012; Anniko et al., 2018; Franz et al., 2018).

Intelligence Quotient

Several different instruments and test batteries have been made to assess cognitive abilities across the lifespan. One aspect often utilized within this theme is the concept of intelligence, and thereby the measurement of intelligence quotient (IQ) in different variations. Intelligence can be defined as the general capacity to comprehend, adapt, and engage with complex abstract ideas, problems, and environments (Hearne et al., 2016). While IQ is the result of a test battery to measure general intelligence by implementing several different aspects of cognitive functions in differing tests. Often using subtests and composite scores to achieve a broader understanding of an individual or a groups' strengths and weaknesses within different cognitive domains (Hearne et al., 2016; Tulsky et al., 2003; Wasserman, 2018).

The results of such a test battery can then be used to create better and more effective interventions in regard to specific individuals or groups that traditionally struggle more in, for example, academic achievement. There has also been critique against the "misuse" of intelligence testing, sometimes resulting in wrongful categorization of the people scoring somewhat lower (or higher) as having fixed developmental or achievement trajectories (Wasserman, 2018). In other words, drawing wrongful conclusions based on tests that mainly maps the general cognitive functions of a person on a specific day, in a specific setting. However, it is still one of the more objective ways to compare groups on different aspects of cognitive functioning (when used right) and thereby implement interventions that will strengthen an individual's abilities instead of hindering them with prejudices (Løhaugen et al., 2010; Tulsky et al., 2003; Wasserman, 2018).

One such test battery is the Weschler Adult Intelligence Scale-III (WAIS-III; Tulsky et al., 2003). This is a rather comprehensive cognitive assessment that result in full-scale IQ scores gathered from 11 subtests and is considered a representative measurement of global intellectual functioning (Løhaugen et al., 2010). These subtests divide into four indices, verbal comprehension, working memory, perceptual organization, and processing speed. Each assesses specified domains of cognitive functions. As mentioned previously, working memory is key to updating and monitoring relevant information to solve tasks, and processing speed measures the speed and accuracy in different tasks. While perceptual organization is a measurement of an individual's understanding of visual information and problem-solving. Lastly, verbal comprehension is the ability to comprehend, use, and think with spoken language (as opposed to written). This index also examines the knowledge acquired from the environment (Tulsky et al., 2003). All of these cognitive abilities rely to some degree on white matter, in order to respond more efficiently and accurately on complex tasks.

White Matter Tracts

White matter tracts are classified in 3 different categories: projection fibers, association fibers, and commissural fibers. Projection fibers are white matter tracts that connect the cortex to other parts of the central nervous system (i.e., brain stem, deep brain nuclei, cerebellum, and spinal cord; Crossman & Neary, 2015; Wycoco et al., 2013).

Commissural fibers are the main communication pathways between the cerebral hemispheres, connecting similar cortical areas on both sides. The two main commissural tracts are the corpus callosum and the anterior commissure (Crossman & Neary, 2015). The corpus callosum is divided into several parts, connecting different areas of the cortices. Through the anterior part of the CC (genu) the white matter tract forceps minor connects the right and left frontal lobes. The splenium of the CC (posterior) contains the white matter fibers of the forceps major, connecting the occipital lobes (Lebel et al., 2012).

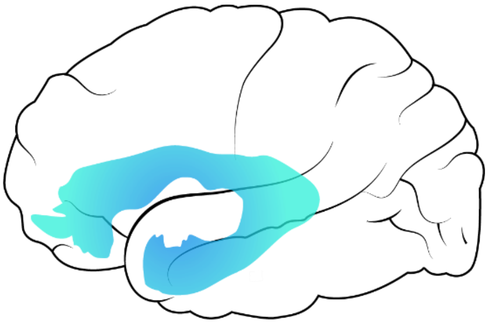
Association fibers, the white matter tracts that connect different regions within the same hemisphere, can be long or short. The long-range association tracts include the cingulum, superior and inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UNC), superior and inferior longitudinal fasciculus (SLF, ILF), as well as the arcuate fasciculus (AF) among others (Wycoco et al., 2013). The white matter tracts have several functions in the hemispheres; efficiency, synchronization, continuous updating, and communication between regions across the brain (Crossman & Neary, 2015; Lebel & Deoni, 2018). Most of these tracts have received attention in research, albeit some more than others, which has resulted in a general understanding of their respective functions.

Uncinate Fasciculus

It seems that the uncinate fasciculus either has very abstract functions, and is therefore difficult to measure neuroanatomically, or that the right measures, technological techniques, and research questions needed, have not yet been tested. However, there have been several studies regarding both the macrostructure and the microstructure of the UNC, attempting to understand the functions of this white matter pathway. In order to understand the possible functions of this white matter tract, one must first understand the neurobiology of both the tract itself and the areas it connects.

Figure 2.0

Visual Depiction of Uncinate Fasciculus



Macrostructure and Connected Regions. The uncinate fasciculus is one of the long-range white matter tracts in the human brain (Von Der Heide et al., 2013). The tract has a distinctive hook shape, that extends from the anterior temporal lobes, arcing around the sylvian fissure, and ends in the lateral orbitofrontal cortex (Hau et al., 2016; Kierońska et al., 2020; Olson et al., 2015; Von Der Heide et al., 2013). Diffusion tensor imaging (DTI) studies have shown that the temporal segment of the uncinate fasciculus is connected to the uncus, entorhinal cortex, perirhinal cortex, the temporal pole, and basolateral amygdala (Bhatia et al., 2017; Ebeling & Cramon, 1992; Ghashghaei et al., 2007; Von Der Heide et al., 2013).

The uncus (Brodmann area [BA] 35), is part of the olfactory cortex, and is simultaneously involved in emotions and formation of new memories, mainly due to its connectivity and location within the parahippocampal gyrus (Amina, 2014; Von Der Heide et al., 2013). The entorhinal cortex is one of the major areas for in- and output from the hippocampus, meaning it has a major role in long-term memory formation (Canto et al., 2008; Von Der Heide et al., 2013). It is also involved in higher-order association, as it has both unique firing patterns, intrinsic organization, and connectivity (See Canto et al., 2008). The perirhinal cortex is mainly involved in high level object perception and memory (Murray et al., 2005). Specifically, it has been found to give a mental representation of an object through the conjunction of its features, thereby creating the possibility of discriminating highly similar objects. Making it possible for humans to, among other things, discern faces from each other, this including very similar faces (i.e., monozygotic twins; Murray et al., 2005).

The temporal pole is considered a cortical convergence zone, in other words, it is a highly complex structure, and its functions reflect that notion (Olson et al., 2007). This complexity ensures that the temporal pole is able to receive and interpret information from different sensory modalities (Herlin et al., 2021). The temporal pole is therefore involved in visual processing and recognition of objects and faces (as well as naming and word-object labelling), autobiographic memory, semantic processing, as well as socio-emotional processing (Herlin et al., 2021; Pascual et al., 2015). It seems that the temporal pole works to bind high-level cognitive processes and perceptual inputs to emotional responses (Herlin et al., 2021; Olson et al., 2007). This is also reflected in the greater anterior temporal lobe (where the temporal pole lies within). Portions of the anterior temporal lobe is believed to be highly involved in social cognition, mainly social knowledge. Social knowledge is the semantic memory of other people (their names and lives), and memory of abstract social concepts, for example traits and/or norms (Olson et al., 2013).

The basolateral amygdala is the last part the temporal stem of the uncinate fasciculus connects (Bhatia et al., 2018). The basolateral amygdala is mainly associated with emotional arousal (Yang & Wang, 2017). It is considered one of the most important areas for fear conditioning and associative learning (Pelletier et al., 2005). The basolateral amygdala has many implications for learning and social interactions, it has been found to encode behavioral output, making it crucial to reward-seeking behaviors (Yang & Wang, 2017). And the inhibition of the basolateral amygdala, as well as the volume of the amygdala in general, has been found to mediate a person’s social life and behavior (Bickart et al., 2011; Wellman et al., 2016). Pelletier and colleagues (2005) also gave further support to the notion that emotional arousal facilitates consolidation of memories, through higher activation in the basolateral amygdala.

On the other end of the UNC the frontal extension splits into two, perhaps three, branches (Bhatia et al., 2018; Von Der Heide et al., 2013). One branch terminates approximately in the lateral orbitofrontal cortex, while another extends into the frontal pole, and the third one to the subgenual cingulate gyrus (Bhatia et al., 2017; Von Der Heide et al., 2013).

The lateral orbitofrontal cortex is mainly associated with processing possible outcomes, making it essential for adaptation and survival (Kringelbach & Rolls, 2004). This monitoring and evaluation of various outcomes directly influence behaviors, either by aversion or approach responses (Kringelbach & Rolls, 2004; Olson et al., 2015; Von Der Heide et al., 2013). The second part of the frontal branch of the uncinate fasciculus leads to the frontal pole. This area has been found to be highly involved in cognitive flexibility, working memory, perception, and a part of affective processing and social cognition (Bludau et al., 2014; Koechlin, 2011). The last and most speculative part of the frontal stem connects to the subgenual cingulate gyrus (Bhatia et al., 2018). The subgenual cingulate gyrus is most commonly associated with mood regulation and the pathophysiology of depression (Bhatia et al., 2018; Riva-Posse et al., 2014).

Microstructure. As for the microstructure of the UNC, fractional anisotropy (FA) is one of the more common measurements (Giorgio et al., 2010; Lebel et al., 2012; Olson et al., 2015). FA is believed to represent density of the fiber tracts, myelination, and white matter organization, meaning an indicator of the overall integrity of the tract (Kochunov et al., 2010; Olson et al., 2015). The uncinate fasciculus is the latest white matter association tract to develop properly, not reaching peak maturation until approximately 28-35 years of age, then starting to decrease at a slower rate (Goddings et al., 2021; Lebel et al., 2012). Mean diffusivity (MD), axial and radial diffusivity show similar reversed developmental patterns in the UNC (i.e., decreasing to a minimum level of diffusivity at about 30-40 years, then increasing at a slower rate; Lebel et al., 2012). MD is used to measure the rotationally invariant amount of water diffusion in a given area of the brain as a measurement of the structural integrity in that area (Assaf & Cohen, 2013). While the axial and radial diffusivity measures are used to get a more specific view of the fiber characteristics, such as axonal status and myelin changes respectively (Kumar et al., 2012; Lebel et al., 2012). In other words, increases in diffusivity (Axial, radial, and/or mean) is indicative of reduced axonal density, loss of myelin integrity, and/or an overall increase in cerebral spinal fluid.

Functional Tasks. According to Von der Heide and colleagues (2013), it is believed that white matter tracts and the cortical regions they connect have a determining influence on each other. Meaning that the nature of information shared through the white matter tracts can be predicted by the functions of the cortical regions it connects. Simultaneously, the function of a given cortical region is determined by its intrinsic properties as well as extrinsic white matter input and output (Passingham et al., 2002; Von Der Heide et al., 2013). Studies have shown that this applies somewhat to the uncinate fasciculus as well (Olson et al., 2015). According to the literature on the functional tasks of the UNC, they can roughly be divided into three main categories; associative and episodic memory functions, linguistic functions, and socio-emotional functions (Von der Heide et al., 2013).

Associative Memory Functions. Associative and episodic memory functions of the UNC have been found to be fairly specific. The UNC does not appear to be of vital importance in general episodic memory formation and consolidation (McCauley et al., 2011).

However, it is involved in specific functions of reversal learning, which refers to a set of paradigms designed to assess cognitive flexibility by examining adaptive responses to changes in stimulus- or response-outcome contingencies (Izquierdo et al., 2016; Olson et al., 2015; Thomas et al., 2015; Von Der Heide et al., 2013). The UNC has also been found to be highly involved in reward and/or punishment associations of behavior (Von Der Heide et al., 2013), thereby also associations motivating different behaviors (Olson et al., 2015). And lastly, the UNC is also important for updating stored representations based on values, grounded in the fact that this white matter tract is a bidirectional pathway, which indicates a continuous updating mechanism of semantic and/or social information based on new reward/punishment associations and experiences (Von Der Heide et al., 2013).

Linguistic Functions. The second function of the uncinate fasciculus, as reviewed by Von der Heide and colleagues (2013), is the specific linguistic implication it seems to have. This function is closely related to semantic memory/knowledge, specifically the lexical retrieval of semantic knowledge. This refers mainly to the ability of naming places, objects, and other people. The UNC is only essential for proper nouns (i.e., names of people, places, and specific objects), meaning that there are no long-term deficits in remembering words in general after removal or damage to the UNC. Simultaneously, there are significant deficits in proper naming in the same studies, supporting a specific linguistic function of the UNC (Olson et al., 2015; Papagno et al., 2011; Von Der Heide et al., 2013).

Socio-Emotional Functions. According to Von der Heide and colleagues (2013), the literature on different social and emotional aspects of the uncinate fasciculus, and the areas it connects, reflects an important yet underspecified role in socio-emotional processing. Emotional pattern separation (i.e., mnemonic discrimination of emotional experiences) is negatively correlated with reduced integrity of the UNC, resulting in poorer memory performance through higher activation in the sub-hippocampal regions (Granger et al., 2021).

Indicating that the UNC allows the orbitofrontal cortex to mitigate this emotional memory network, thereby improving emotional pattern separation (Granger et al., 2021; Von Der Heide et al., 2013). Granger and colleagues (2021), suggests that lower UNC integrity leads to overgeneralization of the stimuli, as the sub-hippocampal region CA3 is implicated in pattern completion. Emotional pattern separation would also entail evaluation of emotional salience both regarding people and situations (emotional tone and significance), social reward processing, value assignment and updating, and parts of emotional control (for full review see: Von der Heide et al., 2013; Olson et al., 2015).

Superior Longitudinal Fasciculus

The white matter tract superior longitudinal fasciculus (SLF) extends across a large area in the human brain, with connections in prefrontal, temporal, occipital, and parietal cortices (Urger et al., 2015; Wang et al., 2015). SLF consists of long bidirectional projections and is commonly divided into four subsets of fibers; SLF-I, SLF-II, SLF-III, and arcuate fasciculus (Schurr et al., 2020; Wang et al., 2015). There is disagreement in the research literature whether the SLF-I is a subcomponent of the SLF, part of the cingulum, or a distinct white matter tract in and of itself in the human brain (for full review see: Komaitis et al., 2020; Wang et al., 2015). SLF-I mainly connects the superior parietal lobule (aspects of attention and visuospatial perception) and precuneus (relations to the self, memory, and navigation) with the dorsal premotor cortex and supplementary motor area complex (Komaitis et al., 2020). Thereby, providing more efficient communication between these areas, making the integration of sensory information, both in the environment and of the self, and planning for movement more efficient. Possibly leading to better visuospatial attention and complex motor behavior.

There is more consensus in the findings regarding the SLF-II and -III subcomponents of the SLF. The SLF-II is the middle part of the SLF, and it connects the angular gyrus (anterolateral parietal lobe; integration of multisensory input), with the posterior parts of the middle frontal gyrus (reading and attention) and precentral gyrus (primary motor cortex) (Wang et al., 2015). The SLF-II therefore seems to further facilitate the integration of sensory stimuli with movement (i.e., complex motor behavior). Language and motor behavior functions are also reflected in the topography of the SLF-III.

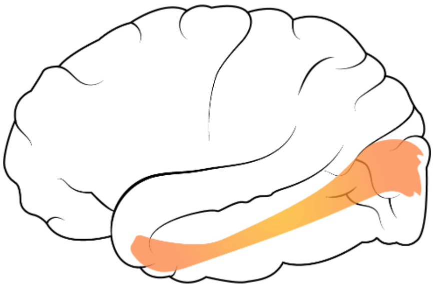
The third branch of the SLF consists of neuronal fibers from the intraparietal sulcus (sensorimotor functions) and supramarginal gyrus (directly anterior to the angular gyrus in the parietal lobe; phonological processing and empathy) to the inferior frontal gyrus (Language comprehension and production; Schurr et al., 2020; Wang et al., 2015). The arcuate fasciculus (AF) is generally considered to be a subdivision of the SLF, but there are some disagreement in the literature regarding this as well (Schurr et al., 2020). The AF resembles the SLF-III, stretching from the temporoparietal junction (attention, social processing, and language) to dorsolateral prefrontal cortex (general executive functions; Kamali et al., 2013; Urger et al., 2015). Intelligence and social language comprehension has been found to correlate with the arcuate fasciculus (Hertrich et al., 2021; Schurr et al., 2020; Wang et al., 2015).

Overall, it seems like the superior longitudinal fasciculus contributes to several cognitive functions, however the most protruding being visuospatial functions and complex motor behavior, including language processing and production (Schurr et al., 2020; Urger et al., 2015). In the left hemisphere the left arcuate fasciculus and SLF as a whole is thought to be involved in verbal working memory, expressive speech, and naming, while the right hemisphere is associated more with nonverbal-auditory information, attention, and visuo-spatial functions (Urger et al., 2015).

Inferior Longitudinal Fasciculus

Figure 2.1

Visual Depiction of Inferior Longitudinal Fasciculus



The inferior longitudinal fasciculus (ILF) is one of the white matter long-range association tracts in the human brain. It has been found to mainly connect the occipital lobe with the anterior temporal lobe (Herbet et al., 2018). The ILF has four distinct branches, the first connect the fusiform gyrus (word and face recognition) with the anterior temporal pole (processing, memory, learning). The second branch connects the anterior temporal regions with the superior, middle, and inferior occipital gyri (visual input). Third, is a lingual branch, connecting anterior middle temporal gyrus with the lingual gyrus. Lastly, there is a minor branch connecting the anterior medial temporal gyri and the cuneus (Herbet et al., 2018; Latini et al., 2017). The ILF is also in direct contact with several other white matter association tracts; UNC, IFOF, the long and the posterior segments of the arcuate fasciculus, and the vertical occipital fasciculus of Wernicke (Herbet et al., 2018). The ILF and the UNC both extend to the anterior parts of the temporal lobe. Thereby, forming an indirect anatomical connection linking the frontal lobe through the UNC, the anterior temporal lobe, and the ILF all the way to the occipital lobe. Some suggests that this anatomical connection could form an indirect ventral stream for language and semantic processing (Herbet et al., 2018). Simultaneously, the converging cortical terminations of the ILF, the arcuate fasciculus, and the vertical occipital fasciculus in the posterior part of the inferior temporal gyrus, creates the possibility for direct interactions between the ventral and dorsal streams (Herbet et al., 2018).

The inferior longitudinal fasciculus is one of the earliest association tracts to show age-related changes in DTI parameters, reaching about 90% of peak fractional anisotropy by 11 years of age (Herbet et al., 2018; Lebel et al., 2008). Although it continues to mature until approximately 25 years of age according to newer studies (Lebel & Deoni, 2018; Lebel et al., 2012). Because of the ILFs early development it is speculated that it is dependent on basic perceptual and cognitive processes, for example language and visual cognition (Lebel et al., 2012)

Functional Tasks. The inferior longitudinal fasciculus is associated with several brain functions, which ranges from visual memory, object recognition, reading, lexical and semantic processing, to face recognition and emotion processing (Herbet et al., 2018). All these functional tasks are involved in visually guided behavior, which is highly consistent with its topography (i.e., connects the occipital lobe, fusiform gyrus, and temporal lobe). Some of the functions listed are bilateral (object recognition), while face processing is more dependent on the right ILF, and lexical processing and reading correlates more to the left ILF (Herbet et al., 2018; Latini et al., 2017).

Visual memory, Object and Face Recognition. Some suggest that the inferior longitudinal fasciculus is important for relaying visually learned information, or visual memory, especially during haptic processing (Herbet et al., 2018; Lee Masson et al., 2017). The role of the ILF (and visual memory) in haptic processing seems to be facilitation of haptic performance when possible, making performance more efficient and accurate in haptic processing tasks (Lee Masson et al., 2017).

Herbet and colleagues (2018) report that the ILF is also involved in the ventral visual stream. The ventral visual stream is mainly linked to visual perception and recognition (Grill-Spector et al., 2018). ILFs association with the ventral stream (and object recognition) is supported by different studies finding correlations between the structural integrity of this white matter tract and the inability to recognize objects, in the absence of any primary visual defects (i.e., visual agnosia; Herbet et al., 2018). The inferior longitudinal fasciculus has also been found to correlate with face recognition (Hodgetts et al., 2015). This function has been more related to the right hemisphere than the left. Several studies of healthy individuals and brain-damaged patients have found that the right ILF is one of the white matter tracts involved in efficient face recognition (Herbet et al., 2018; Hodgetts et al., 2015).

Reading. The ILF has been implicated in several studies regarding different aspects of reading (Herbet et al., 2018). Specifically, the posterior part of the left ILF has been found to be important in the conveying of visual information from occipital areas to the posterior visual word form area, enabling recognition of word forms (Herbet et al., 2018). The ILF is also correlated with reading fluency and comprehension (Feldman et al., 2012; Herbet et al., 2018; Horowitz-Kraus et al., 2014). The left ILF was found to be more correlated to reading comprehension, while both left and right ILF were correlated to word reading (Horowitz-Kraus et al., 2014).

Lexical and Semantic Functions. In line with the findings of ILFs function in reading, it’s theorized that the ILF is one of three major white matter tracts involved in the semantic ventral stream, thereby the ability to learn and comprehend words, and retrieval of semantic information (Herbet et al., 2018). Semantic learning, through novel word-to-meaning mapping, is one of the abilities found to be predicted by integrity in the ILF and UNC (Ripollés et al., 2017). Another component in the semantic visual stream affected by the ILF is semantic autobiographical memory. Meaning that the intricacy and extent of self-related knowledge is depended on the microstructure of the inferior longitudinal fasciculus (Hodgetts et al., 2017). Damage to this function have been found to result in some naming impairments, problems with semantic retrieval, or diminished complexity in semantic autobiographical memory (Herbet et al., 2018).

Emotions and Facial Interpretation. Because of the ILFs topography, it’s most likely involved in the integration of visual and emotional processes as well (Herbet et al., 2018). The ILFs role in the cortical affective network is not completely established, yet there have been cases where specific occipito-temporal lesions extending to the ILF is connected to “visual hypoemotionality” (Fischer et al., 2016; Herbet et al., 2018). Visual hypoemotionality is often conceptualized by feelings of detachment, most likely due to lacking integration of visual input and emotions. For example, when a person sees a family member they love, feelings of care and tenderness usually occur. In patients with visual hypoemotionality these feelings do not arise at the visual input of seeing their loved one. However, these emotions are evoked during other forms of stimuli, like talking or touching (Fischer et al., 2016).

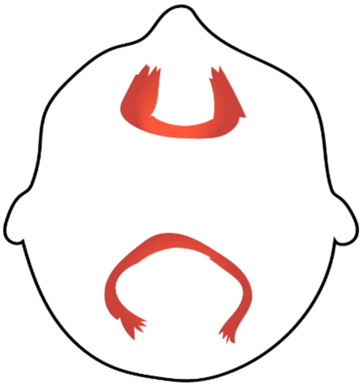
Another function the ILF (and other ventral tracts) is associated with in the cortical affective network is recognition of facial emotions (Herbet et al., 2018). There are several studies supporting this function of the ILF. Generally, the microstructure (as measured by AD, RD, or MD) of the ILF predicts accuracy in identifying facial emotions (Herbet et al., 2018; Unger et al., 2016). Making it important to interpret other people’s mental states efficiently and accurately, in order to respond appropriately in any given social situation.

Forceps Major

The white matter bundle forceps major, also known as the posterior forceps, connects the occipital lobes. It goes through the splenium of the corpus callosum (CC) and is mainly involved in communication between the hemispheres (Lebel et al., 2012). Since forceps major connects the two visual cortices (in the occipital lobe), it is assumed that this white matter bundle facilitates refinement of movements (Fabri et al., 2014; Goldstein et al., 2017).

Figure 2.2

Visual Depiction of Forceps Major and Forceps Minor



Forceps Minor

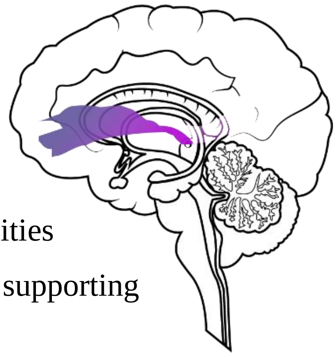
The forceps minor connects the frontal lobes in the opposite end of the corpus callosum. As the alternative name (anterior forceps) implies, it passes through in the genu the most anterior part of the CC. The forceps minor connects the anterior parts of the frontal lobes, thereby facilitating higher cognitive functions (Fabri et al., 2014; Mamiya et al., 2018). Attention is one of the cognitive functions often connected with the forceps minor (Fame et al., 2010; Mamiya et al., 2018). Higher integrity in the white matter pathways connecting the anterior frontal regions (including the forceps minor) has been found to correlate to better attentional control in bilingual individuals (Mamiya et al., 2018). Some have also found that lower integrity of the forceps minor to be correlated with cognitive dysfunction (mainly in attention-deficit-hyperactivity-disorder, and frontotemporal dementia; Lillo et al., 2012; Mamiya et al., 2018; Qiu et al., 2010). Altogether it seems that the forceps minor is mainly involved in communication between anterior parts of the frontal cortices that improves cognitive functioning, especially attentional control.

Anterior Thalamic Radiation

Anterior thalamic radiation (ATR) is a white matter pathway within the anterior limb of the internal capsule. ATR connects the anterior and ventromedial nuclei of the thalamus and the prefrontal cortex, anterior cingulate, and some dorsolateral frontal regions (Mamah et al., 2010; Zhou et al., 2003). These areas are also highly involved in cognition, specifically executive functions and planning of complex behaviors (Mamah et al., 2010; Mamiya et al., 2018). ATR is also associated with cognitive abnormalities and not psychotic symptoms in schizophrenia (Mamah et al., 2010). Further supporting the ATRs role in facilitation of executive functioning.

Figure 2.3

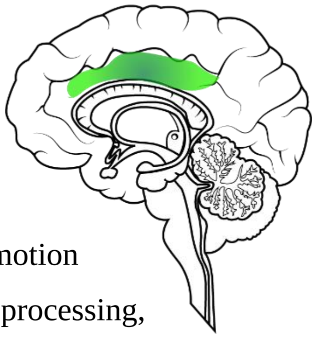
Visual Depiction of Anterior Thalamic Radiation



Cingulate Cingulum Gyrus

Figure 2.4

Visual Depiction of Cingulate Cingulum Gyrus



The cingulate cingulum gyrus (CCG) is a little more complex, as it consists of several parts and thereby connects many different regions within the human brain. The CCG has been found to connect posterior cingulate cortex, orbitofrontal cortex, splenium, parahippocampal gyrus, precuneus, superior parietal lobule, superior occipital lobule, superior frontal gyrus, and supplementary motor area (Shiotsu et al., 2021; Wu et al., 2016). Because of the CCGs involvement in communication between that many areas, its integrity is also found to facilitate/affect several functions including emotion processing, movement, error detection, reward processing and assessment, pain processing, memory, and sensory processing (Shiotsu et al., 2021).

Preterm Born and Very Low Birth Weight

Being born preterm comes with several possible consequences, one of the most detrimental factors in regard to developmental consequences is preterm birth in combination with very low birth weight (VLBW ≤ 1500g; Rimol et al., 2019; Sølsnes et al., 2015; Volpe, 2009). The physical and neurological consequences of being born preterm with VLBW (i.e., focal brain injury etc.) have decreased with better, and more advanced care (Sølsnes et al., 2016). However, there are still several long-term developmental trends that negatively affect these individuals (Sripada et al., 2018; Sølsnes et al., 2016).

Neurobiology

Changes in cortical thickness have been observed in several studies on the preterm very low birthweight population (Nam et al., 2015; Sripada et al., 2018; Sølsnes et al., 2015). Various areas have been found to be affected, one of the most prominent and frequent findings is a reduction in general cortical surface area (Martinussen et al., 2005; Sølsnes et al., 2015; Zhang et al., 2015; Østgård et al., 2014). Specifically, the preterm VLBW participants generally have some cortical reduction/thinning in the posterior temporal and parietal regions, and thicker frontal and occipital regions across all ages (Bjuland et al., 2013; Martinussen et al., 2005; Nam et al., 2015; Sripada et al., 2018; Sølsnes et al., 2015).

There are also some subcortical deviations found in the preterm VLBW population (Aanes et al., 2015; Bjuland et al., 2014; Sølsnes et al., 2016). Mainly, smaller subcortical volumes in both grey matter (thalamus, globus pallidus) and cerebral white matter (corpus callosum, hippocampus), including various white matter tracts (Aanes et al., 2015; Bjuland et al., 2014; Olsen et al., 2018; Rimol et al., 2019; Sølsnes et al., 2016). The combined finding of cortical thinning in the parahippocampal gyrus (Skranes et al., 2013), and the reduced hippocampal volumes in the same cohort (Aanes et al., 2015), suggests that at least some of this reduction may be due to loss of afferent stimuli from the entorhinal cortex (within the parahippocampal gyrus) to the hippocampi, as a result of impaired white matter microstructure (Aanes et al., 2015).

There are several possible reasons and theories as to how these cortical deviations develop. One of these is being born during one of the more important stages for brain development (week 20-37 of gestational age), exposing the neonate to harsh environments in a very vulnerable time. Possibly effecting epigenetic factors on genes controlling normative cortical development through, for example, inflammation (Sølsnes et al., 2015). Inflammation and ischemia (lack of oxygen) could also lead to other detrimental outcomes, such as diffuse periventricular leukomalacia (PVL), one of the most common and severe forms of brain injury in the preterm population (Back, 2014; Volpe, 2009). Diffuse PVL is often associated with diffuse white matter damage caused by a decrease in premyelinating oligodendrocytes, leading to hypomyelination due to immature myelinating cells (Volpe, 2009). Another consequence of inflammation and ischemia is that they affect axonal growth, possibly causing more widespread dysfunction subcortically, thereby also causing secondary grey matter degeneration in the overlying cortex (Volpe, 2009; Wallois et al., 2020). These type of injuries affect neuronal migration and cortical development, possibly explaining the findings of cortical thinning and poor white matter integrity in preterm VLBW (Rimol et al., 2019).

When it comes to the findings of thicker cortical areas in premature VLBW individuals, one possible explanation is a dysregulation of trophic factors that are responsible for the pruning process. Meaning the elimination of synapses, based on activity, in order to increase efficiency in cognition and behavior (Rimol et al., 2019). This dysregulation then leads to halted pruning and thereby a thickening of the cortex. Alternatively, the thicker cortex could also be explained by damage to long-association fibers, that possibly result in the cells being “cut-off” and then transformed into local-circuit interneurons. Which in turn would lead to local neuronal hypertrophy and neuropil, creating a thicker cortex in that area (Marín-Padilla 1997; Rimol et al., 2019).

Based on these findings and theories it seems that the preterm VLBW brain differs from their term-born peers based on changes due to cortical maldevelopment, and some changes based on altered white matter microstructure and connectivity. As previously mentioned, these changes result in both cognitive and behavioral patterns throughout development (Rimol et al., 2019; Sølsnes et al., 2016).

Cognitive Profile

Within the cognitive domain, preterm born VLBW individuals have been found to have increased risk of deficits in executive functioning (Burnett et al., 2013). The preterm VLBW population process information slower, have poorer attentional control, diminished cognitive flexibility (including specific working memory deficits), and limited goal setting abilities compared to their term-born peers (Burnett et al., 2013; Korpela et al., 2018; Murray et al., 2014; Rose et al., 2011). Deficits in executive functions in adolescents have also been found to correlate to smaller surface area in regions involved in higher order cognition (Østgård et al., 2016).

IQ is regularly tested in this population in order to better understand their cognitive abilities and deficits, where findings often support the poorer executive functioning results of other studies (Løhaugen et al., 2010; Rose et al., 2011; Skranes et al., 2013; Sølsnes et al., 2015). Most studies find that the preterm VLBW population generally perform worse than their term-born peers (Eikenes et al., 2011; Rose et al., 2011; Sripada et al., 2018), however some have found normal levels of IQ scores (Weisglas-Kuperus et al., 2009). Rose and colleagues also found that deficits in IQ scores were completely mediated by several areas within the cognitive domain, including processing speed, memory, and attention (2011).

The challenges that accompany poorer executive functioning are also evident in everyday behavior, most prominent in diminished inhibitory control, attentional shifts, initiation of behaviors, and metacognition (Burnett et al., 2013). Meaning that generally people born preterm with VLBW struggle more with controlling behavioral impulses (for example talking over others or not being able to pay attention because of background noises), transitional contexts (i.e., changing tasks), as well as initiating conversations or new tasks on their own. The behavioral phenotype of the preterm born VLBW population is therefore often referred to as being more anxious, inattentive and have more social difficulties (Johnson & Marlow, 2011; Østgård et al., 2016).

A frequent and important consequence of cognitive deficits like these, is poor academic performance. There are many theories and discussions concerning the main reasons underlying this subpar performance. However, there seems to be a general consensus that diminished complex executive functions and cortical maldevelopment are two of the main perpetrators (Best et al., 2011; Collins et al., 2021; Østgård et al., 2016). Mainly due to the fact that these are the areas the preterm VLBW population shows the largest discrepancies from their term-born peers. Because of the preterm behavioral phenotype, the academic struggle of these individuals often goes unnoticed, because they typically have more internalizing symptoms (i.e., anxiety), instead of disruptive behaviors (Burnett et al., 2013; Østgård et al., 2016).

Academic subjects with the most prominent differences in VLBW are math and language (Twilhaar et al., 2018). However, this discrepancy decreases somewhat with age, perhaps because of compensatory mechanisms, or simply because of a delay in development of the prefrontal cortex (Burnett et al., 2013; Collins et al., 2021; Van Ettinger-Veenstra et al., 2017). This struggle in academic achievement often has several cascading long-term consequences, mainly lower socioeconomic status due to lack of higher education, thereby also lower health/more heath related problems, and some psychological struggles as well (Basten et al., 2015; McMahon & Oketch, 2013).

Many of these cognitive deficits are also evident in people with autism spectrum disorder, attention deficit-hyperactivity disorder (ADHD), and anxiety (Ameis & Catani, 2015; Franz et al., 2018). A recent meta-analysis by Anderson and colleagues (2021), found that VLBW individuals had ten times higher odds of meeting diagnosis criteria for autism spectrum disorder, than the control group. For ADHD the VLBW group had five times higher odds than controls to meet the criteria. The VLBW individuals additionally had higher odds of meeting diagnosis criteria for both anxiety and mood disorders as well (Anderson et al., 2021). Supporting the behavioral phenotype in the preterm VLBW population of inattention, internalizing symptoms, and social difficulties.

Social Aspects

Another major area of consequence for this group is that preterm born VLBW individuals have on average worse social competence than their peers (Lund et al., 2012). This is most likely a result of the challenges this population face in regard to inattention and inhibition, making it more difficult to adhere to social norms (Lund et al., 2012). This could lead to more exclusion from social groups, giving the child less opportunities to learn and practice social skills, and over time setting them further and further apart from their peers. These difficulties could also be a result of preterm born VLBW children/adolescents being more prone to autism spectrum disorder, ADHD, anxiety, and depression (Alduncin et al., 2014; Burnett et al., 2013; Indredavik et al., 2004; Lund et al., 2012; Olsen et al., 2018). Anxiety has a bidirectional effect on social relationships, meaning that if a child is being excluded in a group of peers, the anxiety could be facilitated by the exclusion, simultaneously, as level of anxiety grows, a tendency to isolate more and take less risks (both physically and socially) is common (Anderson et al., 2021). Leading the child to engage less and less in social interaction with peers in fear of rejection nevertheless being rejected anyway due to lack of engagement in the social world of their peers.

Research Question of the Master Thesis

White matter has consistently been found to be diminished in preterm born individuals (Eikenes et al., 2011; Loe et al., 2019; Rimol et al., 2019). These individuals also struggle more than term-born peers with cognitive functions, social relationships, and academic performance (Burnett et al., 2013; Collins et al., 2021; Eikenes et al., 2011; Lund et al., 2012). Cognitive functions are key here since cognitive deficits affect both social cognition and academic ability. Some earlier studies have examined white matter integrity and full-scale IQ in VLBW cohorts (Eikenes et al., 2011; Northam et al., 2011; Skranes et al., 2009; Skranes et al., 2007). However, the relationship between these factors still remains fairly unexplored, and somewhat inconclusive. This thesis investigates a cohort of adults born preterm with VLBW and a corresponding control group using probabilistic tractography with anatomical priors. This means that the identification of white matter tracts is less sensitive to the inaccuracies of inter-subject alignment than studies based on non-linear registration to a brain template (for instance Eikenes er al., 2011). Moreover, this thesis took a more specific approach to IQ, investigating the four IQ-indices separately.

In order to understand how deficits in cognitive functions are affected by white matter integrity this thesis examines group differences in structural integrity of different white matter tracts. The first research question posed is therefore: “Is there a group difference in white matter integrity of white matter pathways in VLBW adults compared with controls?” Furthermore, the thesis investigates how these differences affect cognitive functions. The second research question posed here is: “How is cognitive functioning affected by these possible white matter differences?”

Methods

The data used in this thesis comes from three birthyear cohorts (1986-88) born preterm with VLBW (birth weight<1500g) and an age matched term-born control group. These groups have been studied longitudinally from birth at regular intervals (Skranes et al., 2013), this thesis is based on measures taken at approximately 26 years of age. For full descriptions of inclusion criteria and results for previous studies on the same participants (clinical assessments and cerebral MRI) see earlier publications (Bjuland et al., 2012; Indredavik et al., 2004; Martinussen et al., 2005; Rimol et al., 2019; Skranes et al., 2013; Skranes et al., 2007).

Participants

Very Low Birthweight

121 VLBW children were born and admitted to the Neonatal Intensive Care Unit at the University Hospital in Trondheim (St. Olav's Hospital), Norway. Of these 121 children there were 33 who died, two were born with congenital syndromes/malformations and were therefore excluded, and another two were excluded due to severe cerebral palsy (quadriplegia with mental retardation) at follow-up. At 26 years of age the remaining 84 were invited to participate, of whom 47 (57% females) consented and had usable MRI data.

Controls

The control group were children born in Trondheim; whos' mothers had joined a multicenter study before week 20 of pregnancy between 1986-88. There were 1200 pregnant women who enrolled in the multicenter study, expecting their second or third child. There were 120 term-born children with birth weight above 10 percentile, adjusted for gestational age and gender, selected by a 10% random sealed envelope method among the multicenter study children. Two of these were excluded due to congenital malformations. 73 (45% females) of the remaining 118 eligible people consented to participate and had usable MRI data at 26 years of age.

Non-participants

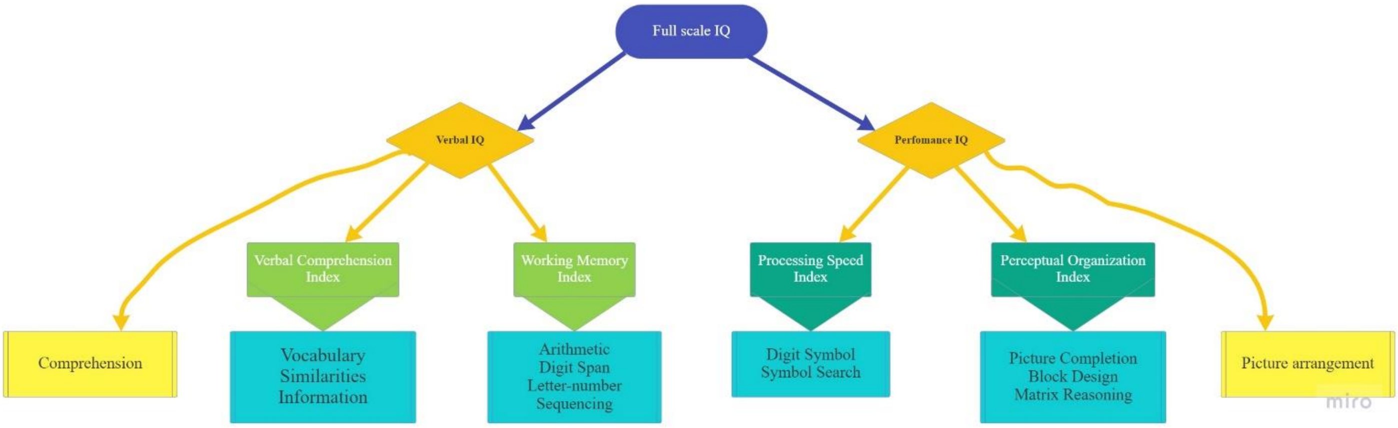
82 participants were lost to follow-up (37 VLBW and 45 controls). Separate independent t-tests were conducted regarding birthweight, gestational age, and socio-economic status comparing participants in the study and the non-participants. The non-participants had on average a lower gestational age than participants in the VLBW group (M =27.9, SD = 2.6 vs. M = 29.5, SD = 2.4) (t(82) = 2.98, p = .004), and in the control group (M = 39.4, SD = 1.2 vs. M = 39.9, SD = 1.2) (t(116) = 2.43, p = .02). Mean birthweight was also lower for the VLBW non-participants (M = 1240, SD = 228 vs. M = 1084, SD = 229) (t(82) = 3.10, p = .003).

Cognitive Assessments

The Weschler Adult Intelligence Scale-III (WAIS-III; Tulsky et al., 2003) was administered to obtain intelligence quotient (IQ) scores. Full-scale IQ scores were gathered from 11 subtests and is considered a representative measurement of global intellectual functioning (Løhaugen et al., 2010). The WAIS-III assesses verbal IQ (verbal knowledge and reasoning), and performance IQ (non-verbal problem solving, visuospatial processing, processing speed). These are divided in four specified domains for cognitive functions: verbal comprehension, working memory, perceptual organization, and processing speed respectively.

Figure 3

Visual Representation of WAIS-III



Note. Full scale IQ: dark blue, Sum scores: mustard; Indices: green and teal, Subtests: light blue and yellow

MR imaging

Image acquisition

A 3 T Siemens Skyra scanner equipped with a quadrature head coil, was used in MRI scanning. Two sagittal T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) scans were acquired (echo time = 3.45 ms, repetition time = 2730 ms, inversion time = 1000 ms, flip angle = 7°; field of view = 256 mm, voxel size = 1 × 1 × 1.33 mm3 , acquisition matrix 256 × 192 × 128, reconstructed to 256 × 256 × 128). The DTI sequence was a single-shot balanced-echo EPI sequence in 30 non-collinear directions, with the parameters: TR = 8800 ms, TE = 95 ms, FOV 192 × 192 mm, slice thickness 2.5 mm, acquisition matrix 96 × 96. Sixty axial slices were obtained without gap, providing full brain coverage. For each slice, four images without diffusion weighting (b = 0), and 60 images with diffusion gradients were acquired, consisting of 30 images with b = 1000 s/mm^2 and 30 with b = 2000 s/mm^2 (Rimol et al., 2019).

dMRI tractography.

The dMRI analysis and tractography was performed using the FreeSurfer 5.3.0 tool TRACULA (TRActs Constrained by UnderLying Anatomy; Yendiki et al., 2011). TRACULA performs global probabilistic tractography based on anatomical priors from the subject's individual anatomy, that is, segmentation labels from T1-weighted MPRAGE images processed in the FreeSurfer morphometry stream. These are used as a "prior" term by TRACULA to estimate the probability of each pathway to pass through, or lie adjacent to, gray matter structures (the segmentation labels). These probabilities are calculated separately for every point along the pathway's trajectory. A likelihood term is included in these calculations, such that each voxel is assigned a probability that it belongs to the pathway.

Thus, TRACULA only considers the relative position of the pathway with respect to its surrounding anatomy in native space, i.e., relative to the subject's own T1-based segmentation labels and does not have to rely on the absolute coordinates of the pathway in a template space. This means that the identification of white matter pathways (tracts) is less sensitive to the accuracy of inter-subject alignment than studies using for instance the TBSS software, which relies on exact alignment of subjects in template space. Finally, TRACULA calculates the expected value of FA by taking each cross-section (defined at each segment along the maximum probability path) of the pathway and estimating a weighted average of the FA values (weighted by the probability that it belongs to the path). Thus, the FA values reported here, are weighted averages across each segment of the pathway.

Mean fractional anisotropy (FA) was assessed in several white matter pathways. These white matter pathways were selected based on previous findings of abnormal cortical regions in preterm VLBW (Rimol et al., 2019). The selected tracts were: uncinate fasciculus, inferior longitudinal fasciculus, forceps major, forceps minor, anterior thalamic radiation, and cingulate cingulum gyrus, all of which are directly or indirectly involved in facilitation of perception, processing, and/or cognitive functions.

The superior longitudinal fasciculus is not included in this thesis because of the abundance of crossing fibers along this white matter pathway. The crossing fibers makes it inherently difficult to assess and interpret, which is also the reason for the lack of consensus in research surrounding both the SLF-I and the arcuate fasciculus (Schurr et al., 2020). A tractography quality control was used to exclude poorly measured participants/data, only data that passed this quality control were included in the analyses (see Rimol et al., 2019).

Statistics

Statistical software

Demographic and clinical variables were examined using the statistical software program STATA 17. General Linear Models (GLM) were used to analyze the data. Separate simple regressions using VLBW as a categorical independent variable and FA as dependent variable were run to compare FA between the groups in all the white matter tracts measured. The conventional alpha level of 0.05 were corrected using Bonferroni corrections of multiple comparisons.

Interactions and Multiple Regression Models

To examine if there was a difference between the groups (VLBW vs controls) in the effect white matter integrity (as measured with FA) had on full IQ scores, regression models with an interaction term were fitted, with full IQ as the dependent variable, FA, and group (controls vs. VLBW) as continuous and categorical predictors respectively, and sex as a covariate. Only tracts with significant findings of group differences in FA were tested. Multiple regression models were also run with the same variables, to understand the relationships between the variables in this data. The tracts were analyzed separately. In order to obtain a more extensive understanding of the associations between the cognitive functions, group differences and white matter integrity, analyses were performed with the four different indices of full IQ as dependent variables. Meaning that interaction regression models were completed post hoc using the different indices in WAIS-III as dependent variables (i.e., perceptual organization, working memory, processing speed, and verbal comprehension).

Results

Descriptive data

Table 1 shows an overview of the demographic and cognitive data based on group. There was a 2464 g difference in mean birthweight between the VLBW (1240g) and control (3704g) groups. The control group also had on average approximately ten weeks more in gestation. Group difference in Full IQ was also found to be statistically significant between the VLBW group (M = 89, SD = 13.0) and the control group (M = 102, SD = 12.7).

Table 1

Demographic and cognitive data for VLBW and term-born controls.

	VLBW		Controls	
	n	M	n	M
Birth weight [a]	47	1240 (550-1500)	73	3704 (2670-5140)
Gestational age	47	29.5	73	39.9
Full IQ***	36	89 (SD=13.0)	56	102 (SD=12.6)
Sex (males/females)	47	27/20	73	33/40

Note. IQ measured at age 20, scans completed at approximately age 26. VLBW: very low birthweight; SD: standard deviation

[a] Birth weight reported with range

***Significant group difference, p-value= >.0001

Analysis of dMRI

Table 2 shows the white matter tracts' group differences in mean FA for the whole tract. There were ten tracts investigated in this thesis, of these ten only the right and left uncinate fasciculus (p=.004 and p=.005 respectively) and the forceps minor (p=.005) showed statistically significant group differences in white matter integrity after Bonferroni correction. These three white matter tracts are also the only ones with medium effect sizes, with the left uncinate fasciculus showing the largest effect of group differences (d=.76).

Table 2

Group differences in FA

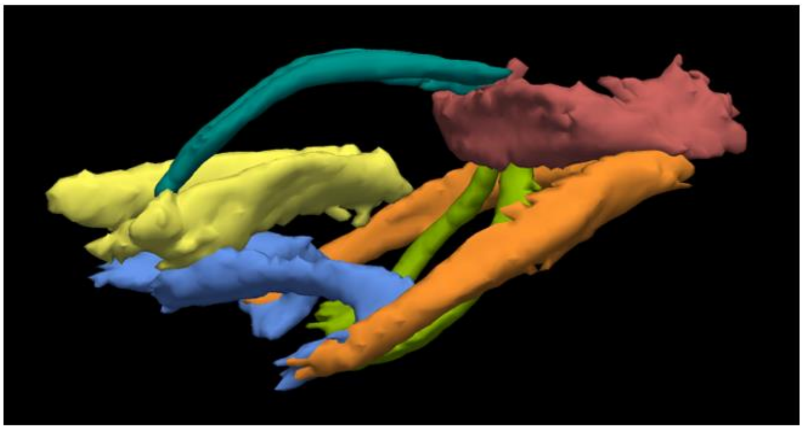
White matter pathways	VLBW		Controls		P-value	Cohen's d
	n	FA	n	FA		
Right UNC	29	0.421	59	0.445	**0.004****	**0.63**
Left UNC	21	0.425	50	0.449	**0.005****	**0.76**
Forceps minor	34	0.551	45	0.580	**0.005****	**0.66**
Forceps major	33	0.612	39	0.628	0.14	0.35
Left atr	35	0.461	54	0.465	0.46	0.16
Right atr	35	0.452	53	0.451	0.94	-0.02
Left ccg	22	0.525	55	0.526	0.98	0.01
Right ccg	21	0.479	55	0.488	0.44	0.20
Left ilf	35	0.531	43	0.544	0.17	0.31
Right ilf	35	0.505	45	0.517	0.25	0.27

Note. VLBW: Very low birth weight, FA: Fractional anisotropy, UNC: Uncinate fasciculus, ILF: Inferior longitudinal fasciculus, ATR: Anterior thalamic radiation, CCG: cingulate cingulum gyrus

** Significant at the 0.005 level (adjusted for multiple comparisons)

Figure 4

Visual Representation of the White Matter Pathways



Note. Yellow: Forceps Minor, Blue: Uncinate Fasciculus, Teal: Cingulate Cingulum Gyrus, Red: Forceps Major, Orange, Inferior Longitudinal Fasciculus, Green: Anterior Thalamic Radiation

Interaction and Effects on IQ

To examine if there was any interaction between group and white matter integrity (FA) on full IQ, interaction models were run individually on each white matter tract. On the right uncinate fasciculus, f(4, 75) 9.33 ($p<0.0001$), there was a main effect of both VLBW and FA on full IQ score, as well as an interaction effect of the two. Meaning that having very low birthweight (<1500g) affects the relationship between FA and full IQ score, as pictured in figure 5. Group difference and FA in right uncinate fasciculus also gave an explanatory power of 0.296, meaning that approximately 29,6% of the variation in IQ scores can be attributed to this model (FA in the right uncinate fasciculus and group affiliation, and the interaction of the two).

On the left uncinate fasciculus, there was only a main effect of group difference: f(4, 66) 5.24 ($P=0.0010$). Neither white matter integrity (FA) nor the interaction was found to have a statistically significant effect on full IQ scores. In forceps minor, there was a main effect of group differences: f(4, 74) 8.20 ($P<0.0001$), and no difference in white matter integrity (FA). However, the interaction between them was significant, revealing that in the very low birthweight group white matter integrity in forceps minor is correlated with full IQ scores, but not in the control group, as shown in figure 6.

Table 3

Interaction analysis, main effects of VLBW and FA on IQ

White matter tracts	Main effects		Interaction		
	VLBW	FA	(VLBW*FA)	95% CI	Adj R^2
Right UNC	10.09*	126.03**	216.39*	[19.07, 413.71]	0.296
Left UNC	9.54*	72.29	53.67	[164.17, 271.51]	0.195
Forceps Minor	12.47*	32.12	152.2*	[9.86, 294.54]	0.269

Note. VLBW: Very low birth weight, FA: Fractional anisotropy, UNC: Uncinate fasciculus

*Significant at the 0.05 level.

**Significant at the 0.001 level.

Figure 5

Graphical Representation of the Interaction Analysis in Right Uncinate Fasciculus

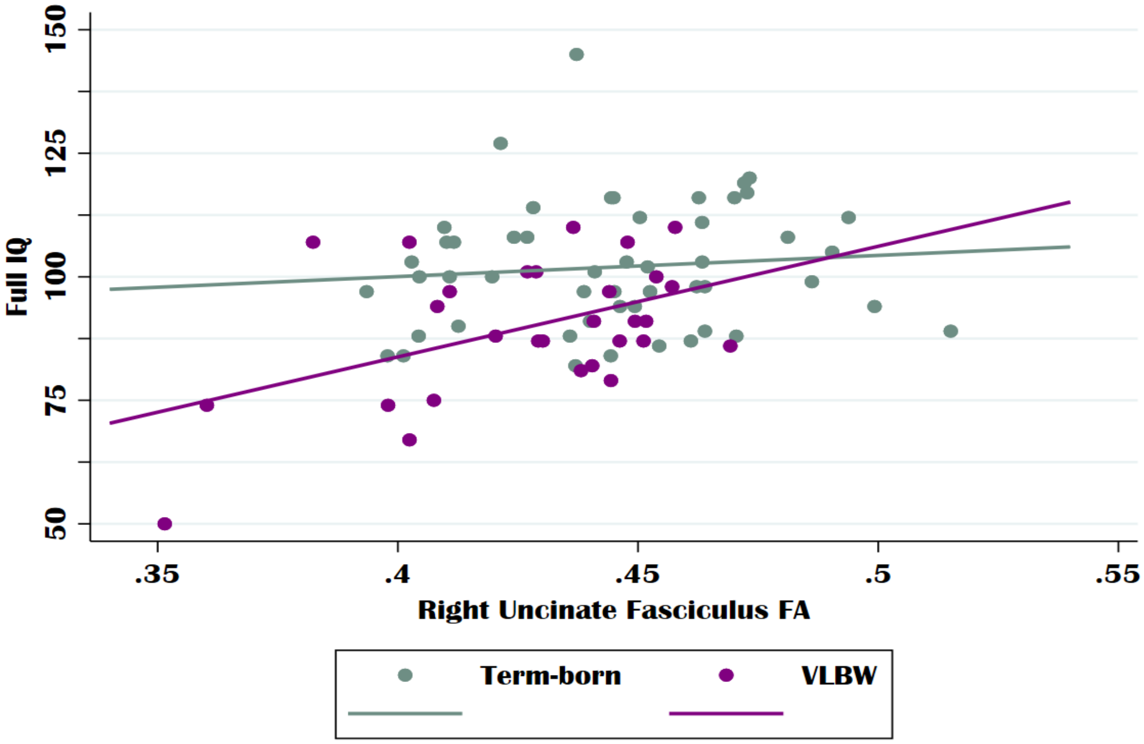
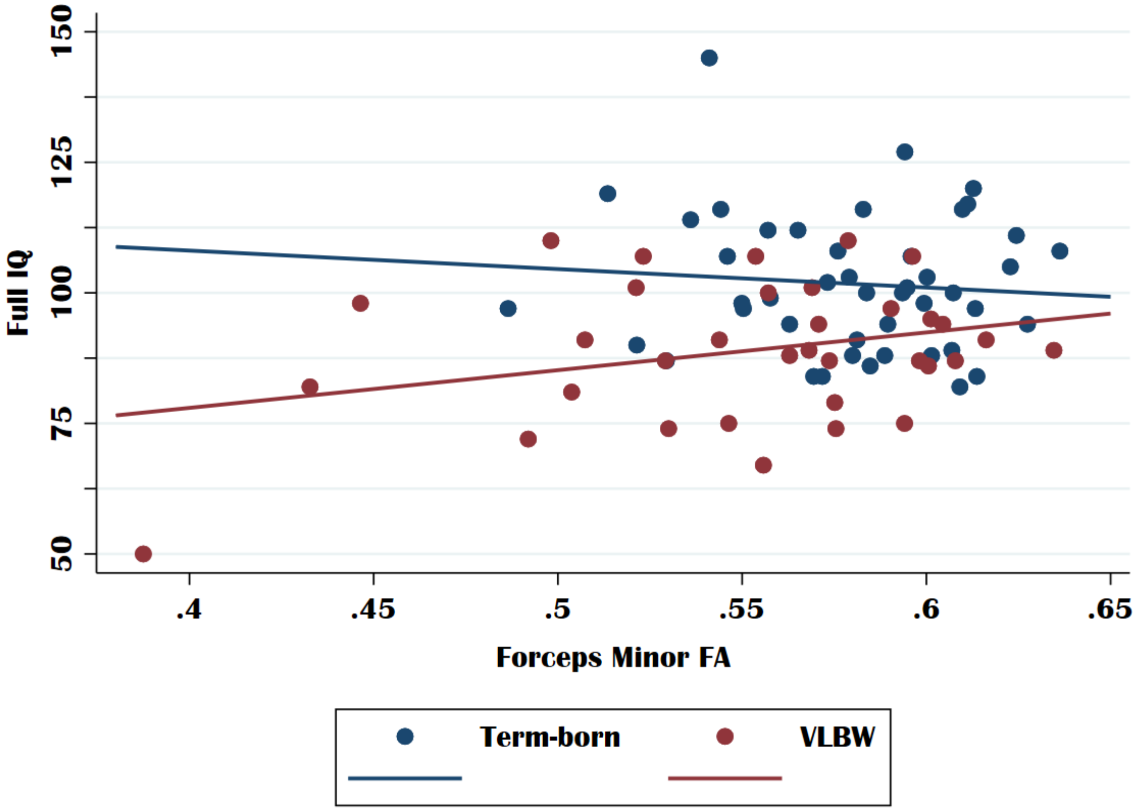


Figure 6

Graphical Representation of the Interaction Analysis in the Forceps Minor



Post Hoc of Cognitive Subcategories

Table 4 shows post hoc analyses of the cognitive indices of the WAIS-III in relation to this thesis. It shows the interaction effect between FA and group differences here as well, in order to get a more in-depth view of their respective roles in different aspects of cognitive functions. In the perceptual organization index, there was only a statistical difference based on group in the left uncinate fasciculus analysis. No other measures revealed effects of statistical significance on perceptual organization.

On the working memory variable, the right uncinate fasciculus were the only measure showing a significant interaction between group and FA (P=0.005). Even though FA in the left UNC had a main effect on working memory, it did not reveal a main effect of group differences nor a significant interaction of the two factors. Processing speed was significantly correlated with group in both the right uncinate fasciculus and forceps minor, shown by the significant main effect of group and the statistically significant interaction of FA and group (P=0.038, P=0.034 respectively). Lastly, on the verbal comprehension part of the WAIS-III, only forceps minor shows a statistically significant interaction between group and FA (P=0.027). Although, group differences were statistically significant in all three analyses on this subscale.

Table 4

Statistical Relationships in Subscales of the Cognitive Profile

	Main effects		Interaction	
	VLBW	FA-c	(VLBW*FA)	95% CI
Perceptual Organization				
Right UNC	79.27	100.70	159.65	[-62.9, 382.24]
Left UNC	22.53*	45.37	29.12	[-217.12, 275.35]
Forceps Minor	42.13	12.74	51.73	[-108.94, 212.41]
Working Memory				
Right UNC	120.06*	19.62	**265.45***	[84.07, 446.83]
Left UNC	30.35	79.60*	63.41	[-124.22, 251.03]
Forceps Minor	56.38	-13.03	92.24	[-49.83, 234.30]
Processing Speed				
Right UNC	107.37*	53.37	**234.83***	[13.29, 456.38]

Left UNC	55.54	103.83*	118.30	[-125.36, 361.96]
Forceps Minor	102.70*	-25.04	**169.49***	[13.59, 325.40]
Verbal Comprehension				
Right UNC	101.56*	-15.06	211.65	[-4.17, 427.47]
Left UNC	37.64*	47.53	68.22	[-174.68, 311.12]
Forceps Minor	111.50*	-118.50	**173.74***	[20.56, 326.93]

Note. Left UNC did not show any significant findings on any interaction models, main effect numbers are derived from multiple regression analysis instead. VLBW: Very low birth weight, FA: Fractional anisotropy, FA-c: Fractional anisotropy for the control group, UNC: Uncinate fasciculus

*Significant at the 0.05 level.

Discussion

White matter integrity in right and left uncinate fasciculus and forceps minor was found to be diminished in the VLBW group compared with the control group. This thesis also found that white matter integrity in the right uncinate fasciculus does affect cognitive functioning overall, however to a significantly greater degree in the VLBW group. Forceps minor was found to significantly affect cognitive functioning in VLBW adults. In the indices of WAIS-III, processing speed was significantly affected by the interaction of group and white matter integrity, both in the right UNC and the forceps minor. The interaction between group and integrity in the right UNC was also significantly involved in working memory scores. While integrity in the forceps minor was significantly correlated with verbal comprehension. White matter integrity in the left uncinate fasciculus was found to have a significant effect on working memory and processing speed unaffected by group.

White Matter Pathways

Of the white matter pathways included here, the left and right uncinate fasciculus and the forceps minor were found to have statistically diminished integrity in the VLBW group. These white matter tracts connect several of the areas found to be deviated in the VLBW population (Rimol et al., 2019; Skranes et al., 2013; Sølsnes et al., 2015; Østgård et al., 2016). Many of these areas, and therefore also these white matter tracts, are highly involved in cognitive functions, memory, and/or socioemotional processing and behavior(KILDE-intro). Possibly explaining some of the behavioral phenotype of the preterm VLBW population.

Uncinate Fasciculus and VLBW

The uncinate fasciculus was one of the white matter tracts with a significant group difference of white matter integrity in the VLBW vs control group, both in the right and left hemispheres. However, there were differences between the hemispheres in the UNCs effect on IQ scores. The left uncinate fasciculus' integrity did not show a significant effect on full IQ scores. This finding gives further support to differing functions of the same areas in the two hemispheres even with approximately the same endpoints of the right and left UNC (Von Der Heide et al., 2013). Looking at the analysis of the subcategories in the WAIS-III, there were effects of FA in the left UNC on working memory and processing speed in the control group. Supporting some previous findings on the role of the UNC in cognitive functions (Olson et al., 2015; Von Der Heide et al., 2013).

The right uncinate fasciculus' integrity, however, had an effect on IQ scores, and an interactional effect with group. The right uncinate fasciculus have been associated with reading skills, verbal IQ, and emotional processing (Feldman et al., 2012; Oishi et al., 2015; Von Der Heide et al., 2013). The findings here suggests that the integrity of right uncinate fasciculus predicts cognitive functioning, and that higher integrity in the right UNC have a greater effect on cognitive functions specifically in VLBW individuals, when compared with term-born controls. Simultaneously, an effect of FA on full IQ was found, meaning that white matter integrity in the right UNC significantly affected IQ scores for the control group as well. Giving some support to the associative learning function of the UNC, as well as the separate roles of right and left uncinate fasciculus (Von Der Heide et al., 2013). Furthermore, working memory and processing speed were found to be significantly affected by the interaction of group and FA in the right UNC. This supports that white matter integrity in the right UNC is more imperative for cognitive functioning (specifically working memory and processing speed tasks) in the VLBW group compared with the term-born control group.

On the other hand, these findings can also result from immaturity of the white matter tract. Since uncinate fasciculus is one of the later tracts to both develop and peak in normative development (age 28-35), it is possible that the later maturation found in the VLBW group (Rimol et al., 2016; Sripada et al., 2018) could explain the group differences in FA found here. Especially with the measures included being tested before or at age 26. Additionally, Rimol and colleagues (2016) found that there are no "catch-up" functions in the brain development of the VLBW group compared with term-born peers between 15 and 20 years of age. If this also applies further along brain development (in early adulthood), it could mean that the VLBW population does not reach peak white matter maturation in the uncinate fasciculus until later in their adult life. Although, it is unlikely that delayed maturation could explain the entirety of the findings in this thesis. It is, however, an interesting, and possibly confounding, factor to consider. One would need further studies (preferably longitudinal) to draw any conclusions regarding brain maturation and development in early adulthood in the VLBW population.

Forceps Minor and VLBW

Forceps minor integrity was also found to be significantly affected by group differences. Furthermore, an interaction of VLBW and white matter integrity was found for this white matter tract as well. Demonstrating that white matter integrity of the forceps minor is more imperative for cognitive functioning in VLBW adults than term-born controls. There was no significant effect of FA in forceps minor of the control group on full IQ scores. Opposing previous findings (to some degree) that integrity of the forceps minor is correlated with cognitive functioning. This might be due to differences in cognitive measurements. This thesis measured cognitive functions through WAIS-III, represented by a full IQ score based on 11 subtests measuring several aspects of cognitive functioning. While previous studies have used differing measures, some including attention and memory while others have used tests focusing more on attention, fluency, and reaction times (Lillo et al., 2012; Mamiya et al., 2018; Qiu et al., 2010).

It could also be because the previous studies with significant findings of forceps minors' effect on cognitive functioning have focused on populations with different diagnoses, and therefore also different pathologies and deficits, like ADHD and dementia patients (Lillo et al., 2012; Qiu et al., 2010). It seems that the deficits these groups have in common could be related to attention and executive dysfunction (Mamiya et al., 2018). Forceps minor have been implicated specifically in attentional control, which is an area that the VLBW population have been found to struggle with as well (Murray et al., 2014; Rose et al., 2011). This thesis did not measure attention directly, so the significant finding of group difference in forceps minor integrity could be explained by attention, or attentional control. To draw any conclusions regarding this one would have to do further studies examining attention in a larger degree within this population.

However, the post hoc tests of the different subcategories of WAIS-III, did reveal that there was an interactional effect of group and FA in forceps minor on the processing speed and verbal comprehension indices. Supporting the notion of VLBW individuals struggling more with these abilities than their term-born peers (Feldman et al., 2012; Murray et al., 2014; Rose et al., 2011). Additionally, that for the VLBW group white matter integrity in forceps minor, found related to these skills (Mamiya et al., 2018), is of more importance than for the control group.

Interactions

The analysis of this thesis provided a significant finding of an interaction between the integrity in the right uncinate fasciculus and VLBW on full IQ scores. It seems that in the VLBW group, white matter integrity in the right uncinate fasciculus affects cognitive functions to a greater degree than in the control group. As demonstrated in Figure 5, the VLBW group generally score lower on full IQ, however as white matter integrity in the right uncinate fasciculus increase so does the full IQ scores in both groups. The interaction does show that on average the VLBW group is affected to a greater degree than the control group. There are several possible interpretations of this finding. The most likely being that with the cortical deviations found in the VLBW group, they rely more on white matter connectivity for communication between brain regions (frontal and temporal) than the control group in cognitive tasks. Perhaps utilizing different cognitive strategies to solve the tasks. There has been some support for altered or compensatory mechanisms of functional neural networks in different cognitive tasks (i.e., reading and attention; Nosarti et al., 2006; Van Ettinger-Veenstra et al., 2017).

The integrity of the forceps minor was also found to have a significant interaction with VLBW on full IQ scores. However, there was no main effect of integrity in forceps minor on full IQ in the control group. This indicates that the forceps minor does not contribute to cognitive functioning in term-born adults, while in the VLBW group it becomes a more important factor, as demonstrated in Figure 6. Giving further support to the notion that in the general population white matter integrity “only” facilitate different cognitive functions, but in the VLBW population it seems to be more imperative depending on the task at hand.

Other white matter pathways

The other white matter pathways included in this study have previously been found to be correlated with cognitive functions in normative groups, for example attention, executive functioning, lexical processing, socioemotional processing, and more. Some have also been found to differ in the preterm VLBW population (ILF, SLF, ATR, corpus callosum, etc., Collins et al., 2021; Feldman et al., 2012; Rimol et al., 2019; Skranes et al., 2007; Unger et al., 2016). As previously mentioned, VLBW is often found to have reduced cortical surface area overall, this includes white matter as well (Rimol et al., 2019). Even though some of these white matter tracts might facilitate parts of different cognitive abilities, they were not found to have any significant effects in this thesis. This finding could be a result of not including all relevant cognitive abilities (i.e., attention, lexical comprehension, and socioemotional processing), or that these white matter tracts have more specific purposes than what is measured here.

Another possible explanation is the plasticity of the human brain. There have been some studies that have found altered association networks in preterm VLBW cohorts (Sripada et al., 2018). Where the VLBW group does not significantly differ in tests, however when analyzing fMRI this group utilized other areas and association networks in the brain than the term-born control groups (Nosarti et al., 2006; Van Ettinger-Veenstra et al., 2017). More specific studies of the different white matter tracts and their relationship with VLBW is needed to draw any conclusions regarding this finding of no significant differences in white matter integrity based on group (VLBW vs term-born adults). However, it does seem to indicate that the most important association pathways in the VLBW population for cognitive functioning is the right uncinate fasciculus, and forceps minor integrity as a possible facilitator for attention.

Associative Learning and Preterm Very Low Birth Weight

According to Von der Heide and colleagues, one of the main functions of the uncinate fasciculus is associative learning. Several executive functions exist within this theme, including cognitive flexibility, information processing, updating, and attentional shifting (Laureys et al., 2022; Von Der Heide et al., 2013). The cognitive profile of the preterm VLBW group portrays deficits within the associative learning function of the uncinate fasciculus.

Executive Functions

Cognitive Flexibility. Cognitive flexibility is essential for appropriate adaptation of behavior and responses in almost all situations (Anderson & Reidy, 2012). It is a big part of general cognitive ability, as it incorporates both working memory, multi-tasking, generalizing conceptual knowledge, learning from previous experience, and set shifting (Burnett et al., 2013). This ability is impaired in the preterm VLBW population. They struggle more than their term-born peers with adapting to rule changes in tasks, learning from mistakes, updating working memory, multitasking, and have poorer performance on visuospatial working memory tasks (i.e., process and manipulation of visual stimuli; Aanes et al., 2015; Burnett et al., 2013).

All of these abilities are directly or indirectly influenced by the uncinate fasciculus (Von Der Heide et al., 2013). Mainly through the areas the UNC connects; the frontal pole, temporal pole, entorhinal and perirhinal cortex. Which then preludes to the speculation that at least some of the impairments in cognitive flexibility is a result of diminished white matter integrity and organization in the uncinate fasciculus. As poorer white matter integrity here would most likely lead to reduced communication between the areas responsible for processing, integrating, and adapting responses to incoming stimuli. This thesis gives support to the association between white matter integrity in the UNC and cognitive flexibility. Mainly, through the right UNC where almost all the subtests in the WAIS-III (except perceptual organization) were found to be significantly worse in the VLBW group compared with the term-born control group.

In other words, this thesis suggests that preterm VLBW adults rely more on white matter integrity (in the UNC and forceps minor) for communication in cognitive tasks, including in the executive function of cognitive flexibility. As shown through results here in combination with previous research, preterm VLBW individuals with lower white matter integrity in the right UNC would probably learn slower, in need of more repetition and more time to process and integrate information, as well as adapting to new tasks. Making it all the more important to recognize these possible deficits in academic settings, in order to better facilitate their learning.

Goal setting. The goal setting aspect of executive functions is also diminished in the preterm VLBW population. Initiative, strategic organization, planning, and conceptual reasoning are all components of goal setting abilities according to Anderson and colleagues (2012). All these abilities rely, to some degree, on communication between the areas the uncinate fasciculus and forceps minor connects (frontal pole, orbitofrontal cortex, temporal pole, and parahippocampal gyrus). To be able to anticipate future events, evaluate and formulate a goal based on both previous experience and anticipation of outcome, creating an achievable and systematic plan of actions to reach this goal, and then monitor and execute these actions, all of these areas must be involved and communicating efficiently. In preterm VLBW cohorts several of these abilities (i.e., planning, initiation of behavior, organization) have been found to be worse than in term-born peers (Burnett et al., 2013; Løhaugen et al., 2010). However, this thesis has no measure of goal setting abilities, and so one cannot infer causality nor associations here, only some connections derived from previous research.

Processing speed. Another major area within the associative learning function of the UNC is the abstract executive function of information processing. Information processing is highly involved with the temporal part (perirhinal cortex, temporal pole) of the UNC, which is also one of the thinner cortical areas in the preterm VLBW brain (Bjuland et al., 2014; Rimol et al., 2019). These areas are presumably responsible for, among other things, binding perceptual information (from several modalities) to high level cognitive processes, and to integrate this perceptual information in order to evaluate and choose appropriate responses. Information processing ability in the preterm VLBW population is often characterized by a slower and less accurate response time (Burnett et al., 2013; Rose et al., 2011).

In the results here, processing speed was the only subcategory where there was an interactional effect of group and integrity in the right uncinate fasciculus and the forceps minor. Neither of these tracts' integrity significantly correlated with processing speed scores in the control group. Giving support to the previously found diminished processing speed characteristics of the VLBW population. Additionally, the left uncinate fasciculus was not found to have a significant difference in processing speed based on group, however a main effect of FA was found. Implying that the left UNC does influence processing speed in a normative cohort but does not affect the VLBW group distinctively.

The interactional findings in this subcategory of the WAIS-III might be caused by the cortical deviations found in preterm VLBW cohorts, not necessarily the white matter tracts in and of themselves. But rather that there is less volume (i.e., less synapses, less activity) in the temporal pole and perirhinal cortex making it more difficult, thereby more time consuming, to process information and appropriately respond. However, white matter is an important aspect of processing speed, as its main purpose is to make the brain more efficient. The findings here also support this and suggests that white matter tracts connected to these cortically deviated regions (UNC and forceps minor) have some influence on processing ability.

Attention. Attentional control does not seem to be influenced by the UNC. Mainly because the areas associated with attention is not generally associated with the areas the uncinate fasciculus connect, in either hemisphere. So, even though attentional control is one of the abilities preterm VLBW people struggle with, it does not seem to be connected to the uncinate fasciculus. However, it does influence both cognitive flexibility, processing speed, and goal setting according to the executive control system (Anderson & Reidy, 2012). As previously mentioned, forceps minor has been found to facilitate attention. This combined with the significantly diminished white matter integrity in the VLBW group here, as well as the significant association between white matter integrity in forceps minor and processing speed, it is likely that attention is a part of these results. With diminished ability to inhibit responses/behaviors, self-regulate, and use selective attention, every other executive function might also suffer. Largely due to the basic functions of attention and attentional control. Meaning, that it gets increasingly difficult (based on complexity of a task or situation) to problem-solve, monitor actions, plan further, etc., if the ability to inhibit impulses, habituate background noise, or calm oneself down is impaired.

Summarized, the findings of this thesis and previous research literature on the preterm VLBW population, as it relates to associative learning and executive functions, suggests that executive dysfunction in VLBW cohorts is, at least partly, affected by integrity in the white matter tracts uncinate fasciculus and forceps minor. Executive functions are dependent on extensive efferent and afferent connections across the brain, not just the areas mentioned and measured here. So, one cannot draw any definitive conclusions other than the UNC and forceps minor does play some role in the communications leading to executive function abilities.

Socioemotional Functions and Preterm Very Low Birth Weight

Socioemotional processing and integration have also been found to be influenced by the uncinate fasciculus (Von Der Heide et al., 2013). It is not something that this thesis measured or included but is an important factor to consider. Especially because preterm VLBW children and adolescents are somewhat delayed in socioemotional processing, often falling behind socially compared to their age matched peers (Lund et al., 2012). There could be many different reasons behind this outcome. One being that with lower uncinate fasciculus integrity and cortical deviations in areas responsible for interpreting social and/or emotional cues in faces, these children are more prone to misinterpret a social situation and respond in a way that is not considered appropriate by peers. In combination with executive dysfunction this possible deficit in social processing could be detrimental to a child’s social integration and development. For example, a twelve-year-old child is quite dependent on being able to learn and navigate an increasingly complex social world, with a disadvantage of slower learning and more social misinterpretations combined with a more anxious and withdrawn behavior (preterm phenotype), this would probably lead to an increasing social gap between the child and their peers.

By this conceptualization of social development in preterm VLBW individuals and the deficits found in associative learning, they would most likely also struggle more than their term-born peers with learning in social situations. Social knowledge is acquired over time and is one of the more important factors in how a person makes and sustains friends, essentially creating a place of social belonging (Lund et al., 2012; Olson et al., 2013). In VLBW individuals social knowledge is somewhat diminished (Alduncin et al., 2014). When considering this with a slower learning curve generally (Aanes et al., 2015), possibly extending to social norms and cues due to slower processing and diminished working memory, this combination of deficits could also explain some of the social delay among the VLBW cohorts.

The uncinate fasciculus is also connecting the frontal and temporal poles, responsible for social cognition and binding perceptual inputs to emotional responses respectively (Bludau et al., 2014; Granger et al., 2021; Olson et al., 2007). As well as the lateral orbitofrontal cortex which contributes to assessment of expected outcome in the form of possible consequences, both positive (rewards) and negative (punishments; Kringelbach & Rolls, 2004). It is therefore possible that when one of the connections binding these regions (like the uncinate fasciculus) is diminished, it affects the ability to evaluate emotional salience in different situations (Granger et al., 2021; Lund et al., 2012). It seems like updating of existing social knowledge due to new information or changes in the social rules is somewhat impaired with deficient emotional pattern separation (Granger et al., 2021). This would make it harder to adapt (and learn) in social situations as well, especially during childhood development. When this is seen in context with the other deficits often found in preterm VLBW cohorts, it could be another possible contributor to the delay in socioemotional functioning.

Considering all the factors brought up in regard to socioemotional processing difficulties in the preterm VLBW population, it supports the notion of a higher prevalence of autism spectrum disorder and/or ADHD in this group (Anderson et al., 2021; Franz et al., 2018; Lund et al., 2012). Mainly because many of these issues are also highly relevant for these psychopathologies, both in social behavior, cognitive deficits, and emotional processing.

Diminished emotional pattern separation could also be a possible contributor to the higher prevalence of depression and anxiety in the preterm VLBW population (Anderson et al., 2021; Lund et al., 2012; Olsen et al., 2018). However, it is more likely that this prevalence comes from an abundance of different reasons. Among others, the behavioral phenotype of this group is more prone to internalizing behaviors, in addition to a greater struggle with attention and memory, therefore falling more behind their peers academically and socially. Possibly experiencing some social consequences of a more distracted, impulsive, and more socially inappropriate behavioral style, being rejected, or even ridiculed. Based on this possibility of events developing anxiety, depression, or both would be likely (Lund et al., 2012).

Limitations

There are several limitations to this thesis. Firstly, the data used were gathered from several previous studies. Meaning that the data have been collected by different people at different times. Some of the factors the author would have liked to include, for a more extensive and complete analysis, were not measured and therefore only included through previous research literature. Having to adapt the analysis according to the variables available and collected previously. To improve the analysis, one could include factors such as attention/attentional control, social ability and belonging, and emotional memory. However, this would become an increasingly complicated study and would probably be very extensive and complex, reflecting a broader and perhaps more correct iteration of the VLBW group, while simultaneously it could become detrimental if not executed and interpreted correctly.

The variables measured and used here gives an interesting perspective and fairly uncomplicated interpretation, so to elaborate by performing a new study considering the limitations mentioned would be quite interesting. The data is also gathered at different timepoints in the cohorts lives. IQ measures were gathered at 20 years old, while the MRI measuring the white matter tracts were done at 26 years of age. This could have influenced the gathered data, at least partly, especially due to the often-found delay in cortical development within the preterm VLBW population (Sripada et al., 2018). Meaning that there might be slightly different IQ scores in the VLBW group at 26 as opposed to 20 years of age.

The second limitation is that the cohorts included were born in the late 80’s. The main reason this could be a limitation is that many of the treatment options from that time has been improved. Since white matter injury is most prone to happen due to postnatal morbidity, improved treatment should lower both prevalence and severity of this complication. Which might affect the long-term consequences for the preterm VLBW group, making results from earlier cohorts less generalizable for newer generations.

The third limitation is that preterm VLBW is used as a descriptive term, however it serves as a proxy for several different factors that could influence brain development (Rimol et al., 2019). There are many possibilities as to why a fetus is born preterm or with VLBW, one being inflammation leading to placental dysfunction which could affect brain development before birth and cause preterm birth, simultaneously creating a vulnerability to perinatal injury as a result of insufficient nutrition, stressors in the hospital, respiratory and circulatory problems etc. This and more could have detrimental effects on cortical development, of both grey and white matter. Such factors could have a substantial influence on the variables measured here, and it could therefore be beneficial to include high quality clinical data describing postnatal morbidity trying to statistically control for any influence affecting brain growth/development.

Conclusion

Based on the results revealed here, preterm VLBW adults significantly differ from their term-born controls in the white matter tracts uncinate fasciculus (left and right) and forceps minor. Further analysis showed that cognitive functions (as measured by full IQ) were significantly predicted by FA in the right uncinate fasciculus. However, the interaction analysis did show that cognitive functioning in the VLBW group was more affected by white matter integrity in the right UNC and forceps minor than their term-born controls. The VLBW group seems to be more dependent on white matter association tracts to solve cognitive tasks compared with controls. This could mean that, with the cortical deviations often found in this group, they utilize alternative functional networks in cognitive tasks.

Furthermore, processing speed in the VLBW group was especially affected, both by the right UNC and the forceps minor. Working memory was also found to be affected by the right UNC, while verbal comprehension was more affected by the forceps minor. The results in this thesis support the notion of preterm VLBW individuals being slower to process and integrate information, and having poorer working memory functions, as well as lower general cognitive functioning. However, more research is needed in order to draw any definitive conclusions from these findings and speculations.

.

References

Aanes, S., Bjuland, K. J., Skranes, J., & Løhaugen, G. C. C. (2015). Memory function and hippocampal volumes in preterm born very-low-birth-weight (VLBW) young adults. *Neuroimage*, *105*, 76-83. https://doi.org/10.1016/j.neuroimage.2014.10.023

Albert, D., & Steinberg, L. (2011). Age Differences in Strategic Planning as Indexed by the Tower of London. *Child Dev*, *82*(5), 1501-1517. https://doi.org/10.1111/j.1467-8624.2011.01613.x

Alduncin, N., Huffman, L. C., Feldman, H. M., & Loe, I. M. (2014). Executive function is associated with social competence in preschool-aged children born preterm or full term. *Early Hum Dev*, *90*(6), 299-306. https://doi.org/10.1016/j.earlhumdev.2014.02.011

Ameis, S. H., & Catani, M. (2015). Altered white matter connectivity as a neural substrate for social impairment in Autism Spectrum Disorder. *Cortex, 62*, 158-181. https://doi.org/10.1016/j.cortex.2014.10.014

Amina, S. (2014). Uncus. In R. B. Daroff & M. J. Aminoff (Eds.), *Encyclopedia of the neurological sciences* (2 ed., pp. 582-583). Academic press.

Anderson, P. J. (2008). Towards a developmental model of executive function. In V. Anderson, R. Jacobs, & P. J. Anderson (Eds.), *Executive functions and the frontal lobes: A lifespan perspective* (pp. 3-22). Psychology Press.

Anderson, P. J., de Miranda, D. M., Albuquerque, M. R., Indredavik, M. S., Evensen, K. A. I., Van Lieshout, R., . . . Doyle, L. W. (2021). Psychiatric disorders in individuals born very preterm / very low-birth weight: An individual participant data (IPD) meta-analysis. *EClinicalMedicine*, *42*, 101216-101216. https://doi.org/10.1016/j.eclinm.2021.101216

Anderson, P. J., & Reidy, N. (2012). Assessing Executive Function in Preschoolers. *Neuropsychol Rev*, *22*(4), 345-360. https://doi.org/10.1007/s11065-012-9220-3

Anniko, M. K., Boersma, K., & Tillfors, M. (2018). Investigating the mediating role of cognitive emotion regulation in the development of adolescent emotional problems. *Nordic Psychology*, *70*(1), 3-16. https://doi.org/10.1080/19012276.2017.1323665

Assaf, Y., & Cohen, Y. (2013). Inferring Microstructural Information of White Matter from Diffusion MRI. In (pp. 185-208). https://doi.org/10.1016/B978-0-12-396460-1.00009-3

Back, S. A. (2014). Cerebral white and gray matter injury in newborns: new insights into pathophysiology and management. *Clinics in perinatology*, *41*(1), 1-24.

Back, S. A., Riddle, A., & McClure, M. M. (2007). Maturation-dependent vulnerability of perinatal white matter in premature birth. *Stroke, 38*(2), 724-730. https://doi.org/10.1161/01.STR.0000254729.27386.05

Basten, M., Jaekel, J., Johnson, S., Gilmore, C., & Wolke, D. (2015). Preterm Birth and Adult Wealth: Mathematics Skills Count. *Psychol Sci*, *26*(10), 1608-1619. https://doi.org/10.1177/0956797615596230

Best, J. R., Miller, P. H., & Naglieri, J. A. (2011). Relations between executive function and academic achievement from ages 5 to 17 in a large, representative national sample. *Learn Individ Differ*, *21*(4), 327-336. https://doi.org/10.1016/j.lindif.2011.01.007

Bhatia, K., Henderson, L., Yim, M., Hsu, E., & Dhaliwal, R. (2017). Diffusion tensor imaging investigation of uncinate fasciculus anatomy in healthy controls: description of a subgenual stem. *Neuropsychobiology*, *75*(3), 132-140.

Bhatia, K., Henderson, L. A., Hsu, E., & Yim, M. (2018). Reduced integrity of the uncinate fasciculus and cingulum in depression: A stem-by-stem analysis. *J Affect Disord*, *235*, 220-228. https://doi.org/10.1016/j.jad.2018.04.055

Bickart, K. C., Wright, C. I., Dautoff, R. J., Dickerson, B. C., & Barrett, L. F. (2011). Amygdala volume and social network size in humans (vol 14, pg 163, 2011). *Nature neuroscience*, *14*(9), 1217-1217. https://doi.org/10.1038/nn0911-1217e

Bjuland, K. J., Løhaugen, G. C. C., Martinussen, M., & Skranes, J. (2012). Cortical thickness and cognition in very-low-birth-weight late teenagers. *Early Hum Dev*, *89*(6), 371-380. https://doi.org/10.1016/j.earlhumdev.2012.12.003

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

Bjuland, K. J., Rimol, L. M., Løhaugen, G. C. C., & Skranes, J. (2014). Brain volumes and cognitive function in very-low-birth-weight (VLBW) young adults. *Eur J Paediatr Neurol*, *18*(5), 578-590. https://doi.org/10.1016/j.ejpn.2014.04.004

Bludau, S., Eickhoff, S. B., Mohlberg, H., Caspers, S., Laird, A. R., Fox, P. T., . . . Amunts, K. (2014). Cytoarchitecture, probability maps and functions of the human frontal pole. *Neuroimage*, *93*(Pt 2), 260-275. https://doi.org/10.1016/j.neuroimage.2013.05.052

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

Canto, C. B., Wouterlood, F. G., & Witter, M. P. (2008). What Does the Anatomical Organization of the Entorhinal Cortex Tell Us? *Neural Plast*, *2008*, 381243-381218. https://doi.org/10.1155/2008/381243

Collins, S. E., Thompson, D. K., Kelly, C. E., Yang, J. Y. M., Pascoe, L., Inder, T. E., . . . Anderson, P. J. (2021). Development of brain white matter and math computation ability in children born very preterm and full-term. *Developmental cognitive neuroscience*, *51*, 100987-100987. https://doi.org/10.1016/j.dcn.2021.100987

Crossman, A. R., & Neary, D. (2015). Cerebral Hemisphere and Cerebral Cortex. In *Neuroanatomy : an illustrated colour text* (5th ed., pp. 131-145). Churchill Livingstone.

Ebeling, U., & Cramon, D. v. (1992). Topography of the uncinate fascicle and adjacent temporal fiber tracts. *Acta Neurochir (Wien)*, *115*(3-4), 143-148. https://doi.org/10.1007/BF01406373

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

Fabri, M., Pierpaoli, C., Barbaresi, P., & Polonara, G. (2014). Functional topography of the corpus callosum investigated by DTI and fMRI. *World J Radiol*, *6*(12), 895-906. https://doi.org/10.4329/wjr.v6.i12.895

Fame, R. M., MacDonald, J. L., & Macklis, J. D. (2010). Development, specification, and diversity of callosal projection neurons. *Trends Neurosci*, *34*(1), 41-50. https://doi.org/10.1016/j.tins.2010.10.002

Feldman, H. M., Lee, E. S., Yeatman, J. D., & Yeom, K. W. (2012). Language and reading skills in school-aged children and adolescents born preterm are associated with white matter properties on diffusion tensor imaging. *Neuropsychologia*, *50*(14), 3348-3362. https://doi.org/10.1016/j.neuropsychologia.2012.10.014

Fischer, D. B., Perez, D. L., Prasad, S., Rigolo, L., O'Donnell, L., Acar, D., . . . Dworetzky, B. A. (2016). Right inferior longitudinal fasciculus lesions disrupt visual-emotional integration. *Soc Cogn Affect Neurosci*, *11*(6), 945-951. https://doi.org/10.1093/scan/nsw011

Franz, A. P., Bolat, G. U., Bolat, H., Matijasevich, A., Santos, I. S., Silveira, R. C., . . . Moreira-Maia, C. R. (2018). Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: A meta-analysis. *Pediatrics*, *141*(1), e20171645. https://doi.org/10.1542/peds.2017-1645

Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex : a journal devoted to the study of the nervous system and behavior.*, *86*, 186-204. https://doi.org/10.1016/j.cortex.2016.04.023

Friedman, N. P., Miyake, A., Altamirano, L. J., Corley, R. P., Young, S. E., Rhea, S. A., & Hewitt, J. K. (2016). Stability and Change in Executive Function Abilities From Late Adolescence to Early Adulthood: A Longitudinal Twin Study. *Dev Psychol*, *52*(2), 326-340. https://doi.org/10.1037/dev0000075

Ghashghaei, H. T., Hilgetag, C. C., & Barbas, H. (2007). Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *Neuroimage*, *34*(3), 905-923. https://doi.org/10.1016/j.neuroimage.2006.09.046

Giorgio, A., Watkins, K. E., Chadwick, M., James, S., Winmill, L., Douaud, G., . . . James, A. C. (2010). Longitudinal changes in grey and white matter during adolescence. *Neuroimage*, *49*(1), 94-103. https://doi.org/10.1016/j.neuroimage.2009.08.003

Goddings, A.-L., Roalf, D., Lebel, C., & Tamnes, C. K. (2021). Development of white matter microstructure and executive functions during childhood and adolescence: a review of diffusion MRI studies. *Developmental cognitive neuroscience*, *51*, 101008-101008. https://doi.org/10.1016/j.dcn.2021.101008

Goldstein, A., Covington, B. P., Mahabadi, N., & Mesfin, F. B. (2017). Neuroanatomy, corpus callosum.

Granger, S. J., Leal, S. L., Larson, M. S., Janecek, J. T., McMillan, L., Stern, H., & Yassa, M. A. (2021). Integrity of the uncinate fasciculus is associated with emotional pattern separation-related fMRI signals in the hippocampal dentate and CA3. *Neurobiol Learn Mem*, *177*, 107359-107359. https://doi.org/10.1016/j.nlm.2020.107359

Grill-Spector, K., Weiner, K. S., Gomez, J., Stigliani, A., & Natu, V. S. (2018). The functional neuroanatomy of face perception: From brain measurements to deep neural networks. *Interface Focus*, *8*(4), 20180013-20180013. https://doi.org/10.1098/rsfs.2018.0013

Guihard-Costa, A.-M., & Larroche, J.-C. (1990). Differential growth between the fetal brain and its infratentorial part. *Early Hum Dev*, *23*(1), 27-40. https://doi.org/10.1016/0378-3782(90)90126-4

Hau, J., Sarubbo, S., Houde, J. C., Corsini, F., Girard, G., Deledalle, C., . . . Petit, L. (2016). Revisiting the human uncinate fasciculus, its subcomponents and asymmetries with stem-based tractography and microdissection validation. *Brain Struct Funct*, *222*(4), 1645-1662. https://doi.org/10.1007/s00429-016-1298-6

Hearne, L. J., Mattingley, J. B., & Cocchi, L. (2016). Functional brain networks related to individual differences in human intelligence at rest. *Sci Rep*, *6*(1), 32328-32328. https://doi.org/10.1038/srep32328

Herbet, G., Zemmoura, I., & Duffau, H. (2018). Functional Anatomy of the Inferior Longitudinal Fasciculus: From Historical Reports to Current Hypotheses. *Front Neuroanat*, *12*, 77-77. https://doi.org/10.3389/fnana.2018.00077

Herlin, B., Navarro, V., & Dupont, S. (2021). The temporal pole: From anatomy to function—A literature appraisal. *J Chem Neuroanat*, *113*, 101925-101925. https://doi.org/10.1016/j.jchemneu.2021.101925

Hertrich, I., Dietrich, S., Blum, C., & Ackermann, H. (2021). The Role of the Dorsolateral Prefrontal Cortex for Speech and Language Processing. *Frontiers in human neuroscience*, *15*, 645209-645209. https://doi.org/10.3389/fnhum.2021.645209

Hodgetts, C. J., Postans, M., Shine, J. P., Jones, D. K., Lawrence, A. D., & Graham, K. S. (2015). Dissociable roles of the inferior longitudinal fasciculus and fornix in face and place perception. *Elife*, *4*(2015). https://doi.org/10.7554/eLife.07902

Hodgetts, C. J., Postans, M., Warne, N., Varnava, A., Lawrence, A. D., & Graham, K. S. (2017). Distinct contributions of the fornix and inferior longitudinal fasciculus to episodic and semantic autobiographical memory. *Cortex*, *94*, 1-14. https://doi.org/10.1016/j.cortex.2017.05.010

Horowitz-Kraus, T., Wang, Y., Plante, E., & Holland, S. K. (2014). Involvement of the right hemisphere in reading comprehension: A DTI study. *Brain Res*, *1582*(Sep), 34-44. https://doi.org/10.1016/j.brainres.2014.05.034

Huizinga, M., Dolan, C. V., & van der Molen, M. W. (2006). Age-related change in executive function: Developmental trends and a latent variable analysis. *Neuropsychologia*, *44*(11), 2017-2036. https://doi.org/10.1016/j.neuropsychologia.2006.01.010

Indredavik, M. S., Vik, T., Heyerdahl, S., Kulseng, S., Fayers, P., & Brubakk, A. M. (2004). Psychiatric symptoms and disorders in adolescents with low birth weight. *Arch Dis Child Fetal Neonatal Ed*, *89*(5), F445-F450. https://doi.org/10.1136/adc.2003.038943

Izquierdo, A., Brigman, J. L., Radke, A. K., Rudebeck, P. H., & Holmes, A. (2016). The neural basis of reversal learning: An updated perspective. *Neuroscience, 345*, 12-26. https://doi.org/10.1016/j.neuroscience.2016.03.021

Johannessen, T. (2022). *For Tidlig Fødsel*. Norsk Helse Informatikk. Retrieved 13.01 from https://nhi.no/familie/graviditet/svangerskap-og-fodsel/sykdommer/fodsel/for-tidlig-fodsel/

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

Kamali, A., Flanders, A. E., Brody, J., Hunter, J. V., & Hasan, K. M. (2013). Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. *Brain Struct Funct*, *219*(1), 269-281. https://doi.org/10.1007/s00429-012-0498-y

Kierońska, S., Sokal, P., Dura, M., Jabłońska, M., Rudaś, M., & Jabłońska, R. (2020). Tractography-based analysis of morphological and anatomical characteristics of the uncinate fasciculus in human brains. *Brain sciences, 10*(10), 1-15. https://doi.org/10.3390/brainsci10100709

Kinney, H. C. (2006). The Near-Term (Late Preterm) Human Brain and Risk for Periventricular Leukomalacia: A Review. *Semin Perinatol*, *30*(2), 81-88. https://doi.org/10.1053/j.semperi.2006.02.006

Kochunov, P., Williamson, D. E., Lancaster, J., Fox, P., Cornell, J., Blangero, J., & Glahn, D. C. (2010). Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. *Neurobiol Aging*, *33*(1), 9-20. https://doi.org/10.1016/j.neurobiolaging.2010.01.014

Koechlin, E. (2011). Frontal pole function: what is specifically human? *Trends Cogn Sci*, *15*(6), 241-241. https://doi.org/10.1016/j.tics.2011.04.005

Komaitis, S., Skandalakis, G. P., Kalyvas, A. V., Drosos, E., Lani, E., Emelifeonwu, J., . . . Koutsarnakis, C. (2020). Dorsal component of the superior longitudinal fasciculus revisited: Novel insights from a focused fiber dissection study. *J Neurosurg*, *132*(4), 1265-1278. https://doi.org/10.3171/2018.11.JNS182908

Korpela, S., Nyman, A., Munck, P., Ahtola, A., Matomäki, J., Korhonen, T., . . . Haataja, L. (2018). Working memory in very-low-birthweight children at the age of 11 years. *Child Neuropsychol*, *24*(3), 338-353. https://doi.org/10.1080/09297049.2016.1260101

Kringelbach, M. L., & Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. *Prog Neurobiol, 72*(5), 341-372. https://doi.org/10.1016/j.pneurobio.2004.03.006

Kumar, R., Nguyen, H. D., Macey, P. M., Woo, M. A., & Harper, R. M. (2012). Regional brain axial and radial diffusivity changes during development. *J. Neurosci. Res*, *90*(2), 346-355. https://doi.org/10.1002/jnr.22757

Latini, F., Mårtensson, J., Larsson, E.-M., Fredrikson, M., Åhs, F., Hjortberg, M., . . . Ryttlefors, M. (2017). Segmentation of the inferior longitudinal fasciculus in the human brain: A white matter dissection and diffusion tensor tractography study. *Brain Res, 1675*(1675), 102-115. https://doi.org/10.1016/j.brainres.2017.09.005

Laureys, F., De Waelle, S., Barendse, M. T., Lenoir, M., & Deconinck, F. J. A. (2022). The factor structure of executive function in childhood and adolescence. *Intelligence (Norwood), 90*, 101600. https://doi.org/10.1016/j.intell.2021.101600

Lebel, C., & Deoni, S. (2018). The development of brain white matter microstructure. *Neuroimage*, *182*, 207-218. https://doi.org/10.1016/j.neuroimage.2017.12.097

Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W., & Beaulieu, C. (2012). Diffusion tensor imaging of white matter tract evolution over the lifespan. *Neuroimage, 60*(1), 340-352. https://doi.org/10.1016/j.neuroimage.2011.11.094

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage, 40*(3), 1044-1055. https://doi.org/10.1016/j.neuroimage.2007.12.053

Lee Masson, H., Kang, H.-m., Petit, L., & Wallraven, C. (2017). Neuroanatomical correlates of haptic object processing: combined evidence from tractography and functional neuroimaging. *Brain Struct Funct, 223*(2), 619-633. https://doi.org/10.1007/s00429-017-1510-3

Lillo, P., Mioshi, E., Burrell, J. R., Kiernan, M. C., Hodges, J. R., & Hornberger, M. (2012). Grey and White Matter Changes across the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia Continuum. *PLoS One, 7*(8), e43993-e43993. https://doi.org/10.1371/journal.pone.0043993

Loe, I. M., Adams, J. N., & Feldman, H. M. (2019). Executive function in relation to white matter in preterm and full term children. *Front Pediatr, 6*, 418-418. https://doi.org/10.3389/fped.2018.00418

Lund, L. K., Vik, T., Lydersen, S., Løhaugen, G. C. C., Skranes, J., Brubakk, A.-M., & Indredavik, M. S. (2012). Mental health, quality of life and social relations in young adults born with low birth weight. *Health Qual Life Outcomes*, *10*(1), 146-146. https://doi.org/10.1186/1477-7525-10-146

Løhaugen, G. C. C., Gramstad, A., Evensen, K. A. I., Martinussen, M., Lindqvist, S., Indredavik, M., . . . Skranes, J. O. N. (2010). Cognitive profile in young adults born preterm at very low birthweight: Cognitive Profile in VLBW Young Adults. *Developmental medicine and child neurology*, *52*(12), 1133-1138. https://doi.org/10.1111/j.1469-8749.2010.03743.x

Mamah, D., Conturo, T. E., Harms, M. P., Akbudak, E., Wang, L., McMichael, A. R., . . . Csernansky, J. G. (2010). Anterior thalamic radiation integrity in schizophrenia: A diffusion-tensor imaging study. *Psychiatry Res*, *183*(2), 144-150. https://doi.org/10.1016/j.pscychresns.2010.04.013

Mamiya, P. C., Richards, T. L., & Kuhl, P. K. (2018). Right forceps minor and anterior thalamic radiation predict executive function skills in young bilingual adults. *Front Psychol*, *9*, 118-118. https://doi.org/10.3389/fpsyg.2018.00118

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

Marín-Padilla , M. (1997). Developmental Neuropathology and Impact of Perinatal Brain Damage. II: White Matter Lesions of the Neocortex. *J Neuropathol Exp Neurol*, *56*(3), 219-235. https://doi.org/10.1097/00005072-199703000-00001

McCauley, S. R., Wilde, E. A., Bigler, E. D., Chu, Z., Yallampalli, R., Oni, M. B., . . . Vásquez, A. C. (2011). Diffusion tensor imaging of incentive effects in prospective memory after pediatric traumatic brain injury. *Journal of neurotrauma*, *28*(4), 503-516.

McKenna, R., Rushe, T., & Woodcock, K. A. (2017). Informing the structure of executive function in children: A meta-analysis of functional neuroimaging data. *Front Hum Neurosci*, *11*, 154-154. https://doi.org/10.3389/fnhum.2017.00154

McMahon, W. W., & Oketch, M. (2013). Education's Effects on Individual Life Chances and On Development: An Overview. *British journal of educational studies*, *61*(1), 79-107. https://doi.org/10.1080/00071005.2012.756170

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to

Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cogn Psychol*, *41*(1), 49-100. https://doi.org/10.1006/cogp.1999.0734

Murray, A. L., Scratch, S. E., Thompson, D. K., Inder, T. E., Doyle, L. W., Anderson, J. F. I., & Anderson, P. J. (2014). Neonatal Brain Pathology Predicts Adverse Attention and Processing Speed Outcomes in Very Preterm and/or Very Low Birth Weight Children. *Neuropsychology*, *28*(4), 552-562. https://doi.org/10.1037/neu0000071

Murray, E. A., Graham, K. S., & Gaffan, D. (2005). Perirhinal cortex and its neighbours in the medial temporal lobe: Contributions to memory and perception. *Q J Exp Psychol B*, *58*(3-4), 378-396. https://doi.org/10.1080/02724990544000077

Nam, K. W., Castellanos, N., Simmons, A., Froudist-Walsh, S., Allin, M. P., Walshe, M., . . . Nosarti, C. (2015). Alterations in cortical thickness development in preterm-born individuals: Implications for high-order cognitive functions. *Neuroimage*, *115*, 64-75. https://doi.org/10.1016/j.neuroimage.2015.04.015

Northam, G. B., Liégeois, F., Chong, W. K., S. Wyatt, J., & Baldeweg, T. (2011). Total brain white matter is a major determinant of IQ in adolescents born preterm. *Annals of neurology*, *69*(4), 702-711.

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

Oishi, K., Faria, A. V., Hsu, J., Tippett, D., Mori, S., & Hillis, A. E. (2015). Critical role of the right uncinate fasciculus in emotional empathy. *Ann Neurol*, *77*(1), 68-74. https://doi.org/10.1002/ana.24300

Olsen, A., Dennis, E. L., Evensen, K. A. I., Husby Hollund, I. M., Løhaugen, G. C. C., Thompson, P. M., . . . Håberg, A. K. (2018). Preterm birth leads to hyper-reactive cognitive control processing and poor white matter organization in adulthood. *Neuroimage*, *167*, 419-428. https://doi.org/10.1016/j.neuroimage.2017.11.055

Olson, I. R., Heide, R. J. V. D., Alm, K. H., & Vyas, G. (2015). Development of the uncinate fasciculus: Implications for theory and developmental disorders. *Dev Cogn Neurosci*, *14*(C), 50-61. https://doi.org/10.1016/j.dcn.2015.06.003

Olson, I. R., McCoy, D., Klobusicky, E., & Ross, L. A. (2013). Social cognition and the anterior temporal lobes: A review and theoretical framework. *Soc Cogn Affect Neurosci*, *8*(2), 123-133. https://doi.org/10.1093/scan/nss119

Olson, I. R., Plotzker, A., & Ezzyat, Y. (2007). The Enigmatic temporal pole: a review of findings on social and emotional processing. *Brain*, *130*(7), 1718-1731. https://doi.org/10.1093/brain/awm052

Papagno, C., Miracapillo, C., Casarotti, A., Romero Lauro, L. J., Castellano, A., Falini, A., . . . Bello, L. (2011). What is the role of the uncinate fasciculus? Surgical removal and proper name retrieval. *Brain*, *134*(2), 405-414. https://doi.org/10.1093/brain/awq283

Pascual, B., Masdeu, J. C., Hollenbeck, M., Makris, N., Insausti, R., Ding, S.-L., & Dickerson, B. C. (2015). Large-scale brain networks of the human left temporal pole: A functional connectivity MRI study. *Cereb Cortex*, *25*(3), 680-702. https://doi.org/10.1093/cercor/bht260

Passingham, R. E., Stephan, K. E., & Kötter, R. (2002). The anatomical basis of functional localization in the cortex. *Nat Rev Neurosci*, *3*(8), 606-616. https://doi.org/10.1038/nrn893

Pelletier, J. G., Likhtik, E., Filali, M., & Paré, D. (2005). Lasting increases in basolateral amygdala activity after emotional arousal: Implications for facilitated consolidation of emotional memories. *Learn Mem*, *12*(2), 96-102. https://doi.org/10.1101/lm.88605

Perin, J., Mulick, A., Yeung, D., Villavicencio, F., Lopez, G., Strong, K. L., . . . Liu, L. (2022). Global, regional, and national causes of under-5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals. *The Lancet Child & Adolescent Health*, *6*(2), 106-115.

Qiu, M.-g., Ye, Z., Li, Q.-y., Liu, G.-j., Xie, B., & Wang, J. (2010). Changes of Brain Structure and Function in ADHD Children. *Brain Topogr*, *24*(3-4), 243-252. https://doi.org/10.1007/s10548-010-0168-4

Rimol, L. M., Bjuland, K. J., Løhaugen, G. C. C., Martinussen, M., Evensen, K. A. I., Indredavik, M. S., . . . Skranes, J. (2016). Cortical trajectories during adolescence in preterm born teenagers with very low birthweight. *Cortex*, *75*, 120-131. https://doi.org/10.1016/j.cortex.2015.12.001

Rimol, L. M., Botellero, V. L., Bjuland, K. J., Løhaugen, G. C. C., Lydersen, S., Evensen, K. A. I., . . . Skranes, J. (2019). Reduced white matter fractional anisotropy mediates cortical thickening in adults born preterm with very low birthweight. *Neuroimage*, *188*, 217-227. https://doi.org/10.1016/j.neuroimage.2018.11.050

Ripollés, P., Biel, D., Peñaloza, C., Kaufmann, J., Marco-Pallarés, J., Noesselt, T., & Rodríguez-Fornells, A. (2017). Strength of temporal white matter pathways predicts semantic learning. *J Neurosci*, *37*(46), 11101-11113. https://doi.org/10.1523/JNEUROSCI.1720-17.2017

Riva-Posse, P., Choi, K. S., Holtzheimer, P. E., McIntyre, C. C., Gross, R. E., Chaturvedi, A., . . . Mayberg, H. S. (2014). Defining Critical White Matter Pathways Mediating Successful Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression. *Biol Psychiatry*, *76*(12), 963-969. https://doi.org/10.1016/j.biopsych.2014.03.029

Rose, S. A., Feldman, J. F., Jankowski, J. J., & Van Rossem, R. (2011). Basic information processing abilities at 11 years account for deficits in IQ associated with preterm birth. *Intelligence*, *39*(4), 198-209. https://doi.org/10.1016/j.intell.2011.03.003

Schurr, R., Zelman, A., & Mezer, A. A. (2020). Subdividing the superior longitudinal fasciculus using local quantitative MRI. *Neuroimage*, *208*, 116439-116439. https://doi.org/10.1016/j.neuroimage.2019.116439

Shiotsu, D., Jung, M., Habata, K., Kamiya, T., Omori, I. M., Okazawa, H., & Kosaka, H. (2021). Elucidation of the relationship between sensory processing and white matter using diffusion tensor imaging tractography in young adults. *Scientific reports*, *11*(1), 12088-12088. https://doi.org/10.1038/s41598-021-91569-6

Skranes, J., Løhaugen, G. C., Martinussen, M., Indredavik, M. S., Dale, A. M., Haraldseth, O., . . . Brubakk, A.-M. (2009). White matter abnormalities and executive function in children with very low birth weight. *Neuroreport*, *20*(3), 263-266. https://doi.org/10.1097/WNR.0b013e32832027fe

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

Skranes, J., Vangberg, T. R., Kulseng, S., Indredavik, M. S., Evensen, K. A. I., Martinussen, M., . . . Brubakk, A. M. (2007). Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain*, *130*(3), 654-666. https://doi.org/10.1093/brain/awm001

Sripada, K., Bjuland, K. J., Sølsnes, A. E., Håberg, A. K., Grunewaldt, K. H., Løhaugen, G. C., . . . Skranes, J. (2018). Trajectories of brain development in school-age children born preterm with very low birth weight. *Sci Rep*, *8*(1), 15553-15514. https://doi.org/10.1038/s41598-018-33530-8

Sølsnes, A. E., Grunewaldt, K. H., Bjuland, K. J., Stavnes, E. M., Bastholm, I. A., Aanes, S., . . . Rimol, L. M. (2015). Cortical morphometry and IQ in VLBW children without cerebral palsy born in 2003-2007. *Neuroimage Clin*, *8*(C), 193-201. https://doi.org/10.1016/j.nicl.2015.04.004

Sølsnes, A. E., Sripada, K., Yendiki, A., Bjuland, K. J., Østgård, H. F., Aanes, S., . . . Skranes, J. (2016). Limited microstructural and connectivity deficits despite subcortical volume reductions in school-aged children born preterm with very low birth weight. *Neuroimage*, *130*, 24-34. https://doi.org/10.1016/j.neuroimage.2015.12.029

Theodoraki, T. E., McGeown, S. P., Rhodes, S. M., & MacPherson, S. E. (2020). Developmental changes in executive functions during adolescence: A study of inhibition, shifting, and working memory. *Br J Dev Psychol*, *38*(1), 74-89. https://doi.org/10.1111/bjdp.12307

Thomas, C., Avram, A., Pierpaoli, C., & Baker, C. (2015). Diffusion MRI properties of the human uncinate fasciculus correlate with the ability to learn visual associations. *Cortex*, *72*, 65-78. https://doi.org/10.1016/j.cortex.2015.01.023

Tulsky, D. S., Saklofske, D. H., Chelune, G. J., Heaton, R. K., Ivnik, R. J., Bornstein, R., . . . Ledbetter, M. F. (2003). *Clinical Interpretation of the WAIS-III and WMS-III*. San Diego: Elsevier Science & Technology.

Twilhaar, E. S., de Kieviet, J. F., Aarnoudse-Moens, C. S. H., van Elburg, R. M., & Oosterlaan, J. (2018). Academic performance of children born preterm: a meta-analysis and meta-regression. *Arch Dis Child Fetal Neonatal Ed*, *103*(4), F322-330. https://doi.org/10.1136/archdischild-2017-312916

Unger, A., Alm, K. H., Collins, J. A., O’Leary, J. M., & Olson, I. R. (2016). Variation in White Matter Connectivity Predicts the Ability to Remember Faces and Discriminate Their Emotions. *J Int Neuropsychol Soc*, *22*(2), 180-190. https://doi.org/10.1017/S1355617715001009

Urger, S. E., De Bellis, M. D., Hooper, S. R., Woolley, D. P., Chen, S. D., & Provenzale, J. (2015). The Superior Longitudinal Fasciculus in Typically Developing Children and Adolescents: Diffusion Tensor Imaging and Neuropsychological Correlates. *J Child Neurol*, *30*(1), 9-20. https://doi.org/10.1177/0883073813520503

Van Ettinger-Veenstra, H., Widén, C., Engström, M., Karlsson, T., Leijon, I., & Nelson, N. (2017). Neuroimaging of decoding and language comprehension in young very low birth weight (VLBW) adolescents: Indications for compensatory mechanisms. *PLoS One*, *12*(10), e0185571-e0185571. https://doi.org/10.1371/journal.pone.0185571

Volpe, J. J. M. D. (2009). Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol, 8*(1), 110-124. https://doi.org/10.1016/S1474-4422(08)70294-1

Von Der Heide, R. J., Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: Disorders, controversies and a hypothesis. *Brain, 136*(6), 1692-1707. https://doi.org/10.1093/brain/awt094

Wallois, F., Routier, L., & Bourel-Ponchel, E. (2020). Impact of prematurity on neurodevelopment. In *Handbook of clinical neurology* (Vol. 173, pp. 341-375). Elsevier.

Wang, X., Pathak, S., Stefaneanu, L., Yeh, F.-C., Li, S., & Fernandez-Miranda, J. C. (2015). Subcomponents and connectivity of the superior longitudinal fasciculus in the human brain. *Brain Struct Funct, 221*(4), 2075-2092. https://doi.org/10.1007/s00429-015-1028-5

Wasserman, J. D. (2018). A history of intelligence assessment: The unfinished tapestry. In *Contemporary intellectual assessment: Theories, tests, and issues, 4th ed.* (pp. 3-55). The Guilford Press.

Weisglas-Kuperus, N., Hille, E. T. M., Duivenvoorden, H. J., Finken, M. J. J., Wit, J. M., van Buuren, S., . . . Verloove-Vanhorick, S. P. (2009). Intelligence of very preterm or very low birthweight infants in young adulthood. *Arch Dis Child Fetal Neonatal Ed, 94*(3), F196-F200. https://doi.org/10.1136/adc.2007.135095

Wellman, L. L., Forcelli, P. A., Aguilar, B. L., & Malkova, L. (2016). Bidirectional control of social behavior by activity within basolateral and central amygdala of primates. *J Neurosci, 36*(33), 8746-8756. https://doi.org/10.1523/JNEUROSCI.0333-16.2016

Wu, Y., Sun, D., Wang, Y., Wang, Y., & Ou, S. (2016). Segmentation of the cingulum bundle in the human brain: A new perspective based on DSI tractography and fiber dissection study. *Front Neuroanat, 10,* 84-84. https://doi.org/10.3389/fnana.2016.00084

Wycoco, V., Shroff, M., Sudhakar, S., & Lee, W. (2013). White matter anatomy: what the radiologist needs to know. *Neuroimaging Clinics, 23*(2), 197-216.

Yang, Y., & Wang, J.-Z. (2017). From structure to behavior in basolateral amygdala-hippocampus circuits. *Front Neural Circuits, 11,* 86-86. https://doi.org/10.3389/fncir.2017.00086

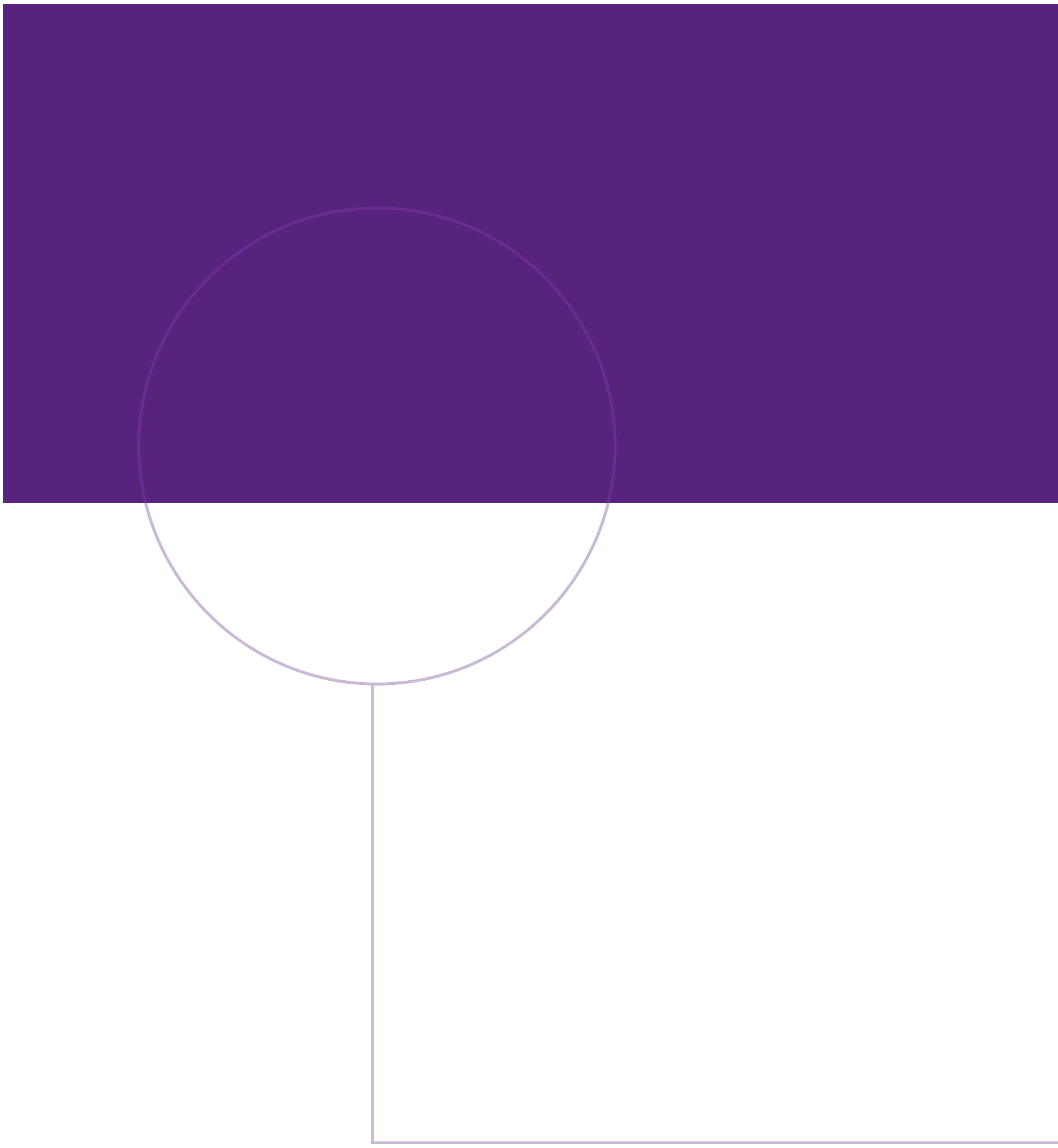
Yendiki, A., Panneck, P., Srinivasan, P., Stevens, A., Zöllei, L., Augustinack, J., . . . Fischl, B. (2011). Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. *Front Neuroinform*, *5*, 23-23. https://doi.org/10.3389/fninf.2011.00023

Zhang, Y., Inder, T. E., Neil, J. J., Dierker, D. L., Alexopoulos, D., Anderson, P. J., & Van Essen, D. C. (2015). Cortical structural abnormalities in very preterm children at 7 years of age. *Neuroimage*, *109*, 469-479. https://doi.org/10.1016/j.neuroimage.2015.01.005

Zhou, S.-Y., Suzuki, M., Hagino, H., Takahashi, T., Kawasaki, Y., Nohara, S., . . . Kurachi, M. (2003). Decreased volume and increased asymmetry of the anterior limb of the internal capsule in patients with schizophrenia. *Biol Psychiatry*, *54*(4), 427-436. https://doi.org/10.1016/S0006-3223(03)00007-6

Østgård, H. F., Løhaugen, G. C. C., Bjuland, K. J. D. M. V., Rimol, L. M., Brubakk, A.-M. M. D., Martinussen, M. M. D., . . . Skranes, J. (2014). Brain Morphometry and Cognition in Young Adults Born Small for Gestational Age at Term. *J Pediatr*, *165*(5), 921-927.e921. https://doi.org/10.1016/j.jpeds.2014.07.045

Østgård, H. F., Sølsnes, A. E., Bjuland, K. J., Rimol, L. M., Martinussen, M., Brubakk, A.-M., . . . Løhaugen, G. C. C. (2016). Executive function relates to surface area of frontal and temporal cortex in very-low-birth-weight late teenagers. *Early Hum Dev*, *95*, 47-53. https://doi.org/10.1016/j.earlhumdev.2016.01.023



NTNU
Norwegian University of
Science and Technology