Lifespan trajectories of corpus callosum:
Regional differences and cognitive relevance

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Abstract

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The thesis collected data from three projects coordinated by the research center for Lifespan Changes in Brain and Cognition (LCBC) at the Department of Psychology, University of Oslo (UiO). I have been involved in the data collection of all projects as an employed research assistant. A short version of the present thesis has been submitted to a scientific journal and is currently under revision. The preprint is available as "Danielsen, V. M., Pineiro, D. V., Mowinckel, A. M., Sederevicius, D., Fjell, A. M., Walhovd, K. B., & Westerhausen, R. (2020). Lifespan trajectories of relative corpus callosum thickness: regional differences and cognitive relevance. *PsyArXiv Preprints*. doi:https://doi.org/10.31234/osf.io/v58s4"

Objectives: The thesis revisit the topic of hemispheric interconnectivity and structural development of the corpus callosum by addressing the issue of proportionality. As the proportionality of callosal growth and decline compared to other brain size measures have been greatly disregarded in the literature, the study aims to give a descriptive account of relative callosal thickness across the lifespan. In addition, the study examines regional differences in lifespan trajectories and possible cognitive consequences of changes in relative callosal thickness.

Methods and participants: The study has a mixed longitudinal and cross-sectional design with a sample consisting of 1867 observations from 1014 healthy participants (age range from 4 to 93 years). Data was collected from three studies coordinated by the Lifespan Changes in Brain and Cognition (LCBC) research center. A measure of callosal thickness was determined on the midsagittal surface of T1-weighted magnetic resonance (MR) images. Relative callosal thickness was estimated by relating 60 callosal thickness segments to forebrain volume. Age trajectories were identified by a cluster analysis and then fitted using generalized additive mixed models (GAMM). Cognitive measures were collected from raw scores on Matrix Reasoning and Vocabulary subtests from either WPPSI/WASI. Finally, a

mediation analysis was completed with the identified age trajectories, change in age and cognitive measures.

Results: The study demonstrates an over-proportional increase of relative callosal thickness in the first three decades of life, mirrored by an over-proportional decline after 60 years of age. Regional specific lifespan trajectories were identified from a five-cluster solution. These trajectories differ substantially on the anterior to posterior division with the most prominent difference being an accentuated growth during development and a ten-year delay of decline in relative callosal thickness for posterior regions (splenium). Significant mediation effects were found for two of the mediation analyses demonstrating that the ventral splenium significantly mediates age-related changes in cognitive performance on both subtests Matrix Reasoning and Vocabulary.

Conclusion: The findings does not only confirm an inverted-u-shaped trajectory of callosal size across the lifespan but demonstrate that this growth and decline in callosal size is over-proportional to what could be expected by change in other brain sizes. It also found that increased relative callosal thickness in posterior callosal regions has beneficial consequences for higher-order cognition. Furthermore, the thesis argues that the observed regional specific callosal trajectories could serve as a segmentation procedure for callosal subdivision as it secures adequate relation between callosal structure and function. Additional research on relative callosal measures are necessary to reaffirm the merits of the current analysis, but it does indicate that analyzing the proportionality of callosal size across the lifespan offers valuable insight into the development of hemispheric interconnectivity, as well as its cognitive consequences. To further advance on this knowledge, future work should also prioritize research on clinical populations in order to investigate atypical brain development.

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1. Introduction

1.1. Hemispheric asymmetry and the need for interconnectivity

Considering that the human brain is perceived as a highly complex cognitive processing unit, one of the most central challenges in the scientific field of cognitive neuroscience is understanding the nature of these cognitive systems and their neural substrates (Baynes, Eliassen, Lutsep, & Gazzaniga, 1998; McClelland & Ralph, 2015). The evolvement of the cerebral cortex is recognized as fundamental for human intelligence and complex problem-solving capacities (Hofman, 2019; Roth & Dicke, 2005). Divided by the medial longitudinal fissure, the cerebral cortex consists of the left and right hemispheres. These are specialized for different cognitive functions and receive different sensory information (Baynes et al., 1998; Grant, 2015; Ocklenburg, 2018). The functionally specialized hemispheres are strongly connected by interhemispheric commissures; White matter tracts crossing the medial longitudinal fissure and ensuring communication between the cerebral hemispheres. In this way, the cerebral cortex is able to integrate information from both hemispheres resulting in coherent and seemingly inseparable cognitive functions and perception (Baynes et al., 1998; van Der Knaap & van Der Ham, 2011). It can be postulated that the complexity of the human brain relies on its connectivity between cerebral regions (Paul et al., 2007). The human forebrain contains three major commissures, which are the anterior commissure, the hippocampal commissure and the corpus callosum. Corpus callosum is the largest and most important interhemispheric commissure as it connects almost all cortical areas (van Der Knaap & van Der Ham, 2011).

Functional cerebral specialization and lateralization was first demonstrated by early behavioral experiments on split-brain patients (Gazzaniga, 2000, 2005; Reuter-Lorenz & Miller, 1998). Split-brain patients are individuals with surgical resected interhemispheric commissures, including a partial or total severing of the corpus callosum (Paul et al., 2007). This line of research illustrates that the left hemisphere is roughly known to be specialized for language and speech, as well as essential problem-solving capacities, while the right hemisphere is more involved in visuospatial processing and facial recognition (Gazzaniga, 2000, 2005; 2014, pp. 135-145; Reuter-Lorenz & Miller, 1998). Furthermore, split-brain research has made it evident that interhemispheric transferring and integration of information through the corpus callosum is essential for human perception and cognition. For instance, neurologically intact individuals perform superior to split-brain patients on several cognitive

measures (Kreuter, Kinsbourne, & Trevarthen, 1972; Zaidel & Sperry, 1974). This has been attributed to the capability of neurologically intact individuals to coordinate and distribute information between the cerebral hemispheres and in particular through the major callosal commissure (Belger & Banich, 1998). Zaidel and Sperry (1974) also found impaired short-term memory in patients with a partly resected corpus callosum indicating that both partly and total resection of corpus callosum have functional consequences. Although split-brain research has provided valuable insight to cerebral specialization and hemispheric interconnectivity, contributions are complicated by the frequent preexistence of seizure disorders and varying extent of white matter resected (Gazzaniga, 2014, p. 134; Paul et al., 2007; Zaidel & Sperry, 1974).

Research on patients with agenesis, that is individuals with a brain malformation resulting in a partial or total absence of the corpus callosum, does not provide clear support for cerebral specialization or consistently result in disconnection syndrome similar to that seen in split-brain patients (Banich & Brown, 2000; Paul et al., 2007). Compared to split-brain patients whom mostly undergo surgery in adult life, patients with agenesis are born with a resected callosal commissure. Hence, neural plasticity processes in early brain development might contribute to establishing alternative neural pathways and, in this way, securing brain functioning. However, although patients with agenesis do not mirror the disconnection syndrome, research does find a general pattern of impaired neuropsychological functioning, in particular for higher order cognition and social skills (Paul et al., 2007). Overall, research on clinical populations such as split-brain patients and patients with agenesis support the integrative role of the corpus callosum in interhemispheric transfer of information. It also suggests that callosal disconnection results in impaired cognitive performance.

Lateralization of cognitive functions is seen as a hallmark of human functional brain organization (Banich & Brown, 2000). However, more recent research on cerebral specialization and lateralization suggest that hemispheric asymmetry and interconnectivity require a more nuanced understanding than first assumed. Although brain lesion studies and studies using advanced imaging techniques support the general tendency of left-hemispheric language dominance (Knecht et al., 2000; Ojemann & Ojemann, 1991; M. J. Pujol, Deus, Losilla, & Capdevila, 1999) and right-hemispheric dominance for spatial attention (Heilman & Abell, 1980; Pardo, Fox, & Raichle, 1991; Weintraub & Mesulam, 1987) in the majority of the population, there is a small proportion of the population with an atypical hemispheric asymmetry (Carey, Johnstone, & Carey, 2014; Knecht et al., 2000). That is, an opposite left

and right hemispheric lateralization pattern. Cai, Haegen, and Brysbaert (2013) suggested a causal origin to this complementary specialization of language production and spatial attention. They argued that the lateralization of language causes the opposite lateralization of spatial attention, or the other way around. However, the framework introduced by Cai et al. (2013) is complicated by research showing the existence of language and spatial attention lateralizing to the same hemisphere in some healthy humans (Flöel et al., 2001). Hence, the left-hemispheric language dominance and right-hemispheric dominance for spatial attention is not an invariable characteristic of human brain organization.

Additionally, certain perceptual or cognitive functions are represented in both hemispheres. This illustrates how specialization of the hemispheres is relative, rather than absolute (Banich, 1998a). For instance, visual information is in general projected to the contralateral hemisphere. Stimuli shown to the right visual field are projected to the left hemisphere, while stimuli presented in the left visual field are projected to the right hemisphere. This information is later integrated through the hemispheric commissures to present the complete visual field perceived by the brain (Gazzaniga, 2014, pp. 121-122, 186). However, humans have a retinal nasotemporal overlap of approximately 1 degree in their visual midline, which project information to both hemispheres. This retinal nasotemporal overlap results in parts of the fovea being represented in both cerebral hemispheres and does not require interhemispheric commissures to transfer and integrate information (Fendrich & Gazzaniga, 1989; Fendrich, Wessinger, & Gazzaniga, 1996; Gazzaniga, 2000; Marzi, Mancini, Sperandio, & Savazzi, 2009).

Furthermore, although it is common to refer to left and right hemispheric dominance for cognitive functions, neuroimaging and neuropsychological research make way for a reconceptualizing of this absolute duality (Vyacheslav, Maurizio, & Michel Thiebaut de, 2019). Recent studies suggest the existence of functional epicentres for cognitive functions. These epicenters are located in different hemispheres, while supported by large neural networks across the cerebral cortex. To solve complex cognitive tasks, the networks involving several structural brain regions are dependent on interhemispheric communication to cooperate and integrate information (Maurizio, 1998; Mesulam, 1998; Nobre & Plunkett, 1997). Language lateralization is one of the major topics in research on functional hemispheric asymmetries. Although many aspects of language processing are controlled by the left hemisphere in the majority of the population, there is also a right hemispheric neural contribution to language (Friederici, Von Cramon, & Kotz, 2007; Specht, 2014). Consequently, some representation of language would still be present in each of the

hemispheres despite a resected callosum. This has been demonstrated by the hemispheric dissociation between written and spoken language in callosotomy patients (Baynes et al., 1998). In addition, a study by Friederici et al. (2007) found evidence of a right hemispheric involvement for linguistic prosody and a left lateralization of phonemic segmental information. Both functions are important to spoken language comprehension but are still represented in the opposite hemispheres. Combined, the notion of cognitive neural networks across the cerebral cortex make the study of hemispheric interconnectivity and human cognition particularly intricate.

The mechanisms underlaying cerebral specialization and lateralization are still partly unknown**,** though it has been suggested there is an evolutionary advantage to the evolvement of hemispheric asymmetry and interconnectivity (Hopkins & Cantalupo, 2008). Evolutionary psychologists have hypothesized that increased demands on limited cortical space resulted in a process of natural selection where only one of the cerebral hemispheres was modified. As this specialization happened, cortical regions that were previously dedicated to certain functions became co-opted. Interhemispheric commissures were ensuring that important information could still be integrated. This entails, there was no overall loss of performance because these former functions were still supported by the other hemisphere and integrated through the commissures. The result is reduced cortical redundancy, as the specialization of the cerebral hemispheres leads to an extension of cortical capacity (Gazzaniga, 2000).

Although functional hemispheric specialization has obvious benefits, it also comes with a cost. The work of Banich and colleagues (Banich & Belger, 1990, 1991; Banich & Brown, 2000; Belger & Banich, 1992, 1998) suggest that callosal integration allow distribution of computations between the hemispheres. In this way, corpus callosum contributes to increasing the brain's information processing power, as compared to unilateral hemispheric activation. However, transferring information through callosal nerve fibers have two important costs: it is time-consuming and pieces of the information might be lost in the process (Banich, 1998b; Banich & Belger, 1991; Belger & Banich, 1998). A series of studies suggested that bilateral hemispheric activation is more essential for complex cognitive tasks as compared to simpler tasks (Banich & Belger, 1990; Belger & Banich, 1992, 1998). This pattern might reflect a cost-benefit analysis where the benefits of interhemispheric communication outweigh the costs for complex tasks that one hemisphere is not able to solve by itself. In simpler tasks, on the other hand, the costs of bilateral hemispheric activation and callosal integration would be greater than the benefits of increased processing power (Belger & Banich, 1998).

Interhemispheric efficiency might also be related to ageing processes. There is evidence of a larger bilateral advantage in older children compared to younger children (Banich & Brown, 2000; Banich, Passarotti, & Janes, 2000). Cabeza et al. (1997) also report that elderly are more likely to show bilateral activation for cognitive tasks, as compared to younger adults. This data could reflect changes in interhemispheric efficiency across the lifespan. It is possible that older children and young adults have less costs to interhemispheric integration compared to younger children. However, the bilateral activation found in older adults have also been tied to a possible reduced capacity of unilateral hemispheric processing (Banich & Brown, 2000). Banich and Brown (2000), however, suggested that the dynamic relationship between costs and benefits of bilateral hemispheric activation could also reflect changes in callosal transfer efficiency.

1.2 The Corpus Callosum: Enabler of interhemispheric communication

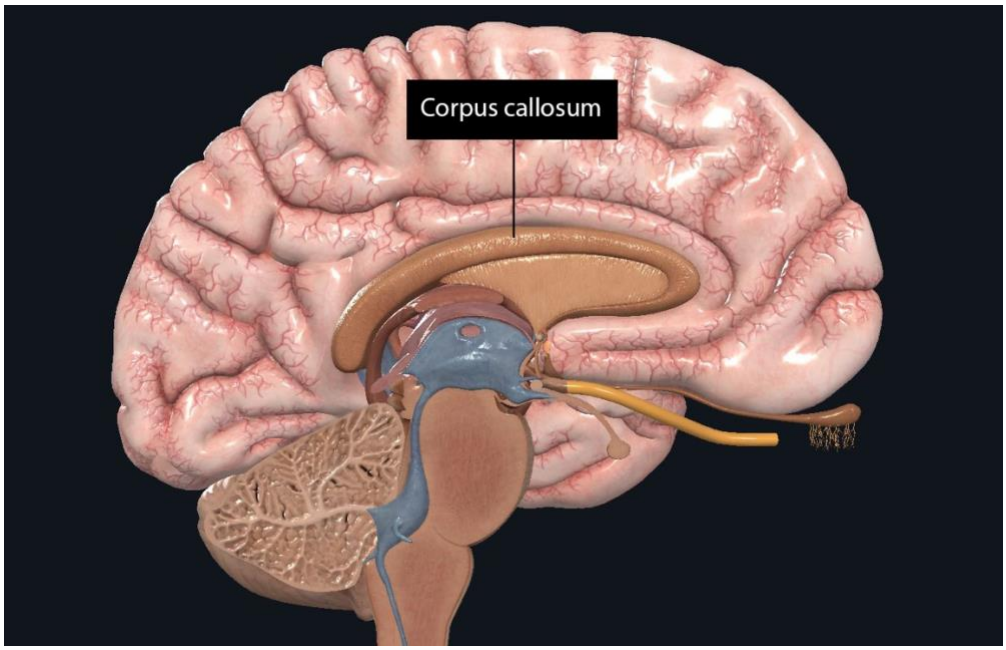
Given that interhemispheric communication is essential for human perception and cognition (Banich, 1998a; Gazzaniga, 2000; Glickstein & Berlucchi, 2008), it is natural to further examine the structure and functional organization of the corpus callosum to understand how it enables such interaction.

With its more than 200 million axons and axon collaterals, the corpus callosum is responsible for the majority of information transferred between the cerebral hemispheres (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Banich, 1998a; Gazzaniga, 2000; Tomasch, 1954). The major connective structure is located just above the lateral ventricles, near the center of the brain, and runs along the longitudinal fissure (Gazzaniga, 2014, p. 128; Rakic & Yakovlev, 1968). As callosal fibers interconnect close to all cortical areas of the human forebrain, the corpus callosum is able to transfer both sensory, motor and higher-order information (Gazzaniga, 2014, p. 128; Schmahmann & Pandya, 2006). It has been suggested that corpus callosum is in fact the only interhemispheric connection able to transfer higher-order information. This might indicate a more vulnerable relationship between callosal functioning and cognitive abilities typically associated with the frontal lobe, such as complex problem solving, as compared to more rudimentary sensory input (Banich, 1998a; Gazzaniga, 2000).

From the midsagittal plane the corpus callosum has a distinct C-shape (illustrated in Fig. 1a) and the callosal structure is commonly divided into different subsections. Most described subsections are the rostrum and the genu at the anterior end of the structure,

followed by the body, including the truncus and isthmus, and finally the splenium at the posterior end. However, the boundaries between the subregions are arbitrary and difficult to define due to the lack of clear macroanatomical landmarks and boundaries (Rauch & Jinkins, 1994; van Der Knaap & van Der Ham, 2011).

Figure 1 a)



b)

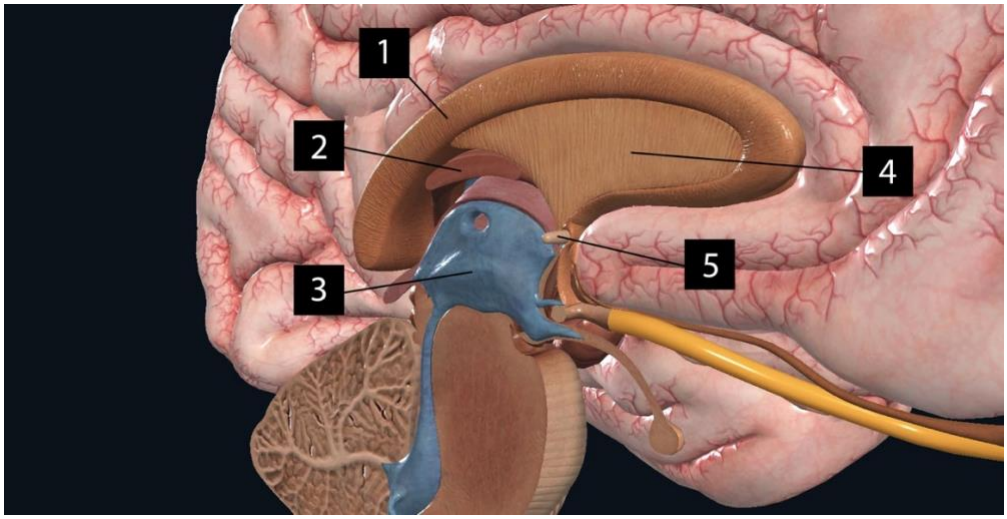


Figure 1. A) Illustration of the distinct C-shape of the corpus callosum on the midsagittal surface. *B)* Image showing the location of the corpus callosum in relation to other anatomical brain structures in the midsagittal plane: 1. Corpus callosum, 2. Commissure of Fornix, 3. The third ventricle, 4. Septum Pellucidum, 5. Anterior commissure. Image courtesy of Complete Anatomy

The corpus callosum has an anterior-posterior functional topographical organization which is consistent with the topography of the cerebral cortex (Pandya & Seltzer, 1986; van Der Knaap & van Der Ham, 2011; Zarei et al., 2006). The notion of a functional topographical mapping of the corpus callosum was first demonstrated in electrophysical and anatomical tracing studies of nonhuman primates (Pandya, Karol, & Heilbronn, 1971) and in early human lesion studies (de Lacoste, Kirkpatrick, & Ross, 1985). It has later been supported by studies using noninvasive diffusion magnetic resonance imaging (Abe et al., 2004; Dougherty et al., 2005; Hofer & Frahm, 2006; Zarei et al., 2006) and functional magnetic resonance imaging (fMRI) (Fabri & Polonara, 2013; Fabri, Polonara, Mascioli, Salvolini, & Manzoni, 2011). Combined, these studies demonstrate that anterior callosal fibers interconnect frontal cortical areas and are involved in higher order cognition and the transfer of motor information. In contrast, posterior fibers encompass interconnections between the parietal, temporal and occipital lobes and are roughly responsible for the integration of somatosensory information through the callosal posterior midbody, auditory information through the isthmus, and visual information through the splenium (Schmahmann & Pandya, 2006). However, this is further complicated by the finding that the corpus callosum contains both homotopical and heterotypical nerve fibers (de Lacoste et al., 1985; Gazzaniga, 2014, p. 128). Meaning, the corpus callosum transfer information to both corresponding and different brain regions in the contralateral hemisphere. In short, corticocallosal specific connections transfer information between equivalent parts of the cerebral hemispheres (Banich, 1998a; Zarei et al., 2006), while heterotypical nerve fibers connect different cortical areas (Hofer & Frahm, 2006).

Furthermore, callosal fibers vary in both number, diameter and degree of myelination based on regional location. Thinner and less myelinated axons are situated in anterior callosal regions, while posterior sections consists largely of thicker highly myelinated nerve fibers (Aboitiz et al., 1992; Björnholm et al., 2017). The size of the nerve fibers is also related to interhemispheric transfer time. Thicker callosal fibers are faster compared to less myelinated and thinner axons (Aboitiz et al., 1992; Ulusoy et al., 2004). The function of callosal fibers on the contralateral hemisphere has been debated. A review by Bloom and Hynd (2005) suggest that callosal nerve fibers are primarily excitatory in promoting interhemispheric integration, but some nerve fibers also seem to be involved in inhibiting the function of the contralateral hemisphere.

During the last decades, a number of empirical studies have demonstrated individual differences in callosal morphology based on factors such as age, sex, handedness, degree of

handedness lateralization and brain size in both developmental and adult samples (J. M. Clarke & Zaidel, 1994; Driesen & Raz, 1995; Giedd et al., 1996; Hasan, Ewing-Cobbs, Kramer, Fletcher, & Narayana, 2008; Hasan, Kamali, et al., 2008; Luders, Cherbuin, et al., 2010; Prendergast et al., 2015; D. Salat, Ward, Kaye, & Janowsky, 1997; van Der Knaap & van Der Ham, 2011; Witelson, 1989).Witleson (1989) suggested that these individual differences in callosal morphology are related to hemispheric specialization and have functional consequences. The issue of sex differences especially has received a lot of scrutiny and findings are often controversial due to lack of consistency in findings between studies (van Der Knaap & van Der Ham, 2011). Contradictory findings are likely a result of methodological differences between studies, including a lack of controlling for brain sizes and differing approaches to partitioning the corpus callosum (S. Clarke, Kraftsik, Van Der Loos, & Innocenti, 1989; Hofer & Frahm, 2006; Smith, 2005; van Der Knaap & van Der Ham, 2011; Witelson, 1989).

1.3 Structural developmental: A lifespan perspective on the corpus callosum

It is widely recognized that the cerebral cortex undergoes significant changes in both white and grey matter across the lifespan (Tamnes et al., 2013; Westlye et al., 2010). As the corpus callosum has a central role in transferring information between the cerebral hemispheres, the question is whether age related changes in callosal morphology also have functional consequences during development. To investigate this, we first have to examine the structural growth and ageing of the corpus callosum.

The callosal commissure has a relatively long developmental trajectory (van Der Knaap & van Der Ham, 2011). It originates, together with other interhemispheric commissures, from the rostral wall of the embryonal telencephalon at approximately 10-11 weeks of gestation. Then, the callosal fibers form the callosal commissural plate and becomes distinct from the anterior commissure. At 18-20 weeks after gestation, the structure has a form and position similar to that of an adult (Rakic & Yakovlev, 1968). The prenatal anatomical direction of callosal developmental progression has been debated. Rakic and Yakovlev (1968) reported that the fibers extend in a rostral-caudal direction, meaning that anterior callosal sections develop before posterior areas. There is one exception being the rostrum which develop at a later stage than the splenium.

It is recognized that the number of callosal nerve fibers is fixed at birth (Luders, Thompson, & Toga, 2010). However, empirical evidence has established that the corpus

callosum undergoes significant structural changes in both size and shape across the entire lifespan. These structural changes seem to follow an inverted-u-shaped trajectory and are likely a result of axonal myelination, redirection and pruning (Hasan, Kamali, et al., 2008; Luders, Thompson, et al., 2010; Prendergast et al., 2015).

Rauch and Jinkins (1994) argued that even though the number of callosal nerve fibers are fixed at birth, the callosal size is underdeveloped compared to the size of the cerebral cortex. Studies demonstrate a significant increase in overall callosal size in the first period of life (Tanaka-Arakawa et al., 2015; Vannucci, Barron, & Vannucci, 2017). For instance, there has been demonstrated a doubling of callosal size in the first year of life alone (Vannucci et al., 2017). This rapid maturation in infancy and early childhood is believed to be due to substantial gain of axon myelination and might contribute to reducing the perceived early underdevelopment of corpus callosum compared to cerebral size (S. Clarke et al., 1989; Rauch & Jinkins, 1994; Tanaka-Arakawa et al., 2015; Vannucci et al., 2017). Furthermore, a recent MRI study by Vannucci et al. (2017) reported increased expansion of the genu compared to the splenium during the first six years of life. This indicate that the anterior-posterior wave of maturation continues into early postnatal development. There is some debate regarding the linearity of callosal growth during this early stage of life. Early studies suggested a linear increase in callosal size with age (Giedd et al., 1996). However, a more recent study by Tanaka-Arakawa et al. (2015) report a non-linear developmental trajectory of the corpus callosum.

During later childhood and adolescence, the rapid maturation seen in early childhood is followed by an increasingly decelerating growth (Ansado et al., 2015; Chavarria, Sanchez, Chou, Thompson, & Luders, 2014; S. Genc, Malpas, Ball, Silk, & Seal, 2018; Giedd et al., 1999; Luders, Cherbuin, et al., 2010; Luders, Thompson, et al., 2010; Tanaka-Arakawa et al., 2015; Westerhausen et al., 2016). There are also demonstrated regional differences in development during childhood and adolescence. In contrast to regional prenatal and early postnatal maturation, several studies demonstrate a more pronounced growth in the posterior sections compared to anterior callosal regions in later childhood and adolescence. (Giedd et al., 1999; Giedd et al., 1996; Luders, Thompson, et al., 2010; Vannucci et al., 2017; Westerhausen et al., 2016). However, not all reports are in agreement. For instance, Luders, Thompson, et al. (2010) and Ansado et al. (2015) agrees with the general trend of a posterior to anterior callosal maturation in this age group, but they also observed a positive correlation between age and increased callosal area in the genu, an anterior section of the corpus callosum.

Furthermore, histological, morphometric MRI and diffusion imaging studies suggest that callosal size peak in the third decade of life (Hasan et al., 2009; Lebel, Caverhill-Godkewitsch, & Beaulieu, 2010; Prendergast et al., 2015; J. Pujol, Vendrell, Junque, Marti-Vilalta, & Capdevila, 1993; Yeatman, Wandell, & Mezer, 2014). There is some disagreement between studies regarding what age callosal growth ends. For instance, J. Pujol et al. (1993) found evidence that the size of the corpus callosum increases until the mid-twenties, while Prendergast et al. (2015) recently reported the existence of callosal growth until at least the third and even fourth decade of life. This indicate that corpus callosum is one of the latest matured white matter structures in the human brain (Giedd et al., 1996). There are also indication of different development peaks for different callosal sections as one study observed that the genu and isthmus reached peak area values first, followed by the body, the splenium and finally the rostrum (Prendergast et al., 2015).

Structural callosal changes in the period between the third and seventh decade of life is less investigated. A longitudinal study by Raz, Ghisletta, Rodrigue, Kennedy, and Lindenberger (2010) indicates that following the third decade of life, there is a phase of relative stability with regards to structural changes in the corpus callosum. This is further supported by the early works of Rauch and Jinkins (1994). These studies did not consider regional differences in the connective structure.

It is well established that ageing is related to deterioration in brain structure (Allen, Bruss, Brown, & Damasio, 2005; Giorgio et al., 2010; Walhovd et al., 2011). This also applies for the callosal commissure. Above the age of 60 years, there is observed a more prominent decline in callosal thickness (Doraiswamy et al., 1991; Hou & Pakkenberg, 2012; D. Salat et al., 1997; Sullivan, Rohlfing, & Pfefferbaum, 2010). This age-related thinning of corpus callosum also differ based on callosal regions. Studies suggest that anterior and middle callosal sections are more susceptible to age related atrophy compared to posterior regions (Madden, Bennett, & Song, 2009; Persson et al., 2006; Salami, Eriksson, Nilsson, & Nyberg, 2012; D. Salat et al., 1997; D. H. Salat et al., 2005; Sullivan, Adalsteinsson, & Pfefferbaum, 2006). A study by Allen et al. (2005) also indicate that the relationship between aging and decline in callosal thickness is non-linear during this period of life.

In summary, research from the last couple of decades demonstrate an inverted-u-shaped trajectory of callosal size across the lifespan. The peak of growth is reported for the third decade of life. It is noteworthy that there are clear indications of region-specific rates of change in callosal size for both periods of maturation and decline. There is seen an anterior to posterior wave of maturation in prenatal and early postnatal development which in later

childhood and adolescence reverse to a larger increase in posterior compared to anterior regions. Decline of the callosal size in older age seem to be more prominent in anterior sections, indicating that the sections first to mature are also the first to deteriorate.

1.4 Callosal size and general cognitive ability

Although it is widely recognized that the corpus callosum undergoes significant structural changes during both development and ageing, many of the functional consequences of variability in callosal morphology are still unknown (Banich & Brown, 2000). A significant effort has been dedicated to understanding the role of interhemispheric interaction on cognition (Belger & Banich, 1998; Peterson, Feineigle, Staib, & Gore, 2001). Research suggest that intellectual abilities are supported by large neural networks encompassing association areas in both frontal, parietal and temporal lobes (Deary, 2012; Jung & Haier, 2007; Luders, Narr, Thompson, & Toga, 2009). As the corpus callosum is shown to support cognitive functions by facilitating cerebral connectivity, it is a natural step to further investigate callosal morphological contributions to higher-order cognition and intellectual abilities.

Several studies on both clinical and healthy populations have indicated that callosal morphology modulate intellectual abilities (Luders et al., 2007; Westerhausen et al., 2018; Westerhausen et al., 2011). There is also evidence of an association between callosal development and cognitive changes across the lifespan. This is documented by studies on both developmental and ageing samples (Chicoine, Proteau, & Lassonde, 2000; Dougherty et al., 2007; Fryer et al., 2008; Gootjes et al., 2006; Hinkley et al., 2016; Kennedy & Raz, 2009; Penke et al., 2010; Prendergast et al., 2015; Westerhausen et al., 2011; Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). This line of research suggests that morphological changes in corpus callosum serve as both a marker of individual cognitive abilities and a facilitator for the development of higher-order cognition across the lifespan.

Possibly most investigated is the relationship between callosal size and individual cognitive abilities, which is often measured as IQ scores from standard intelligence tests. Callosal size, as measured from the midsagittal plane, has been of interest due to the assumption that a larger corpus callosum means greater processing power in the human brain (Ganjavi et al., 2011). It is postulated that a larger callosum indicate either increased number or more extensive myelination of axons, and that either of these facilitate cerebral connectivity, which further promote cognitive performance (Rauch & Jinkins, 1994).

In accordance with this theory, most studies on adult samples have found a positive correlation between callosal size and intellectual abilities (Allin et al., 2007; Chiang et al., 2009; Dunst, Benedek, Koschutnig, Jauk, & Neubauer, 2014; Luders et al., 2007; Strauss, Wada, & Hunter, 1994). However, the field has been characterized by methodological differences. Luders et al. (2007) criticized early studies investigating corpus callosum and cognitive abilities for failing to consider the relation between total brain volume and intelligence (McDaniel, 2005), as well as between total brain volume and callosal size (Jancke, Staiger, Schlaug, Huang, & Steinmetz, 1997). Statistically controlling for these aspects, Luders et al. (2007) still found a positive relationship between callosal thickness and intelligence scores in adults, but mainly in the posterior sections of the structure. They further suggested that this selective association between posterior callosal thickness and intelligence most likely represent the topographical organization of the callosum.

In contrast, one lifespan study by Peterson et al. (2001) using automated factor-based measures of callosal morphology reported that IQ measures were associated with a reduced thickness of the anterior portion of the corpus callosum. This is the callosal section mainly consisting of axons interconnecting the prefrontal and premotor parts of the cerebral cortex. Thus, these results show an inconsistency in the relationship between callosal size and intellectual abilities, possibly influenced by methodological differences. In addition, the divergent findings between callosal subsections indicate that regional callosal thickness might be significant for modulating general cognitive capacity in adults.

Studies on typically developing samples further complicate the relationship between callosal size and cognition. While some studies have not been able to find any relationship between callosal size and general cognitive abilities in healthy younger age populations (Nosarti et al., 2004), others have suggested that decreasing callosal size is associated with improved neurocognitive performance in children (Allin et al., 2007; Ganjavi et al., 2011; Hutchinson et al., 2009; Luders et al., 2011; Westerhausen et al., 2011). Interestingly, Ganjavi et al. (2011) also found a negative correlation between callosal size and cognitive performance, though only for children between six and twelve years of age and not in older adolescents. It is important to note that as with the adult population, research on typically developing children and adolescents is influenced by differing designs and methods. An important difference is how empirical studies measure callosal size. For instance, Luders et al. (2011) used total callosal thickness while Ganjavi et al. (2011) used total callosal area as a measure of callosal size.

A large scale study by Westerhausen et al. (2018) also shed light on the importance of the cognitive measure chosen for studying the relationship between intellectual abilities and callosal size. They point out that prior studies examining callosal size and intelligence has utilized age-standardized norm-deviation IQ scores. As a result, their findings reflect the relative level of performance in the norm group and not absolute performance to all ages as with the use of raw scores. Westerhausen et al. (2018) found a positive correlation between absolute level of performance and absolute callosal thickness for people aged 6 to 21 years of age. Thus, the relationship between callosal size and intelligence in children and adolescences were comparable to that of adults when considering absolute performance. Hence, the use of norm scores might explain prior discrepancies in findings for young developmental samples.

Combined, these findings demonstrate how the relationship between intellectual abilities and callosal size might be dynamic and age specific. They also illustrate the importance of solving divergency in methodologies between studies in order to secure valid findings when examining the relationship between callosal size and cognition.

1.5 Methodological challenges: The issue of proportionality

The study of neuroscience draws on a wide range of research methods and approaches. In consequence, it has been challenging to integrate insights derived from these methods and form a common theoretical framework (McClelland & Ralph, 2015). As illustrated above, research on hemispheric interconnectivity through the corpus callosum is no exception to this challenge.

The issue of proportionality between callosal size and other brain size measures is an important challenge for the neuroscientific field of hemispheric interconnectivity and callosal development. This issue derives from the many divergent methods of controlling for parallel changes in brain sizes when studying callosal growth and ageing. It is widely recognized that callosal size correlate with total brain size (Jancke et al., 1997). For this reason, parallel changes in callosal size and total brain size are commonly considered a potential confounding factor by the research community. In addition, the forebrain volume undergoes significant changes in both grey and white matter across the lifespan (Tamnes et al., 2013; Westlye et al., 2010). As the human forebrain volume and callosal size is related, it is also likely that these changes in white and grey matter would affect callosal morphology (Jancke et al.,

1997). Moreover, a study by Rauch and Jinkins (1994) found a positive correlation between callosal size and cerebral size with a larger correlation in children than adults.

Although the importance of considering differences in brain size measures is acknowledged in the literature, the method used to do this vary between studies. It is most common to consider brain size as a confounding variable and correct for it in statistical analysis (Smith, 2005). This can be practiced by including brain-size measures, such as total intracranial or forebrain volume, as a covariate of non-interest in the analysis. The result of this approach is a removal of the variance in callosal size that is explained by differences in brain size. However, a discussion brought forward by Smith (2005) reveals concerns regarding the outcome of this procedure. In particular, he points out that removing the effect of brain size from statistical analysis could obscure important information about the proportionality of callosal development in the human brain.

Based on the work of Smith (2005), it can be argued that analyzing the relation between callosal size and brain size is a promising alternative to statistical controlling for brain sizes. Examining callosal size in relation to other brain sized could provide important additional information about hemispheric interconnectivity and callosal morphology. The proportionality of callosal size in differently sized brains can be studied by calculating ratios of the two variables (Holloway & de Lacoste, 1986; Smith, 2005). It can be argued that such ratios are especially appealing when conducting lifespan studies on the corpus callosum, because the presence of any growth of decline of the ratio studied will indicate over-proportional changes in hemispheric interconnectivity. Over-proportional growth would also potentially represent changes in the way the two cerebral hemispheres interact during the time period studied. Therefore, it is surprising that such ratios between callosal and brain size are rarely used in lifespan research. The few studies that do include ratios have small, cross-sectional samples with restricted age ranges (Rauch & Jinkins, 1994; D. Salat et al., 1997; Skumlien, Sederevicius, Fjell, Walhovd, & Westerhausen, 2018). These studies suggest that during periods of growth there is an an over-proportional increase in relative corpus callosum size (Rauch & Jinkins, 1994), while in older age there are an over-proportional decline (D. Salat et al., 1997; Skumlien et al., 2018). In addition, the functional consequence of the over-proportional changes on higher order cognition are understudied, as of the three studies identified, D. Salat et al. (1997) was the only study to include a measure of cognition in their analysis. They studied the relationship between relative callosal thickness and memory and visual construction in older age.

1.6 Aim of the present study

The overarching goal of the present study is to study hemispheric interconnectivity in healthy individuals across the lifespan. Hemispheric interconnectivity will be represented as the structural development of the corpus callosum and its cognitive consequences. By utilizing a lifespan perspective to changes in the corpus callosum, the study is able to cover both the developmental processes of childhood and degenerative processes of ageing. To be more specific, the primary objective of the study is to revisit the issue of proportionality by giving a descriptive account on lifespan changes in callosal size in relation to other brain size measures. The thesis will extend on previous research by using ratios between callosal size and brain sizes in a large mixed cross-sectional and longitudinal sample (1867 datasets). Secondly, the study aims to examine the relationship between callosal size in relation to other brain size measures and higher-order cognition throughout the lifespan, as this is largely overlooked in the literature. Finally, the study revisits the significance of regional callosal areas for both callosal development and intellectual abilities by extending on previous research by utilizing relative callosal measures. Also, as the study focus on normal developmental profiles, it aims to provide reference data that can be used to relate and interpret research on changes in callosal morphology and its cognitive relevance in clinical populations.

In order to achieve the objectives of the study, the corpus callosum was sectioned into 60 segments. By sectioning the corpus callosum, the study is able to account for potential regional differences within the connective structure. Callosal thickness was measured at each of the 60 segments. The ratio of segmental thickness by adjusted forebrain volume was used as a dependent variable in all analyses and will throughout the thesis be referred to as relative callosal thickness. Prior research including ratios between callosal and brain sizes suggest a non-linear relationships between age and changes in relative corpus callosum thickness (Rauch & Jinkins, 1994; D. Salat et al., 1997; Skumlien et al., 2018). Therefore, generalized additive mixed models (GAMM) were employed to fit lifespan trajectories for each of the 60 segments of callosal thickness. The trajectories were further clustered to subsections of comparable callosal development across the lifespan. Lastly, mediation analyses were used in order to determine if changes in relative callosal thickness for each of the clusters contribute to age-related trajectories in higher-order cognition**.** The subtests Matrix Reasoning and Vocabulary from the Wechsler scale (Wechsler, 1999) were used as measures of cognition.

2. Material and methods

2.1.Participants

The study has a mixed longitudinal and cross-sectional design. By utilizing a longitudinal design, the study is tries to eliminate possible cohort effects of different age groups (Lezak, 2012, p. 356). The sample contains a total of 1867 observations from 1014 participants with a sex distribution of 608 women (59.96%) and 406 men (40.04%). As the study aims to investigate lifespan changes, the age covered spans from 4 to 93 years of age. The sample has a mean age of 33.8 years and standard deviation (sd) of 24.4 years. All data material, including magnetic resonance imaging (MRI) scans and cognitive measures were obtained from three projects at the research center of Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo (UiO). The sample included datasets from the first and second wave of both the Norwegian Mother and Child Cohort Neurocognitive study (NeuroCogMoBa, (Krogsrud et al., 2016)), and the Neurocognitive Development study (NeuroCogDev, (Tamnes et al., 2010)). In addition, datasets from the first, second, third, and fourth wave of the Cognition and Plasticity through the Lifespan project (Fjell et al., 2008) were included. The NeuroCogMoBa is a subproject of the large scale Norwegian Mother and Child Cohort study (MoBa) conducted by the Norwegian Institute of Public Health (Magnus et al., 2006). The two other projects included in the study recruited participants independently via means such as newspaper advertisements and local schools and workplaces (Fjell et al., 2008; Tamnes et al., 2010).

All participants answered a structural interview to ascertain participant eligibility. The current sample was restricted to right-handed individuals. Exclusion of left-handed individuals restrict the possibility of conflicting results as atypical brain lateralization patterns are more common in left-handed individuals (M. J. Pujol et al., 1999). Several studies have also indicated that both handedness (Westerhausen et al., 2004) and degree of handedness lateralization (Luders, Cherbuin, et al., 2010) might affect callosal size. Therefore, the current study went for homogenous righty sample in order to restrict variables that affect callosal morphology. Handedness was determined via self-report. In addition, all participants included in the study were fluent Norwegian speakers and had a normal or corrected to normal hearing and vision. This was in order to conduct neuropsychological testing in Norwegian with reliable and valid results.

Furthermore, the study aims to investigate structural and functional brain development in healthy individuals. Studying alterations of relative callosal size in normal brain maturation and ageing is important because it provides a framework for later examining the possibility of deviating changes in clinical populations. Hence, all participants with neurological or neuropsychiatric conditions known to affect the central nervous system (CNS) were excluded from participation. This includes those with a history of concussions, severe head trauma and seizure disorder, as well as individuals receiving treatment for mental illnesses or using psychoactive drugs with a known effect on the CNS. Additional exclusions criteria due to both practical and ethical considerations were low birth weight, claustrophobia and any counter-indications for MRI.

2.2.Ethical considerations

Ethical clearance was received by the Regional Ethics Committee for medical research (REK-Vest or REK-Sør) for each of the studies. The participants received an information brochure about the project before attending and written informed consent was obtained from all participants above 16 years of age and by a parent or guardian if the participant was a minor. In regard to health considerations a minor is identified as below 16 years of age according to Norwegian law. Participants below this age was given special considerations when obtaining an informed consent, including an age appropriate oral explanation of the projects. All minors above the age of 12 also gave written consent in addition to their parent or guardian, while minors below the age of 12 expressed oral consent at both time points before magnetic resonance imaging (MRI) and neuropsychological testing. Informed consent from eligible participants was also obtained for data integration across the original studies.

2.3. Structural magnetic resonance imaging (sMRI) acquisition

Acquisition of sMRI data was conducted at the Oslo University Hospital. Two scanners were used for sMRI. They were both Siemens Medical Solutions, Erlangen, Germany, but one scanner had a 1.5 Tesla Avanto system and the other a 3 Tesla Skyra system. Comparable 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was obtained on both platforms. T1-weighted images are produced by a short repetition time between radio frequency (RF) pulses and a short signal recovery time (Katti, Ara, & Shireen, 2011). On the Avanto system, a 12 channel head coil was used and the sequence (repetition time, TR = 2400 ms; echo time, TE = 3.61 ms; inversion time, TI = 1000 ms; flip angle = 8 degrees)

covered 160 sagittal slices (1.2 mm thickness, 192 × 192 scan matrix, field of view of 240 × 240 mm^2), yielding an image resolution of 1.25 × 1.25 × 1.20 mm^3. On the Skyra system, a 24-channel head coil was used, and a turbo field echo pulse sequence (TR/TE/TI = 2300 ms/2.98 ms/ 850 ms; flip angle = 8 degrees) with 176 sagittal slices (256×256 scan matrix) and an isometric resolution of 1 mm^3. Integrated parallel acquisition techniques (iPAT) were used for most children under nine years. This involves acquiring multiple T1-weighted scans within a short scan time in order to discard scans with residual movement and average the scans with sufficient quality. The data collection was divided between the scanners with 1408 datasets (75.4% of all) conducted with the Avanto system and the remaining 459 datasets (24.6%) conducted with the Skyra system.

2.4 Prospective and retrospective image quality control

Immediately after the data acquisition, the T1-weighted images (MPRAGE) were reviewed and screened for obvious motion artifacts by a member of the research team. If such artifacts were identified, participants were rescanned when possible. As discussed by Backhausen et al. (2016), retrospective quality control is important to rule out image distortions and excess motion artifacts that can bias the results or exclude participants from the study. This is especially important for developmental studies because of the inclusion of younger age groups as there is a negative correlation between age and increased motion artifacts (Blumenthal, Zijdenbos, Molloy, & Giedd, 2002). A more detailed quantitative rating system was introduced at the fourth wave of the Cognition and Plasticity through the Lifespan project to secure standardized rating procedures. The T1-weighted images were visually ranked on a five-point scale from no detectable artifacts to the presence of severe motion. Rescans were advised at the two worst rating scales.

To avoid motion artifacts all original studies also focused on prospective motion-reduction techniques. For the NeuroCogDev project and the Cognition and Plasticity through the Lifespan project, this mostly involved preparing the participants for the scanner procedure, reminding them between image sequences about the importance of not moving during scanning and letting them listen to radio during the structural scans. For the younger children in the NeuroCogMoBa-project, even more effort was put into preparing the children for the MRI-scanning. For the first wave, this included introducing the children for a mock version of the scanner to acclimatize them to the scanner environment and decrease possible anxiety during the actual data acquisition. In addition, they were shown a video recording of a child undergoing all procedures at the scanner at the Oslo University Hospital. For the

second wave, only children expressing concerns regarding the scanning were again introduced to and familiarized with the mock scanner (Krogsrud et al., 2016). For the youngest children, it was also sometimes necessary to let the parents sit in the scanning room to provide extra comfort for the child. However, if the discomfort was obvious the scanning would be stopped and the child excluded from the original study as participation was not perceived as voluntarily.

Additionally, structural scans obtained during the data collection were reviewed for gross neuroanatomic pathology by radiologist Paulina Due-Tønnesen at the Oslo University Hospital. If such pathology was present the participant would be excluded from the study.

2.5 Callosal thickness measurement

A measure of callosal thickness was determined on the midsagittal plane of the white-matter segmentation of the T1-weighted images in native space. The midsagittal surface area was measured to quantify the strength of anatomical connectivity between the hemispheres. Midsagittal surface is used as a reference because of the assumption that it reflects degree of hemispheric connectivity (J. M. Clarke & Zaidel, 1994). Also, by using the midsagittal surface instead of the parasagittal plane (Luders, Narr, Zaidel, Thompson, Jancke, et al., 2006), the study is able to consider both regional differences and compare the findings to prior research employing the same methodological approach. Callosal thickness was used as a measure of callosal size because it has higher spatial specificity than well-known geometrical-based solutions for segmentation of the midsagittal callosal area (Luders, Narr, Zaidel, Thompson, & Toga, 2006), such as the Witelson's parcellation scheme (Witelson, 1989) or the straight-line methods and curved-line methods introduced by J. M. Clarke and Zaidel (1994). In addition, individual differences in the callosal curvature seems to not be substantially affected by callosal thickness as compared to callosal area (Luders, Narr, Zaidel, Thompson, & Toga, 2006)

In the current study, thickness measures were extracted from MRI-scans by first conducting a semi-automated segmentation of the corpus callosum and thereafter an outline-based thickness determination. This approach is based on the work of Skumlien et al. (2018), Westerhausen et al. (2016) and Westerhausen et al. (2018). Similar approaches have also been used in several prior studies, including S. Clarke et al. (1989), Luders, Narr, Zaidel, Thompson, and Toga (2006) and Walterfang et al. (2009).

The semi-automated segmentation started by conducting a rigid-body coregistration using Statistical Parametric Mapping routines (SPM12 routines, Wellcome Department of

Cognitive Neurology, London, UK). This was in order to preserve the size and shape of the corpus callosum. It was implemented for the raw images of each individual image to a T1-template. The primary aim of the process was to ensure a non-tilted midsagittal plane as located between the cerebral hemispheres in the longitudinal fissure. After the initial rigid-body coregistration, the midsagittal slice was identified and a preliminary segmentation of the corpus callosum was obtained. This was achieved by segmenting the reoriented images using standard SPM12 segmentation routines. From this point only the white matter maps in native space were included in the analyses. Moreover, the thickness segmentation of the corpus callosum was visually inspected for each of the observations. They were also manually corrected if necessary. This procedure was based on routines written by René Westerhausen in Matlab (MathWorks Inc. Natick, MA, USA). Manual correction was most common for instances were voxels not belonging to the corpus callosum were included in the image, which was especially frequent for the fornix. In these cases, manually determining the structural borders of the corpus callosum was needed, as well as the removal of redundant voxels. This step was followed by a manually identification of the tip of the rostrum and the base of the splenium. The tip of the rostrum was determined as the posterior-most voxel of the in-bend anterior half, while the base of splenium was recognized as the ventral-most voxel in the posterior half. In order to ensure that the imagined line between the rostrum tip and splenium base was horizontally oriented, the total callosal mask was rotated. Important to this work was avoiding over-rotating the callosal mask because this resulted in an unwanted stretching and reorientation of the structure.

Furthermore, a random sample was selected for quality control in which my supervisor René Westerhausen and myself performed these manual steps independently. The random sample consisted of 143 datasets for those participants who had available images for both Avanto (1.5T) and Skyra (3T) scanners. Inter-rater reliability was then calculated for the total number of voxels in the corpus callosum mask which represent the midsagittal surface area. This was calculated as two-way random effects, considering the single measure and absolute agreement, and resulted in intra-class correlations (ICC) of r_{icc}=.86 and .96 for Avanto and Skyra data. While the commonly used interclass correlation coefficient measure bivariate relation of variables representing different measurements classes, ICC measure homogeneity among variables in a common class. That is, the variables share both their metric and variance (McGraw & Wong, 1996). ICC of r_{icc}=.86 and .96 for Avanto and Skyra data is thereby indication of decent homogeneity between the scanner and rater variables.

The next step was to determine a callosal thickness measurement. In order to do this, the outline of the midsagittal plane of the corpus callosum was first determined. The identified tip of the rostrum and the base of the splenium was used to divide the ventral and dorsal part of the outline. The midline between the ventral and dorsal part of the outline was then identified by spacing 100 support points with equal distance on the two outlines. Determining the midline was essential to obtain a reference line for the thickness measurement. With the reference line, regional thickness could be measured as the distance between either the ventral or dorsal outline to the midline. The midline was determined by using 100 support points. However, the midline was resampled into 60 equally distanced points for the actual thickness measurement. The reason for selecting 60 measurement points is that it represents a compromise between the 29 and 100 measurement points which have been used in prior research (S. Clarke et al., 1989; Luders, Narr, Zaidel, Thompson, & Toga, 2006). In addition, 60 measurement points was used because the number har proven to provide high enough density of sampling points to be able to capture the callosal structure and it does not inflate the number of statistical tests more than necessary (Westerhausen et al., 2016).

In a final preprocessing step, as the present analysis aims to examine the proportionality of the corpus callosum relative to brain size across the lifespan, the raw 60 segment thickness estimates were related to the forebrain volume (see section 2.6). As illustrated by Smith (2005), the ratio of two features of a geometrically object (like the radius and volume of a sphere) only is invariant to the size of the object, if both features (numerator and denominator of the ratio) are expressed in the same unit. As callosal thickness is a measure of distance and forebrain size represents a volume, the forebrain volume was transformed by raising it to the power of 1/3 (i.e, $FBV_{0.333}$) before the division. In other words, forebrain volume was converted to a unit that remains proportional to callosal thickness if the brain maintains geometric similarity with changing size. Thus, the ratio is expected to be stable across the lifespan if corpus callosum thickness changes proportional to forebrain volume. However, any positive or negative deviation from a stable ratio indicates over-proportional growth and decline of the corpus callosum. In order to supplement the current analysis, the study also calculated the ratio of segmental callosal thickness to white matter volume ($WMV_{0.333}$) following the same approach.

2.6 Measurement of forebrain and white-matter volume

Forebrain volume was assessed from the T1 images using the supratentorial volume provided by the segmentation routines of Freesurfer (version 6.1, (Fischl, Sereno, & Dale, 1999)). The forebrain volume is arguably the optimal measure for the ratio of relative callosal thickness. It includes all brain structures with nerve fibers going through the callosal commissure, as well as excluding brain areas without callosal axons, such as the cerebellum and the brain stem. In addition, an extraction of the total white-matter volume was conducted of both cerebral hemispheres for the supplementary analysis.

2.7 Fitting and clustering of callosal lifespan trajectories

The lifespan trajectories of relative corpus callosum thickness were fitted using generalized additive mixed models (GAMM, "mgcv" package, v1.8-28, (Wood, 2017), in R 3.6.1) for each of the 60 segments. Generalized additive models (GAMs) was used instead of standard generalized linear modelling (GLM) because of the presence of nonlinear predictors. For each of the 60 segments, relative thickness served as dependent variable while the participants' age was the predictor of interest. Age was smoothed using cubic regression splines with the basis dimension set to 10 knots. The participants' Sex and Scanner Type were added as covariates of non-interest as part of the fixed-effects model, while a participant identifier was included as random effects (intercept). The model fitting was done using restricted maximum likelihood (REML) estimations. Effect size of the Age effect was expressed as proportion of explained variance (ω_2).

In a next step, the first derivatives of the fitted trajectories were calculated, representing the slope (i.e., the change) of the lifespan trajectories at a given age. A dissimiliarity matrix was then obtained and trajectories were submitted for a cluster analysis. Clustering was performed using the Partitioning Around Medoids (PAM) algorithm as implemented in the "cluster" R package (v2.1, (Maechler, 2019), in R 3.6.1). Cluster solutions between 2 and 10 clusters were estimated, and the mean silhouette widths was used to determine the optimal cluster solution. The resulting cluster solution was additionally inspected for their topographical organization, that is, clusters which contained thickness segments at different, non-adjacent locations where split up into sub clusters for spatial consistency. Finally, for each resulting cluster mean thickness across all segments assigned to that cluster was calculated for subsequent analysis steps.

For descriptive purposes, the lifespan trajectories of the obtained cluster mean values were also submitted to GAMM modelling using the same model as for the analysis of the

original segments. Then, the derivate of the fitted cluster trajectories were used to determine the estimated age marking the end of growth (EoG) and the beginning of decline (BoD). End of growth is defined as the last estimate of the slope above, while beginning of decline is defined as the first estimate of the slope below zero. Confidence intervals (95%) around the derivative trajectory served to determine where the slope deviated from zero. All the above analysis steps were also conducted for the ratio of callosal segmental thickness and $WMV_{0.333}$. For details see Fig. S1 and Table S3 in the supplement.

2.8 Cognitive measures and assessment

A measure of cognitive ability was collected from neuropsychological testing for an available subsample of 479 participants and a total of 1117 observations. 320 participants had available scores for two time points, while 159 were assessed at three time points. The restriction of a subsample with at least cognitive measures from two time points were necessary to be able to examine change scores on individual level. The cognitive measure collected was raw scores for both subtests Vocabulary and Matrix Reasoning from the Norwegian versions of the well-known Wechsler intelligence test battery. To assess children below the age of 6.5 years, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III, (Wechsler, 2002)) was used. This was applicable for 131 observations. The remaining 986 observations from participants above the age of 6.5 were assessed using the Wechsler Abbreviated Scale of Intelligence test (WASI, (Wechsler, 1999)). All neuropsychological testing was administrated within a month of the MRI acquisition.

The subtests Vocabulary and Matrix Reasoning was used because they are well-established measures of higher-order cognition in clinical neuropsychology (Lezak, 2012, pp. 553-554, 632-634). Moreover, the subtests complement each other in regards of function tested. Vocabulary provides a measure of word knowledge and crystallised cognitive abilities (Lezak, 2012, p. 553). In contrast, Matrix Reasoning, provides a measure of perceptual organization and visual-spatial abilities. In this way, Matrix Reasoning assesses fluid intelligence and non-verbal abilities (Lezak, 2012, p. 633). In an effort to assess absolute cognitive ability and change, raw tests were used as a cognitive measure instead of the often used age-standardized, norm-deviation scores (Neisser, 1998; Westerhausen et al., 2018).

Lifespan trajectories of both of the cognitive variables were fitted using GAMM in an effort to confirm the premise of further analyses. In the fixed-effect part of the model, cubic regression splines were used to smooth Age. Covariates of non-interest was Sex ad test version, that is either WPPSI-II or WASI. Participant identifier was also included as a

variable of random effect (intercept). The results are illustrated in Fig. 2. For Matrix Reasoning, there is observed an inverted-u-shaped lifespan trajectory. More specifically, cognitive performance on Matrix Reasoning is characterized by a pronounced increase until the 20s. After peaking in the beginning of the 20s, the trajectory shows a slow decline in performance. This decline appears stronger after the age of 60 years (F = 134.0, effective degrees of freedom, *edf*, of 8.13, yielding a p<.0001, explained variance, ω_2 = .49). Performance on the Vocabulary subtest also show a strong increase for the first two decades of life. However, the performance continues to increase until the age of 40 years (F = 620.6, edf = 7.87, p<.0001 ω_2= .81). The results are in line with previous research. Both Vocabulary and Matrix Reasoning test score show age trajectories predicted from the literature (Craik & Bialystok, 2006).

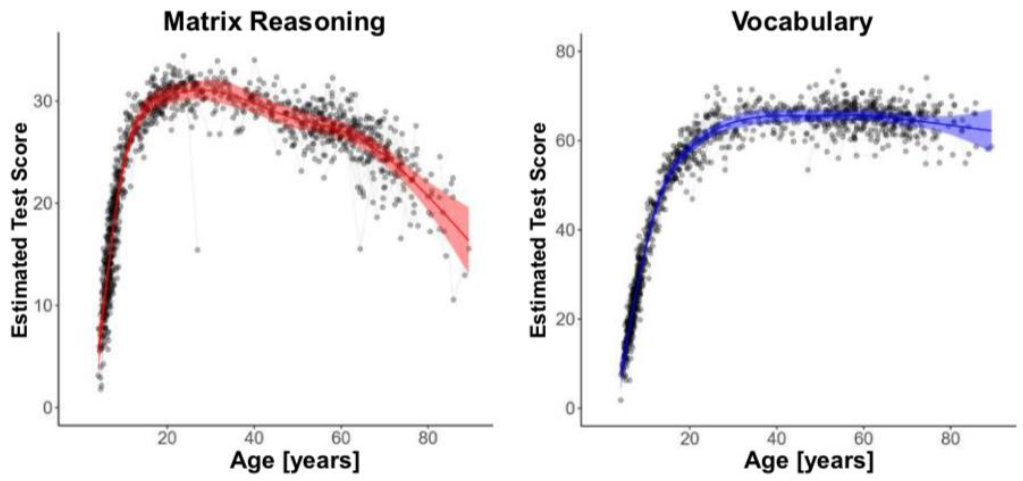


Fig. 2. "The figure illustrates lifespan trajectories of cognitive variables. That is, the fitted trajectories for test scores on WASI/WPPSI subtests Matrix Reasoning and Vocabulary using generalized additive mixed modelling (GAMM). The trajectories are shown as the solid line while the 95% confidence bands are represented as the shaded area. The effective degrees of freedom, edf, was 8.13 for Matrix Reasoning and Age explained 49% of the variance in the test score. The test score for Vocabulary had an edf of 7.87 and Age explained 81% of the variance." Figure and text from "Lifespan trajectories of relative corpus callosum thickness: regional differences and cognitive relevance" by Danielsen (2020), Preprint.

2.9 Mediation analysis

The second research question address the relation of callosal and cognitive development across the lifespan. In the present analysis this was formulated as mediation hypothesis and is illustrated in Fig. 3. The question is if age-related (predictor, X) changes in cognitive abilities (dependent variable, Y), are substantially mediated by changes on corpus callosum measures (mediator, M)? To test this hypothesis, change scores for each callosal cluster and each cognitive test were calculated separately. In order to reduce the complexity of the mediation analysis, the change score mediation was preferred over using raw scores. That is, for the present between testing time intervals for which change scores were assessed (for the 320 participants with two time points the mean interval was 2.54 years with a standard deviation of 1.46 years; for the participants with 3 time points it was 7.82 ± 0.81 years), linear associations can be assumed so that non-linear associations had not to be considered during the mediation analysis. Change scores were obtained as follows. Considering cognitive and corpus callosum variables, linear regressions were fitted for each participant (i.e., across 2 and 3 individual time points) and the obtained slopes were extracted as individual change scores, representing estimated annual change in callosal and cognitive measures. The change in age was calculated as difference in age between first and last testing.

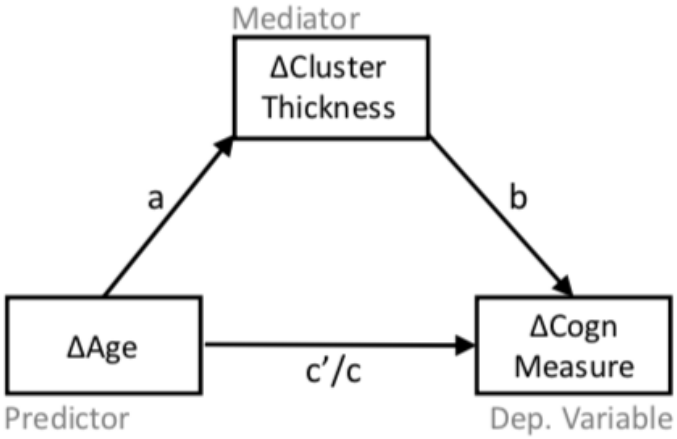


Fig. 3. "The figure shows the path diagram for the change mediation analysis model. Parameter a is the unstandardized regression weight for ΔAge for the prediction of changes in mean relative thickness within a cluster. That is, ΔCluster Thickness which is the mediator variable. Parameter b is the regression weight for the mediator predicting the change in the dependent variable (ΔCogn Measure). Parameter c' represents the regression weight of the

*direct effect of ΔAge on the change in cognition and parameter c represents the same prediction without considering the mediator variable. The indirect effect (mediation) is estimated as combined effect a*b. As mediator served changes in mean relative thickness as obtained from all clusters (see section 3.1). Changes in Matrix Reasoning or Vocabulary test score served as dependent variables." Figure and text from "Lifespan trajectories of relative corpus callosum thickness: regional differences and cognitive relevance" by Danielsen (2020), Preprint.*

The change mediation analysis was conducted using the Lavaan package (version 0.6-4, (Rosseel, 2012), in in R 3.6.1). Bootstrapping with 5000 iterations was used to estimate both p-values and parameter confidence intervals. In order to achieve a false discovery rate (FDR) of 5%, the p-values were corrected. As according to Hayes (2009) mediation analysis are only considered meaningful if there are established pairwise associations between both the predictor and mediator, as well as the mediator and dependent variable. Thus, a formal mediation analysis was only considered for the clusters showing significant associations ($p<.05$), which was tested using pairwise linear regressions. The mediation of change analysis was then set up as illustrated in Fig. 3. The effect of interest was the indirect (or mediation) effect, constituted by the multiplication of the coefficients of regression coefficients of pathways *a* and *b*, and will be expressed as *ab*. The total effect of the model, that is, the combined effect of change in age and the mediator on the cognitive change score, was also calculated (*c*). Effect size of all effects were expressed as ω_2. An estimate of the proportion of variance of the age effect on cognition which is mediated via changes in callosal thickness is obtained by dividing the effect size of the indirect effect by the effect size of the total effect.

3 Results

3.1 Lifespan trajectories and clustering

Significant age-trajectories were fitted for all 60 segments of the corpus callosum. This is illustrated in Table 1 of the supplementary material. Effective degrees of freedom (edf) is between 1.00 and 6.73. Thus, there is considerable variability in the complexity between the identified callosal segments. The effect size (ω_2) of Age smooth term is between .3 and .20.

Combined, this support the notion of developmental differences between the 60 callosal segments and give grounds to further complete the cluster analysis.

The clustering analysis using PAM proposed a five-cluster solution for the trajectories of callosal segments. This was based on the local maximum in the silhouette coefficient (See fig. 4A). The result provides clusters which are organized topographically along the anterior-to-posterior division of the midsagittal surface of the corpus callosum. For illustration see Fig. 4B. Trajectories of the estimated mean and derivatives for the initial cluster solution is also illustrated in Fig. 4C.

Fig. 5 illustrates the fitted lifespan trajectories of each cluster. The first and most-anterior cluster (Cluster 1) contains five segments which are placed in the rostrum and ventral genu of the corpus callosum. These segments encompassing Cluster 1 shows an edf of 2.25 and sd. of 0.86 from the GAMM fitting. This indicate a low complexity to the segments and can best be described as a linear decline across the lifespan. The second cluster (Cluster 2) consists of segments located in the genu and the splenium of the corpus callosum. To address this spatial division between the genu and the splenium, the cluster can be separated into two sub-clusters. This is illustrated by the green segments Fig. 4B. Then, the anterior cluster (Cluster 2a) includes seven segments with a mean edf of 4.90 (± 0.21). The posterior cluster (Cluster 2p), on the other hand, contains three segments and has a higher mean edf of 5.54 (± 0.42). The trajectory analysis showed that both clusters have trajectories characterized by a slow and over-proportional increase in relative thickness until the end of growth which is assessed as the age of 24 years for Cluster 2a and 17 years for Cluster 2p. This is followed by a stable period, before a slow decline starts at the age of 43 years for Cluster 2a and 51 years for Cluster 2b. The third cluster (Cluster 3) includes all of 33 segments. The segments are located in the posterior genu, the truncus, and the isthmus. In addition, two single segments were included in Cluster 3. They represented spatial outliers as one was situated in the genu and the other in the splenium (cf. Fig. 4B). As they were spatially located far from the main cluster segments, they were not included in further analyses. The remaining 31 segments which was included in Cluster 3 had a mean complexity of edf = 4.67 (± 0.27). The cluster trajectory showed that relative thickness increases until approximately 22 years of age. As with Cluster 2a and 2b, this is followed by a plateau. A slow decline begins at the age of 41 years and continue into older age. The fourth cluster (Cluster 4) contains 8 segments in the dorsal part of the splenium. It has an average edf of 6.34 (± 0.08) and is characterized by an increase in the mean ratio until the age of 23 years. It is immediately followed by a slow decline. However, this decline is not significant until 53 years of age. In the end, Cluster 5

includes four segments in the ventral splenium, which is the most posterior part of the corpus callosum. With an edf of 6.53 (± 0.16), Cluster 5 shows the highest complexity. The trajectory analysis further demonstrated that Cluster 5 is characterized by a clear increase in relative thickness until the age of 23 years. This is followed by a longer period with a stable ratio as compared to the prior clusters. Cluster 5 shows a significant decline first at the age of 59 years.

Supplementary cluster analysis and results for WMV are illustrated in Fig. S1 and Table S3 in the supplement. There was proposed a four-cluster solution for the ratio of segmental callosal thickness and $WMV_{0.333}$. There spatial distribution for WMV is mostly consistent with the original analysis for forebrain volume. However, in the WMV-analysis the splenium is included in one cluster, as compared to the forebrain volume analysis where it is separated in two clusters

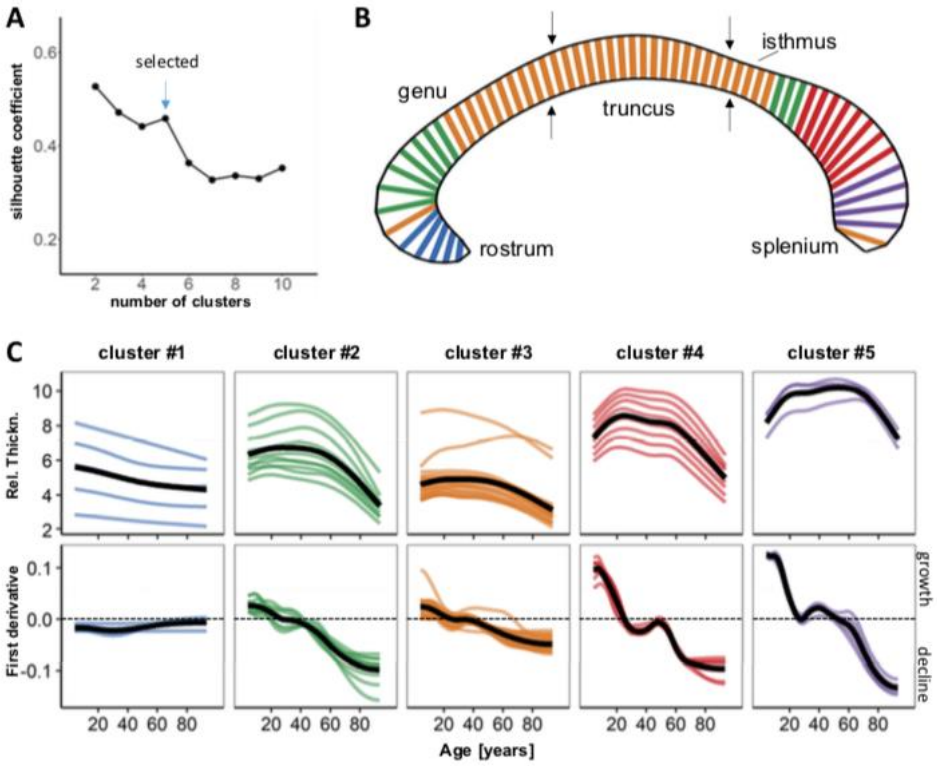


Fig. 4. "The figure shows the initial PAM clustering of the callosal segments based on the first derivative of the lifespan trajectories. Dependent variable was callosal thickness relative to total forebrain volume. Panel A shows the silhouette coefficient for cluster solutions between two to ten clusters. Here a five cluster solution was selected as it showed a clear peak in the silhouette coefficient and yielded a consistent cluster topography as seen in Panel

B. Panel B depicts the segment-wise color-coded topography of the clusters within the corpus callosum (left: anterior) for the five cluster solution. Black arrows indicate the location which divides the corpus callosum into thirds relative to the anterior-posterior length. This marks the subdivision approach suggested by Witelson (1989). Panel C presents the lifespan trajectories of mean relative thickness (top row) and their first derivatives (bottom row) for each segment (different lines) per cluster. Bold black lines in each graph represents the mean trajectory. Of note, positive values in the derivative plots indicate an over-proportional growth of relative thickness while negative values indicate an over-proportional decline." Figure and text from "Lifespan trajectories of relative corpus callosum thickness: regional differences and cognitive relevance" by Danielsen (2020), Preprint.

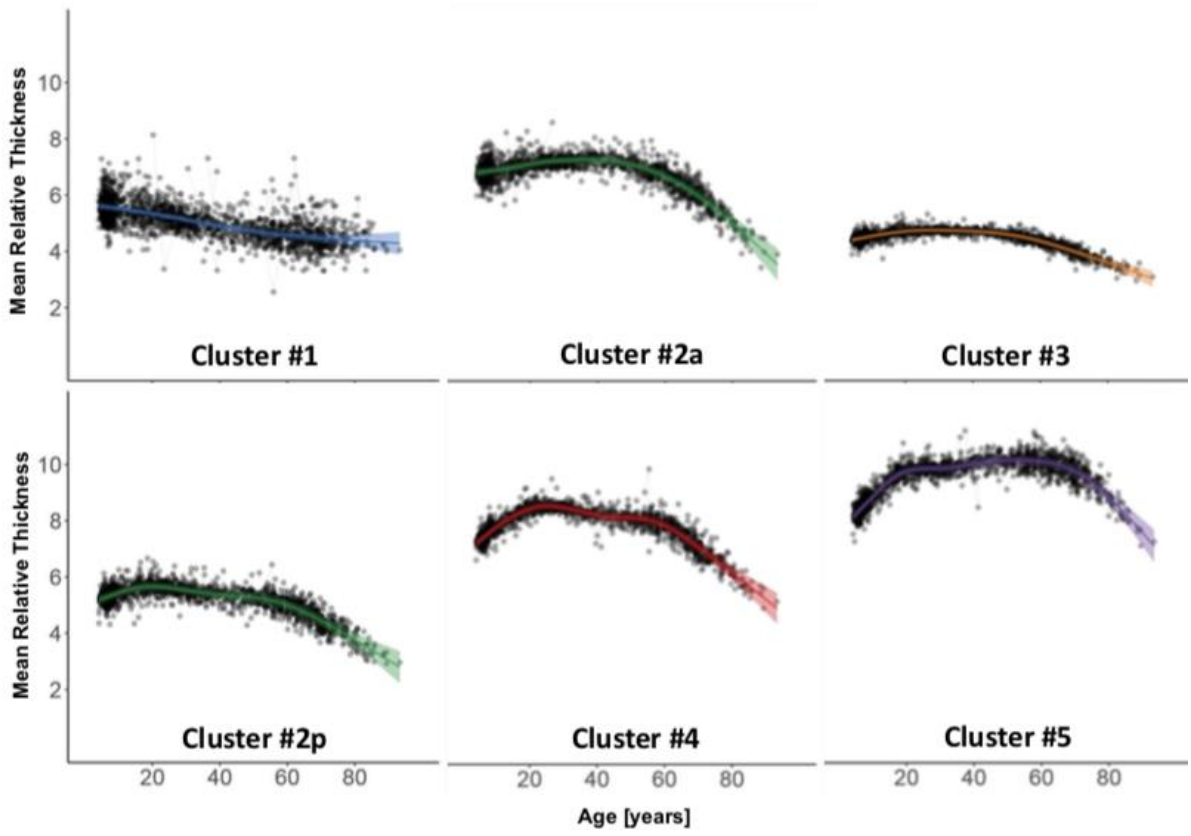


Fig. 5. "The figure illustrates the fitted lifespan trajectories of mean relative callosal thickness (solid line; shaded area 95% confidence bands) for the final cluster solution. Colors correspond to the color coding used in Figure 4B and C. For details see Results section." Figure and text from "Lifespan trajectories of relative corpus callosum thickness: regional differences and cognitive relevance" by Danielsen (2020), Preprint.

3.2 Corpus callosum and cognitive abilities

With six identified clusters and two cognitive variables, there was a possibility of twelve combinations for the mediation analysis. Only six out of twelve combinations showed a pairwise association of change in relative callosal thickness and change in age, as well as having significant values for both cognitive changes and relative callosal thickness (see Table 2). In result, these six combinations were considered for the mediation analysis. The mediation effect was again only significant for two of these combinations (see Table 1).

Firstly, the mediation effect is significant for Cluster 1, Age changes and the Vocabulary score. That is, change in relative thickness in cluster 4 significantly mediated the effect of Age changes on the Vocabulary test (indirect effect: *ab* = -0.05, s.e. = 0.02, Z = -2.5, p_{corr} = .049, CI95% = [-0.090, -0.012]. 1% of the variance is explained by Cluster 1. The total effect was significant (*c* = -0.43, s.e. = 0.05, Z = -8.94, p_{corr} <.001) and had an effect size of ω_2 = 0.14. Hence, about 7% of the total effect is explained by the indirect effect.

Secondly, the mediation effect is significant for Cluster 4 and the Matrix Reasoning score (*ab* = -0.04, s.e. = 0.02, Z = -2.40, p_{corr} = .049, CI95% = [-0.073, -0.007]). The effect size was .1 (ω_2). The total effect was significant (*c* = -0.19, s.e. = 0.04, Z = -5.08, p_{corr} <.001), with an effect size of ω_2 = .049. Hence, 20% of the total effect was explained by the indirect effect for the mediation analysis with Cluster 1 and Matrix reasoning. The indirect effect was not significant in the other four analysis conducted (all p_{corr}> 0.169, all ω_2 < 0.004). Details of the results of the change mediation analysis are shown in Table 1.

Table 1. Results of the change mediation analysis

		Path *a*		Path *b*		Path *c'* (direct)		Path *c* (total)		Path *ab* (indirect)	
Dep. Variable	Cluster	b-value	p	b-value	p	b-value	p	b-value	p	b-value	p
Matrix Reason.	2p	-0.012	<0.001*	1.199	0.104	-0.174	<0.001*	-0.188	<0.001*	-0.014	0.150
	4	-0.019	<0.001*	2.068	0.012*	-0.148	<0.001*	-0.188	<0.001*	-0.040	0.016*
Vocabulary	3	-0.008	<0.001*	2.56	0.131	-0.406	<0.001*	-0.427	<0.001*	-0.021	0.177
	2p	-0.012	<0.001*	1.913	0.039	-0.405	<0.001*	-0.427	<0.001*	-0.022	0.085
	4	-0.019	<0.001*	2.594	0.008*	-0.377	<0.001*	-0.427	<0.001*	-0.05	0.012*
	5	-0.018	<0.001*	0.766	0.36	-0.413	<0.001*	-0.427	<0.001*	-0.014	0.384

Notes. Path naming refers to Fig. 2. P-values are based on 5000 bootstrap permutations and uncorrected. However, * indicates effects surviving FDR correction across the six mediation analyses (see text)

Tabell 1. Results of the change mediation analysis. From "Lifespan trajectories of relative corpus callosum thickness: regional differences and cognitive relevance" by Danielsen (2020), Preprint.

4 Discussion

4.1 General pattern of callosal growth

Hemispheric interconnectivity, as measured through the corpus callosum, has been a subject of investigation for several decades (Gazzaniga, 2014, pp. 121-159; van Der Knaap & van Der Ham, 2011). Numerous studies have established that the connective structure undergoes significant developmental changes across the entire lifespan. These studies suggest that callosal thickness follow an inverted-u-shaped trajectory of growth and decline. Total callosal thickness increases substantially until it peaks in the third decade of life. This is suggested by both histological, MRI and diffusion imaging studies (Hasan et al., 2009; Lebel et al., 2010; Prendergast et al., 2015; J. Pujol et al., 1993; Yeatman et al., 2014). The peak in total callosal thickness is followed by a period of relative stability before it starts declining about the age of 60 (Doraiswamy et al., 1991; Hasan, Kamali, et al., 2008; Hou & Pakkenberg, 2012; D. Salat et al., 1997; Sullivan et al., 2010). This line of research is characterized by several methodological challenges. One important challenge is the lack of consistency in ways of controlling for parallel change in callosal size and brain sizes, also referred to as the issue of proportionality. In an effort to address this issue, the present study examines relative callosal thickness across the lifespan, shown as the ratio between callosal thickness and brain size measures such as forebrain volume. The findings are consistent with the general pattern of change in the corpus callosum, but they also provide important specifications and details to the literature.

The findings demonstrate that lifespan changes in callosal size are not proportional to changes in forebrain size. In other words, callosal thickness does not follow the exact trajectory of change as forebrain volume. There is observed an over-proportional increase in relative callosal thickness in most callosal segments from childhood until young adulthood. This is demonstrated by an increase in the ratio of callosal thickness to forebrain volume in this period of life. As callosal growth continue until the late teenage years and first half of the twenties, end of growth is reached in the third decade of life. However, the specific age of end of growth in the corpus callosum does depend on the subsection studied (discussed in section 4.2). In older age, the present findings demonstrate an over-proportional decline of relative hemispheric connectivity. This is indicated by a substantial decrease in the ratio of callosal thickness to forebrain volume. In other words, callosal thickness declines at a faster rate than forebrain volume in this age period. This finding of an inverted-u-shaped trajectory

of callosal size is in line with prior studies which controlled for parallel change by using brain size measures as covariates in statistical analysis (Prendergast et al., 2015), as well as studies using diffusion parameters (Hasan, Ewing-Cobbs, et al., 2008; Hasan et al., 2009; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008).

Previous studies have examined change in relative callosal measures in healthy participants (Rauch & Jinkins, 1994; D. Salat et al., 1997; Skumlien et al., 2018). For instance, D. Salat et al. (1997) controlled for the supratentorial area compared to callosal size in older age while studying sex differences in the corpus callosum. Thus, their findings only relate to individuals from 65 to 95 years of age and does not represent the entire lifespan. However, these observations are in line with the current findings of an over-proportional decline in relative callosal size in the elderly. Rauch and Jinkins (1994) examined callosal thickness relative to cerebral area in a wider age group spanning from 0 to 87 years of age. In this way, they were able to represent a complete lifespan. Nevertheless, their study relied solely on cross-sectional data and in their article, they did not specify the spread of the younger age groups. A more recent study by Skumlien et al. (2018) did include both cross-sectional and longitudinal data, but had a rather small sample size. The present findings are able to extend on prior research utilizing relative callosal size by including a large sample size (1867 datasets), a lifespan perspective with participants between 4 and 93 years of age and a mixed model design with both cross-sectional and longitudinal data.

Although the present study has important methodological contributions, it is unable to empirically study the neurobiological mechanisms thought to mediate structural changes in hemispheric interconnectivity. A number of studies have advanced on this aspect demonstrating that increased callosal thickness during development likely reflects an increase in axon myelination or axon diameter. It is unlikely that this increase reflects the formation of new axons considering that the number of axons is fixed at birth and decreases across the lifespan (S. Clarke et al., 1989; Innocenti & Price, 2005; LaMantia & Rakic, 1990). In contrast, the changes seen in older age are likely driven by both alterations of axon myelination and a decrease in the number of callosal axons. This has been documented by histological studies in both humans and other primates (Aboitiz, Rodriguez, Olivares, & Zaidel, 1996; Hou & Pakkenberg, 2012; A. Peters & Sethares, 2002).

4.2 Regional callosal lifespan trajectories

Looking beyond the general pattern, the current study demonstrates that corpus callosum has regional specific lifespan trajectories. Five clusters were identified which are roughly located

on the anterior to posterior dimension and represent unique age trajectories. The findings demonstrate a marked deviant age trajectory for Cluster 1, which encompass the rostrum and parts of the ventral genu. There is observed a significant increase in relative callosal thickness into young adulthood in clusters 2-5, while Cluster 1 is characterized by a slow decline in relative callosal thickness across the entire lifespan.

Another noteworthy observation is that comparable age trajectories differ based on anterior or posterior location on the callosal structure. The study observes that posterior clusters 4 and 5, which are located in the splenium, differ significantly from the more anterior clusters. That is, clusters 2a, 2b and 3 which encompass the genu truncus and isthmus. The anterior-posterior distinction is illustrated by two important differences. Firstly, the posterior corpus callosum experience a more prominent growth in relative thickness during development (illustrated in Fig 4C). Secondly, there is an approximately 10-year delay in decline of relative callosal thickness for posterior regions compared to the anterior sections of the corpus callosum. It is also interesting that when using WMV rather than FBV as denominator in the ratio, the accentuation of maturation in posterior corpus callosum is especially prominent (illustrated in supplement, Fig. S1). The posterior cluster which includes the entire splenium was also the only cluster demonstrating significant developmental growth in relative thickness in the studied age period for the WMV analysis.

The observed differences between anterior and posterior callosal age trajectories are in line with the previous literature. Prior research have reported both a stronger posterior compared to anterior callosal development during childhood and adolescence (Giedd et al., 1999; Luders, Thompson, et al., 2010; Rajapakse et al., 1996; Thompson et al., 2000; Westerhausen et al., 2016) and an earlier decline in anterior as compared to posterior sections in older age (Madden et al., 2009; Salami et al., 2012; D. H. Salat et al., 2005; Sullivan et al., 2006). It is noteworthy that this tendency is observed in both studies using brain size as covariate and relative callosal measures, perhaps indicating that regional findings between anterior and posterior trajectories are not substantially masked by the issue of proportionality discussed in the current study.

4.3 Functional hemispheric neural networks

It can be argued that the observed anterior to posterior distinction of callosal ageing trajectories reflect the development of different functional hemispheric neural networks. This is especially likely as the callosal topography is comparable to the organization of the

cerebral cortex (Zarei et al., 2006). Research illustrate how the splenium and other posterior callosal subregions encompass axons interconnecting parietal, temporal and occipital regions of the cerebral cortex (Schmahmann & Pandya, 2006). Hence, these connections are relevant for both attentional processes (Bozzali et al., 2012; Tomaiuolo et al., 2010) and the integration of sensory information between the hemispheres (E. Genc, Bergmann, Singer, & Kohler, 2011; Westerhausen, Gruner, Specht, & Hugdahl, 2009). Anterior regions, on the other hand, are relevant for higher order cognition as subsections like the genu and truncus encompass connections between prefrontal cortical areas (Schmahmann & Pandya, 2006). It has been documented that anterior connections are highly active in the production of language, as well as processing of semantic information (Putnam, Wig, Grafton, Kelley, & Gazzaniga, 2008; Thiel et al., 2006). This entails that it is likely that the anterior connections of the corpus callosum support a neural network of higher order cognition, including language processes, while posterior connections are more involved in a cortical network of perceptual processes.

Furthermore, as these neural networks are related to different callosal aging trajectories, they could also represent different functional needs across the lifespan. For instance, it is observed an earlier decline in anterior callosal regions supporting higher order cognitive functions compared to posterior sections supporting perceptual functions. Perhaps then, the splenium is protected against detectable decline in older age because of its involvement in basic perception processes and not higher-order cognition (Madden et al., 2009; Scally, Burke, Bunce, & Delvenne, 2018). However, this is not in line with research showing an earlier decline of fluid intelligence and problem solving capacities as compared to crystalized intelligence and verbal functions in elderly (Craik & Bialystok, 2006). Perhaps the cognitive compensation hypothesis (Morcom & Johnson, 2015) and increased bilateral hemispheric activity in older adults (Cabeza et al., 1997) could shed some light on this issue. Is it possible that the maintenance of crystalized intelligence and verbal abilities is a result of specific neural compensation for these functions in elderly?

It is also possible that the regional specific age trajectories in the corpus callosum are related to regional axon composition. Histological studies indicate that anterior callosal subsections are predominated by thin axons which are lightly myelinated. In contrast, posterior regions of the corpus callosum, such as the truncus and splenium, consist of thicker axons which are more strongly myelinated (Aboitiz et al., 1992; Björnholm et al., 2017; Riise & Pakkenberg, 2011). Hence, the regional specific trajectories of the corpus callosum might reflect different myelination processes. The posterior callosal growth until third decade of life

could reflect increased axon myelination compared to anterior nerve fibers which both have thinner and less myelinated axons and does not show the same trajectory of accentuated early growth. Another possibility is that the myelination process is completed at an earlier age for anterior regions. This seems likely as for instance the anterior corpus callosum encompass connections between motor and sensorimotor regions which are known to develop at an early age. In contrast, it is not as likely for connections between higher order cognition since the frontal lobes are shown to continue maturing until the third decade of life (Arain et al., 2013; Casey, Jones, & Hare, 2008). Perhaps then, less myelination of frontal connections represents a functional need of interhemispheric transfer time. Is it possible that higher order functions as represented by the frontal lobes and anterior callosal connections are less reliant on fast hemispheric interaction compared to connections in a perceptual neural network?

4.4 Implications for callosal subdivision

The establishment of regional specific lifespan trajectories of the corpus callosum could have implications for callosal subdivision, in particular because these trajectories likely reflect functional neural networks. Given the lack of clear macroscopic anatomical landmarks partitioning callosal areas, several parcellation schemes have been designed to divide the corpus callosum and guide research on the connective structure (M. Peters et al., 2002). Most of these approaches are based on a geometrical subdivision of the midsagittal callosal surface (S. Clarke et al., 1989; Duara et al., 1991; Rajapakse et al., 1996; Weis, Kimbacher, Wenger, & Neuhold, 1993). This includes the widely employed Witelson's classification which suggests dividing the callosal structure into thirds along its rostro-caudal extent of the midsagittal plane (Hofer & Frahm, 2006; Witelson, 1989). The result is a roughly identification of the genu, truncus, and splenium (the division is indicated by arrows in Fig. 3B). As the Witelson's classification is based on research on primates, it is reasonable to question the validity of the approach when used on human brains. This notion is further supported by evidence that the subdivision is only roughly associated with cortical regions relevant to the functional asymmetry in humans. Given that the regions overlap considerably, it is likely that the boundaries have reduced accuracy in describing structural changes in the corpus callosum and its functional consequences (Hofer & Frahm, 2006; M. Peters et al., 2002; Witelson, 1989).

Based on the current findings, it is argued a need to reformulate callosal segmentation to concur with recent research and a more refined agreement with functional cortical asymmetry. The present clustering solution offer an appealing subdivision of the corpus

callosum into five sections. These areas are defined in accordance with regional developmental trajectories as compared to the former geometrically derived segmentation models. The benefit of this approach is the likely increased association between structure and function. Comparable regional age trajectories can be argued to reflect inclusion in related functional hemispheric neural networks. In this way, the age trajectories can be considered as a data-driven approach to segmenting the callosal structure from within and in relation to functional brain networks. However, the resulting subdivision differs partially from previously suggested subdivisions and will consequently not benefit from direct comparisons with previous research in the field. Still, the thesis argues for the importance of a more correct subdivision to advance research in the field. A subdivision with increased relation between structure and function would contribute significantly to the study of structural and functional hemispheric connectivity as it ensures valuable interactions that can enhance our understanding in the field.

Previous work has tried to improve callosal subdivision by introducing various methods for segmentation. One suggestion has been to utilize results from diffusion MRI and tractography to inform callosal subdivision. This approach divide the corpus callosum according to the origin of reconstructed fiber pathways (Hofer & Frahm, 2006). Hofer and Frahm (2006) modified the Witelson's parcellation scheme based on findings using diffusion tensor imaging (DTI). One of the major differences compared to the standard Witelson's parcellation scheme was a more posterior crossing of callosal motor and sensory fiber bundles. Hence, Hofer and Frahm (2006) was able to modify the existing division to a somewhat more representative version in regard to callosal topography. This approach appears promising, but tractography studies suffer from several restrictions including difficulties reconstructing fiber pathways using existing imaging sequences and tracking algorithms. This is particularly vulnerable when analyzing the corpus callosum since the suggested tractography-based parcellation schemes are mainly based on connections originating from the midsagittal surface and thereby missing most of the lateral callosal connections (Hasan et al., 2009; Lebel et al., 2010; Sullivan et al., 2010).

Other promising attempts to subdivide the corpus callosum into anatomically and functionally distinct subareas are based on factor analytic techniques combined with traced MRI images (Denenberg, Kertesz, & Cowell, 1991; M. Peters et al., 2002). Studies using these techniques have in general agreed on a stable 6 or 7 factor solution (M. Peters et al., 2002). This method has been criticized by the lack of evidence documenting relation between factor structure and function. A direct mapping of the factor-defined callosal regions and

anatomical connections has been difficult. This is demonstrated in studies using both human data (de Lacoste et al., 1985) and anatomical analysis in other animals (Pandya & Seltzer, 1986). It is also complicated by the existence of heterotypical callosal connections since this means anatomical region and function does not always correlate (M. Peters et al., 2002).

Our study differs from most geometrically based subdivision approaches, DTI and tractography informed subdivision and subgrouping-based factor analytic methods by including a lifespan perspective and regional specific age trajectories to inform on relations between structure and function. Although the current approach requires more research to reaffirm its merits, it does demonstrate an appealing solution to restrictions shown in prior attempts to increase connection between the suggested regional callosal subsections and functional relevance.

4.5 Cognitive consequences

The study further examined cognitive consequences of changes in relative callosal thickness. As illustrated in Table 1, parameter *b* is positive in the mediation analysis, which suggests that relative callosal thickness mediates age-related changes in cognitive performance. More specifically, that proportionality of increase and decline across the lifespan modify changes in cognitive performance. An increase in relative callosal thickness is associated with an increase in cognitive performance, while a decline is associated with a decrease in performance. This indicates that increased callosal size has beneficial effects on cognition. The finding is in line with prior studies reporting positive associations between callosal measures and intellectual abilities. A number of cross-sectional studies have demonstrated a correlation between performance on standard intelligence tests and callosal morphology in both developing and adult samples (Chiang et al., 2009; Dunst et al., 2014; Luders et al., 2007; Tang et al., 2010; Westerhausen et al., 2018). As with callosal development, the current study contributes to the already existing literature by including ratios of relative callosal measures in a mixed model design with both cross-sectional and longitudinal data.

However, the mediation effects were only significant for the dorsal part of the splenium (Cluster 4). This indicate a regional specific relationship between higher-order cognition and relative callosal thickness in posterior regions of the corpus callosum. Prior research has provided evidence of a dynamic and possible age specific relationship between callosal size and cognitive performance. For instance, D. Salat et al. (1997) suggested that because of observed regional differences, a larger callosal size might not be equivalent to increased cognitive performance across the lifespan. Our research is also in line with the

work of Luders et al. (2007), as they demonstrated a special relevance of posterior callosal regions to intellectual abilities in adults. However, Luders et al. (2007) measured relative cognitive performance by using age-standardized, norm deviation scores. The current study illustrated the contribution of posterior corpus callosum in absolute cognitive performance.

The findings are complicated by the notion that comparable age trajectories represent different neural networks in the cerebral cortex. Given that a neural network of higher-order cognition is thought to be represented by anterior callosal age trajectories, it is a natural assumption that the size of anterior callosal regions should be most involved in mediating intellectual abilities. This is not in consensus with the present finding that the posterior corpus callosum has the largest involvement in mediating cognitive performance for both subtests Matrix Reasoning and Vocabulary. However, it does give support to the Parieto-Frontal Integration Theory (P-FIT) of intelligence which argue for a broad neural substrate supporting intellectual abilities beyond the influence of the frontal lobes (Jung & Haier, 2007).

Given that the mediation effects only explain about 1% of the variance, the cognitive relevance of changes in relative callosal thickness could be interpreted as small or negligible. However, there is a clear indication of a stronger contribution between relative callosal thickness and test score on Matrix Reasoning, as compared to the Vocabulary subtest score. There was only a 7% observed contribution of relative callosal size to changes in scores on the Vocabulary subtest score. In contrast, the Matrix Reasoning score has a total effect of 5% explained variance. Hence, 20% of the total effect of ageing on cognitive changes (parameter *c*) is explained by changes in relative callosal thickness. This is arguably a noteworthy contribution and considerably stronger than for the Vocabulary score. Prior research supports the special relevance observed for the Matrix Reasoning subtest. For instance, one recent meta-analysis by Westerhausen and Karud (2018) indicated that performance IQ was affected by callosotomy, but verbal IQ scores had no observed effect. Both this work and the findings of Westerhausen and Karud (2018) could reflect the topography of the corpus callosum. The Matrix Reasoning subtest measure perceptual abilities to a greater extent than the Vocabulary subtest (Lezak, 2012, pp. 553-554, 632-634). Due to this it is natural to expect a larger involvement of posterior callosal regions representing a cortical neural network of perception in Matrix Reasoning as compared to Vocabulary.

There is also a possibility that the small mediation effects are a result of the cognitive measure included in the study. As neither the Vocabulary or Matrix Reasoning test are timed, they are possibly not the best instruments for assessing callosal functioning and hemispheric

interconnectivity. Prior studies has demonstrated that the association of white-matter volume and intellectual abilities is mediated by general information-processing speed (Penke et al., 2012). This indicate the importance of including timed cognitive measures when estimating the cognitive consequences of callosal morphology. It is likely that by including tests with high demand on fast stimulus processing, we would get larger mediation effects between relative callosal size and cognition (Kennedy & Raz, 2009; Salami et al., 2012). As processing speed was not included in the study, this hypothesis remains to be tested by future studies in the field.

4.6 Validity of the cognitive measures

There are several procedural considerations of neuropsychological testing that might affect the validity of current findings. An assessment of characteristics defining the participants included in the original studies is necessary to conclude on the generalizability of the cognitive measures in the current study. There might be systematic differences between individuals choosing to participate in research, which could question the representativeness of our findings to the general population. Individuals choosing to participate in research tend to have good health and high social status (Lezak, 2012, p. 356). As education is related to neuropsychological functioning (Lezak, 2012, pp. 376-377) and intelligence scores (Strenze, 2007), this tendency will likely skew the scores on subtests Vocabulary and Matrix Reasoning upwards. Nevertheless, we argue that a valid measurement of intelligence or ability level in relation to the rest of the population is not important for the aim of the present analysis which is to examine degree of change and stability during the lifespan.

Given that the study includes longitudinal data from serial neuropsychological testing, there is a possibility of practice related measurement errors, also referred to as retest effects (Lezak, 2012, p. 138). Retest effects encompass a collection of factors which result in an advantage from prior testing, such as learned strategies, memory of test items and decreased situational anxiety (Calamia, Markon, & Tranel, 2012; Lezak, 2012, p. 138). A failure to account for practice related factors could result in an erroneous conclusion regarding cognitive stability and change across the lifespan (Calamia et al., 2012). As of 2014 there was no available formal investigation of retest effects on the administration of WASI in Norwegian samples (Siqveland, Dalsbø, Harboe, & Leiknes, 2014), and to the author's knowledge there has not been attempted to conduct one since. Moreover, healthy subjects are especially susceptible to practice effects with repeated testing (Lezak, 2012, p. 138), in this

way making our sample particularly vulnerable. Given that many studies examining practice effects have short test-retest intervals (Beglinger et al., 2005; Benedict & Zgaljardic, 1998), it is natural to question their generalizability to the current design, where retesting tended to be administrated after a few years. However, a longitudinal study by Salthouse, Schroeder, and Ferrer (2004) has demonstrated that retest effects are not eliminated until at least seven years after the first assessment. In addition, studies have addressed possible differences in retest effect based on age with diverging conclusion (Scharfen, Peters, & Holling, 2018). Although the retest effects of the present study are unknown, advantages of testing are unlikely to have large between-subject variability. Studies demonstrate that the greatest practice effects occur between the first and second neuropsychological examination (Benedict & Zgaljardic, 1998; Ivnik et al., 1999), which all participants in the present study completed.

Furthermore, participants underwent testing either at daytime or after work and school obligations in the evening. The latter might affect the participants´ motivation or ability to use cognitive resources due to tiredness. In addition, the test protocols included extensive measures of different cognitive functions, often making the testing period last several hours depending on the project and project wave. To cancel out these variables frequent breaks were advised, and all tests were validated by the test administer for obvious signs of tiredness or decreased motivation. Research does indicate that motivation during neuropsychological testing in research settings vary significantly between subjects and might affect the validity of the intelligence scores (Angela Lee, Patrick, Donald, Rolf, & Magda, 2011). Other common sources of errors relevant to neuropsychological assessment are differences between technicians administrating testing and punching mistakes of data material (Lezak, 2012, p. 139). These sources may also apply to the current study despite efforts to ensure standardized procedures and control for mistakes.

4.7 Further limitations and future directions

In the end, a few limitations regarding the study design and sample will be presented. Although the findings greatly contribute to a lifespan perspective on relative callosal size, the sample does not include participants below the age of 4 years. Thus, the youngest age group is not adequately represented in the present study. Given that early postnatal development is a period of life shown to be particularly important to callosal maturation (S. Clarke et al., 1989; Rakic & Yakovlev, 1968; Tanaka-Arakawa et al., 2015; Vannucci et al., 2017), dismissing the youngest age group have implications for both the suggested clustering solution and callosal subdivision. It could also affect the analysis regarding cognitive consequences of

structural changes in the corpus callosum. Future studies on relative callosal size should therefore seek to include the youngest developmental samples. This is especially encouraged as this period of life, to the author's knowledge, has not been studied systematically for relative callosal size.

Additionally, the study systematically excluded left-handed individuals in order to control for possible variations of functional hemispheric lateralization. In result, the findings are only applicable to right-handed individuals. Limitations of the study include self-reporting as a method for assessing handedness and the following assumed lateralization based on this knowledge. It is widely acknowledged in the literature that simply asking for preferred handedness is not sufficient if the aim is to ensure a valid assessment (Lezak, 2012, p. 368). A more comprehensive method is necessary. Variations of the Edinburgh Handedness Inventory (EHI (Oldfield, 1971)), are the most well-used self-report measure for handedness (Edlin et al., 2015). It incorporates questions from several relevant aspects, including preferred hand for writing, drawing, brushing teeth and preferred foot for kicking a ball (Oldfield, 1971). Even with a seemingly more valid assessment of handedness, it is still problematic to make inferences about hemispheric asymmetry based on self-reported handedness. Research has documented that approximately 90% of right-handed individuals have a left hemispheric dominance for language and right-hemispheric dominance for spatial attention (M. J. Pujol et al., 1999). In this way, a study sample exclusively consisting of right-handed participants has a smaller probability of including individuals with an atypical lateralization pattern, compared to samples with left-handed individuals as well. However, there is still a possibility of including participants which self-identify as right-handed but have an atypical lateralization pattern. This illustrate how assessing hemispheric asymmetry in individuals is highly intricate as most methods are based on inferences about outer behavior as an indication of inner structural organization. Consequently, the present study is not able to dismiss the possibility that atypical functional hemispheric patterns affect the present analysis and findings. Studying relative callosal development in both left-handed and right-handed individuals, as well as in people with both typical and atypical lateralization patterns can provide essential information on differences between these groups. However, this will require a well thought-out method of assessing and controlling for hemispheric asymmetry.

Furthermore, the current study investigates relative callosal thickness in normal developing and aging samples. In this way, the study is able to provide a much-needed control group for investigating the possibility of abnormal developmental trajectories in

neurological or neuropsychiatric populations seen to be affected by changes in callosal morphology. A number of studies have examined callosal involvement in neurodevelopmental and degenerative disorders such as Autism Spectrum Disorders (ASD) (Brambilla et al., 2003; Paul, 2011; Prigge et al., 2013; Travers et al., 2015; Wolff et al., 2015), Attention Deficit Hyperactivity Disorder (ADHD) (Gilliam et al., 2011; Krain & Castellanos, 2006; Paul, 2011), schizophrenia (Zhuo, Liu, Wang, Tian, & Tang, 2016) and Alzheimer's disease (AD) (Walterfang et al., 2014; Zhu et al., 2014). As these studies do not utilize relative callosal size, comparisons with developmental trajectories in the current study are restricted. Interestingly, one longitudinal study by Gilliam et al. (2011) found an indication of deviant growth trajectories in anterior parts of corpus callosum in patients with ADHD. The disruption of growth was assumed to reflect a possible disruption in the development of the prefrontal cortex. This indicate a need of to further shed light on the relationship between regional specific developmental trajectories and functional hemispheric connectivity in neurological and neuropsychological populations.

In summary, limitations of the current study design and sample include a restricted age group for younger participants and the assumed hemispheric homogeneity of an exclusive right-handed sample. Moreover, the study is not able to compare the current findings to abnormal trajectories in clinical populations. This could provide valuable insight into the relationship between structure and function during development. Thus, a future focus on increasing the generalizability of the research is important in order to ensure a complete view on hemispheric interconnectivity and structural development of the corpus callosum.

5 Conclusion

In conclusion, the present mixed longitudinal and cross-sectional study contributes to research on the development of hemispheric interconnectivity by providing a descriptive account of lifespan changes in relative callosal size in neurologically and neuropsychiatric healthy individuals. The current findings support the general pattern of an inverted-u-shaped trajectory of callosal development. In an effort to address the issue of proportionality, the study also demonstrates an over-proportional increase of callosal thickness compared to forebrain volume in childhood and adolescence, which is mirrored by an over-proportional decline in older age. The study further observed regional specific lifespan trajectories of relative callosal thickness. These trajectories differ substantially on the anterior-to-posterior division of the corpus callosum with an accentuated increase in relative callosal thickness until the third decade and 10-year delay of the beginning of decline in posterior callosal regions. This anterior-to-posterior division is likely a reflection of functional hemispheric neural networks. The thesis suggests a modification of the well-established Witelson's parcellation scheme in line with the present clustering solution as it ensures a closer relation between structure and function of the corpus callosum. Finally, the study demonstrates that increased relative callosal thickness has a beneficial effect on cognitive performance with posterior callosal regions mediating performance on higher-order cognitive measures. Taken together, the present study contributes with important insight into the lifespan development of structural hemispheric interconnectivity. It also provides valuable reference data of callosal development in healthy individuals. A future investigation of relative callosal developmental trajectories in clinical populations could further shed light on the importance of callosal development and its contribution to cognition.

6 References

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