

**Handedness and the Corpus Callosum: Challenging  
Previous Notions of Larger Callosal Regions Among Non-  
Consistent Right-Handers**

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Regions Among Non-Consistent Right Handers

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## Summary

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**Title:** Handedness and the Corpus Callosum: Challenging Previous Notions of Larger Callosal Regions Among Non-Consistent Right Handers

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**Author Statement:** This thesis is part of a larger project at the The Oslo Laterality Group. The idea for the thesis was provided by René Westerhausen. The study was preregistered in an open science framework (Raaf & Westerhausen, 2021). The reasoning behind preregistration of the project protocol is the fundamental idea of open collaboration within scientific fields. By preregistering and openly describing the protocols for the study, we hope to contribute to the mission of reproducibility in the multidisciplinary world of research (Aarts et al., 2015; Lakens, 2022). The data used in the present study was collected by the Human Connectome Project (HCP).

### Abstract:

Interindividual differences in neural anatomy have typically been linked to functional lateralization. For instance, the role of anatomical connectivity in supporting or establishing functional hemispheric specialisation, has been supported by evidence for correlations between handedness and callosal morphology. After publishing a number of influential post-mortem studies in the late 1980s, Sandra Witelson reinforced the notion that the corpus callosum of left-handers is larger than that of right-handers. However, critiques towards the validity and reliability of the Witelson studies, and the varied success of attempted replications of the findings, has led researchers to question the true relationship between handedness and callosal morphology. Hence, the primary aim of the present study is to conceptually replicate the findings of Witelson, by repeating the study with a larger sample ( $N > 1000$ ), utilizing a dataset of callosal measures from structural MRI borrowed from the Human Connectome Project (preregistration DOI: <https://doi.org/10.17605/OSF.IO/3WS5C>). The findings of the present study argue against the assumptions made by Witelson. The analyses of the midsagittal callosal surface area demonstrated no significant main effect of the different hand groups on total corpus callosum size, whilst controlling for sex and handedness, assessed using different criteria. Likewise, for analyses of the often-indicated isthmus subsection, the findings revealed no significant main effect of handedness, or any moderator effects of sex. These findings indicate that previous statements regarding the

relationship between handedness and corpus callosum morphology should be considered imprecise.

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## 1. Introduction

The human cerebral cortex is divided between two hemispheres, which are separated by the medial longitudinal fissure and connected by the corpus callosum. This callosal structure is pivotal for communication between the hemispheres, and it has been suggested that its existence is the reason for neurological lateralization (Gazzaniga, 2000). Though the hemispheres have a multitude of similar responsibilities, some functions and responsibilities are lateralized, meaning they are unique for or dominant in one of either hemisphere (Ocklenburg & Güntürkün, 2018a). Interindividual difference in brain anatomy has traditionally been linked to functional lateralization, and thus, the relationship between neurological architecture and behavioural-cognitive functioning has become a well-explored topic within the field of neuroscience (e.g., Annett, 1992; Beaton, 1997; Budisavljevic et al., 2021). Especially handedness has long been of immense interest within lateralization studies, as it is a clear behavioural asymmetric function that is constant across the total population (Ellis et al., 1988). Despite strong interest for the topic, the origin of this functional asymmetry, and the relationship between neurological structure and handedness is yet to be understood. Interindividual variations in size and morphology of the corpus callosum has been indicated to have a functional significance which is reflected in the lateralization of handedness (Ocklenburg & Güntürkün, 2018b; Manhães et al., 2005; Witelson, 1985; Witelson, 1989; Witelson & Goldsmith, 1991; Westerhausen et al., 2004). When Witelson (1985) published her article describing differences in corpus callosum size between individuals with different hand-preferences, the belief that non-consistent right handers (NcRH) had a larger callosal structure than consistent right-handers (cRH), was established as a foundation for future handedness research. These pivotal findings have been solidified as a part of laterality research, as the Witelson studies (1985; 1989) continue to be cited to this day (e.g., Parker et al., 2017). However, a recently published meta-analysis presented the lack of evidence and support for the Witelson-findings, emphasising that there is little to no evidence within the literature for a clear association between callosal morphology and handedness (Westerhausen & Papadatou-Pastou, 2022). Heterogeneity between studies in the definition of handedness and measuring of the corpus callosum, as well as comparatively small sample sizes makes it difficult to draw firm conclusions. Thus, the present study aimed to conceptually replicate the studies of Witelson (1985; 1989) using a larger sample ( $N > 1000$ ) than that of the original studies ( $N = 42$ , and  $N = 50$ , respectively).



## **1.1 Functional Hemispheric Asymmetry**

Paul Pierre Broca, a famous pioneer within laterality research, once stated that “man is, of all the animals, the one whose brain in the normal state is most asymmetrical” (Broca, 1877, pp. 527–528). The term ‘functional hemispheric asymmetry’ refers to the difference between the left- and the right hemisphere’s processing of stimuli and performance of tasks (Berretz et al., 2022; Bisazza et al., 1998; Güntürkün & Ocklenburg, 2017; Ocklenburg, et al., 2019), indicating that while the hemispheres have a multitude of similar responsibilities, some functions and responsibilities are specialized in each hemisphere (Geschwind & Galaburda, 1985). Laterality of function was originally discovered by Broca (1861), when he demonstrated that patients with lesions in their inferior frontal gyrus showed an inability of correct speech, often producing only one or two single-syllable words. Hence, regions responsible for processing and production of language was demonstrated to be located in the left hemisphere. Subsequently, research on laterality continued, uncovering that multiple cognitive abilities were lateralized in the brain (e.g., Davidson, 1995; van der Knaap & van der Ham, 2011). For instance, the typical hemispheric specialisation shows the left hemisphere as dominant for language, calculation and problem solving, focused attention, and approach-related behaviour (Christman, 2018; Gazzaniga, 2000). Meanwhile, the right hemisphere has been found to be specialised in facial recognition, emotional processing, prosody of speech, spatial attention, coordinate relations, and withdrawal-related behaviour (Levy et al., 1972; Levy & Trevarthen, 1976; Vingerhoets, 2019). Among the lateralized functions, handedness is one of the most obvious indications of cerebral asymmetry expressed through behavioural conduct (Nicholls et al., 2010). According to Pfeifer et al. (2022), handedness is often considered a proxy for functional brain lateralization, and the interaction between handedness and the corpus callosum is an area of high scientific interest. Many studies of laterality and handedness have directed the spotlight towards the corpus callosum as a possible originator or mediator for the asymmetry of human handedness (e.g., Aboitiz & Montiel, 2003; Bloom & Hynd, 2005; Clarke & Zaidel, 1994; Gazzaniga, 2000; Witelson, 1985; Witelson & Goldsmith, 1991). As pointed out in Habib et al. (1991), the topic of handedness is of theoretical importance as a possible connection between callosal morphology and functional brain lateralization would give immense, clear support to the suggestion of a correlation between human morphologic and behavioural characteristics.

### ***1.1.1 The Corpus Callosum and Asymmetric Functioning***

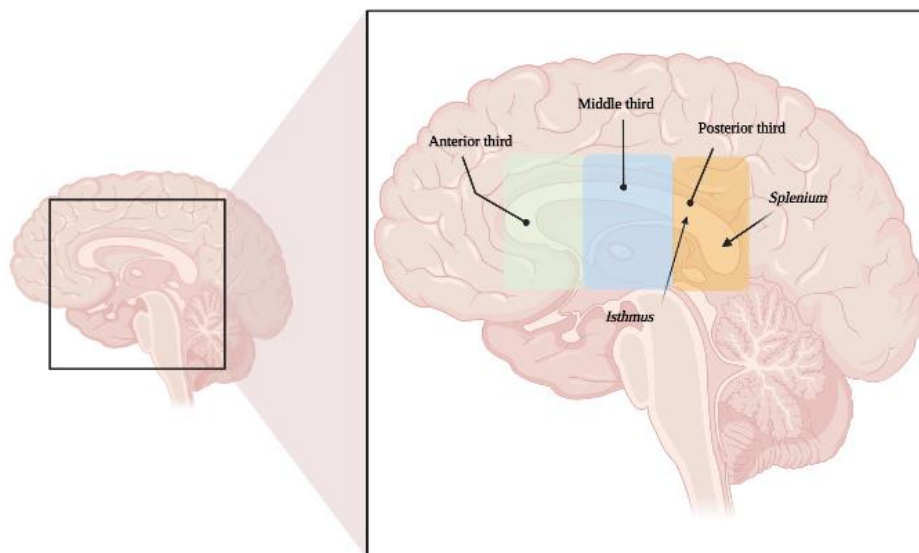
The two halves of the cerebral cortex are connected through the 200 to 300 million nerve fibres that makes up the major hemispheric commissure: The corpus callosum (Aboitz et al., 1992; Chao et al., 2009; Luders et al., 2010a). The corpus callosum, along with the anterior commissure, is one of the two main commissural fibre connections of the cerebral hemispheres (Gazzaniga, 2014), and is uniquely present in placental animals (Aboitz & Montiel, 2003, van der Knaap & van der Ham, 2011). Anatomically, the structure is a broad band of myelinated fibres which interconnects cortical regions in one lobe with regions in the opposite lobe (Ocklenburg & Güntürkün, 2018a). Quigley et al. (2003) highlights the notion of the functional importance of the corpus callosum in interhemispheric transportation of information, stating that synchronous blood flow changes in corresponding brain regions implies neuronal connections between the specific regions, through the corpus callosum. This interconnection is primarily homotopic, meaning that callosal fibres connects the same areas of the left and right hemisphere (Chao et al., 2009; Clarke and Zaidel, 1994). However, some heterotypical callosal projections occurs as well, connecting different areas across the two hemispheres (Aboitz & Montiel, 2003). Interhemispheric transfer is considerably less efficient than intrahemispheric transfer, but the occurrence of interhemispheric transfer is undeniably present, underlining the importance of the corpus callosum.

As there is no clear anatomical distinction between the different regions of the structure, it has been difficult to objectively define any specific callosal subregions. Nonetheless, a series of suggestions have been made to establish the substructures of the corpus callosum (Aboitz et al., 1992; Habib et al., 1991; Jäncke et al., 1997; Raybaud, 2010). Aboitz et al. (1992) revealed a significant positive relationship between separate regions of the corpus callosum and the quantity of small callosal fibres located within these regions. Accordingly, the callosal structure is often divided into individual segments across the callosal body, based on functionally and morphologically discrepancies between them, and the number of individual fibre tracts within each subregion (e.g., van der Knaap & van der Ham, 2011; Witelson, 1989). A range of approaches have been made in order to identify and determine the callosal substructures. Witelson (1989) suggested a seven-part subregion division, identified in an anterior-to-posterior direction, starting with the rostrum. At the rostral end of the corpus callosum, the callosal fibre curves anteriorly, creating the genu, as to form the anterior forceps. Posterior to the genu, fibres of the callosal body emerges, making up of the rostral body, anterior midbody, and posterior midbody. The callosal body connects with the callosal fibres making up the posterior part of the corpus callosum. The isthmus, and

the splenium is located within the posterior part of the corpus callosum and makes up the forceps major. At a later occurrence, Habib et al. (1991) partitioned the midsagittal callosal area into six subregions, after calculating the structure's centre of gravity. A geometrical subdivision schema, closely related to Witelson's, was suggested by Jäncke et al. (1997), and this schema is subsequently followed in the present study (see Figure 1). This straight-line method divides the midsagittal corpus callosum surface into thirds across the anterior-to-posterior stretch of the structure. Additionally, the isthmus and splenium regions are identified within the posterior third, with the splenium making up the posterior fifth region of the corpus callosum (see Westerhausen & Papadatou-Pastou, 2022).

### Figure 1

*Parcellation schema of callosal sectors*



*Note.* Illustrates the location of the corpus callosum in a cross-section of the human brain, and the callosal sectors roughly identified according to the parcellation schema established by Jäncke et al. (1997). The corpus callosum is located medially between the left – and right hemisphere, in a midsagittal direction. The main structures of the corpus callosum is identified in an anterior-to-posterior direction, starting with the anterior third area (green area). Following this region, the callosal fibre curves anteriorly, creating the middle third of the corpus callosum (blue area), as to form the anterior forceps. Posterior to the middle third region, fibres of the callosal body emerges, and connects with the callosal fibres making up the posterior third of the corpus callosum (orange area). The isthmus is located within the posterior third from which the posterior fifth, i.e., the splenium, was removed. Image created using BioRender.

The different regions of the corpus callosum has been shown to connect to specific region of the cerebral cortex. The information transferred through these exact callosal regions subsequently correspond to the functions of the respective cortical areas, making the corpus callosum topographically organized (Aboitiz & Montiel, 2003; Chao et al, 2009; De Lacoste et al., 1985; Habib et al., 1991; Ocklenburg & Güntürkün, 2018a; Roland et al., 2017). The anterior forceps of the corpus callosum, known as the genu and the rostrum (See Chao et al, 2009; Raybaud, 2010), connects prefrontal and higher order sensory cortical areas. According to Aboitiz and Montiel (2003), this region is comprised of a large amount of high density, less myelinated, and slow-conducting fibres (see also: van der Knaap & van der Ham, 2011). Posterior to the genu of the corpus callosum, fibres of the callosal body connects regions of the temporal, parietal, and frontal lobes. The posterior midbody connects primary and secondary auditory areas, whilst the central midbody connects primary and secondary somatosensory areas, as well as cortical motor regions. The central midbody contains thicker axons, which are highly myelinated and fast conducting (Aboitiz et al, 1992; Aboitiz and Montiel, 2003; Raybaud, 2010). Following the callosal body, the isthmus emerges, containing fibres of thinner density, and connecting the motor, somatosensory, and primary auditory areas. Finally, the callosal fibres making up the posterior part of the corpus callosum, the splenium, emit caudally as the posterior forceps. This area contains dense, less myelinated fibres, and connects visual areas in the occipital lobe. As specified in Aboitiz and Montiel (2003), the difference in fibre types across the corpus callosum might indicate functional differences in interhemispheric communication. Areas of the corpus callosum which contain more myelinated fibres are primarily responsible for rapid processing of stimuli, as opposed to the less myelinated areas, which are responsible for slower cognitive processes, such as decision making (Aboitiz & Montiel, 2003; van der Knaap & van der Ham, 2011). Importantly, as some callosal fibres are not homotopic, the corpus callosum is not completely topographically organized, connecting different areas of the cortex with each other, allowing for heterotypical interhemispheric interaction (Raybaud, 2010).

### ***1.1.2 Functionality of the Corpus Callosum: Theories***

Whilst the specific functionality of the corpus callosum is yet to be decided, the primary theory is that the corpus callosum objectively enhances and streamlines interhemispheric integration (e.g., Aboitiz & Montiel, 2003). Aboitiz and Montiel (2003) proposes that the corpus callosum, and especially its topographic callosal mapping, originated to integrate the two topographic sensory representations across the midline. Mainly, the

authors point to the ontogenesis of the corpus callosum of placental organisms. The callosal structure originates from the hippocampal commissure, from which it stretches to the dorsal hippocampal formation (Gloor et al., 1993). As so, the corpus callosum allows axons to travel shorter distances, by avoiding ventrally crossing through the anterior commissure. It is hypothesized that enhanced integration between the hemispheres have positive functional and behavioural effects. Some studies support the idea that corpus callosum size and cognitive abilities are positively correlated (e.g., Chao et al., 2009; Chiang et al., 2009; Jäncke et al., 1997; Luders et al., 2007; Strauss et al., 1994). Based on such findings, it is generally assumed that the purpose of the corpus callosum is to enhance integration between the hemispheres. However, opposing findings defy indications of a positive relationship between regional callosal thickness and general cognitive ability, suggesting either no significant relationship at all (e.g., Nosarti et al., 2004; Peterson et al., 2001), or advocating for a negative relationship between callosal size and cognitive performance (Allin et al., 2007; Westerhausen et al., 2011). Evidently, the specific role of the corpus callosum in interhemispheric interaction is still a matter of debate, as studies continue to present opposing results regarding the structure's relationship with neurocognitive performance. A majority of studies have theorised the callosal structure as responsible for functional cerebral specialization and lateralization (Habib et al., 1991), some going as far as stating that the corpus callosum is solely responsible for the emergence and occurrence of lateralization of functions (Gazzaniga, 2000; Witelson & Nowakowski, 1991). Findings of the relationship between the callosal structure and laterality have historically been largely supported by studies on split-brain patients. These patients are individuals whose corpus callosum has been surgically severed, either partly or completely (Paul et al., 2007; Sperry, 1962). Such procedures are typically performed in order to reduce epileptic foci spreading between the hemispheres (Gazzaniga, 2000, Gazzaniga, 2005; Zaidel & Sperry, 1974). Research on split-brain patients has been a crucial part of the investigation of callosal functioning as it has allowed investigators to study significant differences in behaviour and function between the two hemispheres, when the hemispheres are unable to communicate, and forced to perform separately.

The exact functional role of the corpus callosum in neural lateralization has been explained by both the inhibitory and the excitatory model (see Bloom & Hynd, 2005; Clarke & Zaidel, 1994; van der Knaap & van der Ham, 2011). Hellige (1993) defines the difference between the models as “whether processing that involves specific regions of one hemisphere tends to activate or suppress processing in similar regions of the other hemisphere” (p. 173).

On a neural level, excitation means that increased firing in neurons causes the receiving neuron of the synapses to fire as well, and activating the unstimulated hemisphere, whilst inhibition occurs when an increased firing of one neuron causes a decrease in the firing of a receiving neuron (Hellige, 1993). As noted by Ocklenburg & Güntürkün (2018a), the majority of axons located in the corpus callosum are dependent on the excitatory neurotransmitter glutamate (Conti and Manzoni, 1994), supporting the excitatory model. However, interhemispheric communication occurs primarily via inhibitory neural connections (Aboitiz & Montiel, 2003; Clarke & Zaidel, 1994; Bloom & Hynd, 2005; Westerhausen & Hugdahl, 2008), as the inhibitory neurotransmitter GABA is the most common neurotransmitter in the brain (Kawaguchi, 1992; Khoshdel-Sarkarizi et al., 2019). This indicates that, on a neural level, both inhibitory and excitatory interhemispheric callosal interaction occurs. On a functional level, however, the literature is divided between supporting the inhibitory (e.g., Cook, 1984; Denenberg, 1983; Kawaguchi, 1992; Toyama et al., 1969) and excitatory model (e.g., Berlucchi, 1983; Conti & Manzoni, 1994; Sperry, 1962).

The literature predominantly supports the excitatory model (Bloom & Hynd, 2005). According to the excitatory model, information integration from each cerebral hemispheres is enforced by the corpus callosum (Berlucchi, 1983; Bloom & Hynd, 2005; Sperry, 1962; van der Knaap & van der Ham, 2011). Split-brain studies give evidence for increased activation due to integration of information through the corpus callosum, as callosotomy is effective in treating intractable epilepsy (Bloom & Hynd, 2005). Some researchers (e.g., Galaburda, 1984) postulate that brains that are more symmetric, have stronger interhemispheric connections, suggesting that cerebral asymmetry is a result of lack of excitatory hemispheric connections. Additionally, according to excitatory theories, it is assumed that laterality is inversely correlated with callosal size, meaning that the corpus callosum will decrease as laterality increases (Hopkins and Rilling, 2000), an assumption that has been supported by a number of primate studies (Corballis, 1983; Galaburda, 1984). Therefore, individuals who are more strongly lateralized for asymmetric functions such as handedness or language, should be expected to have a smaller callosal structure than individuals who are less strongly lateralized.

Although the excitatory model is highly supported, there is evidence showing that callosal transmission often results in inhibitory effects (Kawaguchi, 1992; Toyama et al., 1969). The asymmetric inhibition model suggests that the degree of functional asymmetry is affected by one hemisphere inhibiting the other hemisphere through the corpus callosum (Berretz et al., 2022, Clarke & Zaidel, 1994; Cook, 1984; Kinsbourne, 1975). According to Netz et al. (1995), neurons involved in specific tasks must inhibit neighbouring neurons

during transcallosal communication, in order to ensure lateralization of higher functions. Theories supporting the inhibition model state that hemispheric asymmetry appears because the corpus callosum makes it possible for each hemisphere to suppress the other (Hellige, 1993). Following this theory, callosal size is positively correlated with laterality, meaning the size of the corpus callosum should increase when laterality increases (Yazgan et al., 1995).

While there are studies clearly supporting each model for callosal function in interhemispheric interaction, Banich and Belger (1990) demonstrated that when a task is complex, the hemispheres divide processing working in parallel or performing two distinct actions simultaneously. Meanwhile, when a task is largely automatic or non-complex, reduced laterality, and increased callosal activation, might be present. Evidently, the corpus callosum might not have a purely excitatory or inhibitory function (Bloom & Hynd, 2005). A subcortico-cortical network that balances hemispheric activation has been suggested, explaining that the relationship between degree of callosal connectivity and lateralization may be explained by the task-demands of different lateralized functions. To further understand the relationship between callosal morphology and laterality, measures of different lateralized functions have been done together with structural and functional neuroanatomical measures (Banich, 1995; Ocklenburg et al., 2014; Ocklenburg & Güntürkün, 2018a). As human handedness is a relatively clear asymmetric function, consistent across a plethora of demographic variables (Papadatou-Pastou et al., 2020), the relationship between handedness and callosal morphology is heavily researched (McManus, 2019). However, research of handedness as a concept has proven to be easier said than done. Conceptual disagreements regarding handedness, and methodological differences when assessing and measuring the variable impacts the literature. Nevertheless, many assumptions have been drawn regarding the asymmetry of handedness, and the topic is of immense scientific interest within the field of laterality research (Nicholls et al., 2010).

## **1.2 Handedness**

Psychologist and laterality-enthusiast Michael C. Corballis once wrote that “the illusion that cerebral asymmetry is uniquely human may stem from the fact that the most obvious manifestation is handedness” (Corballis, 2008, p. 868). *Handedness* can be defined as the manifestation of skills and activities between the left and the right hand (Corballis, 2008; Corey et al., 2001; Ocklenburg and Güntürkün, 2018b). Approximately 90% of the total population is considered to be right-handed, whilst the remaining 10% are categorised as left-handers (e.g., Corballis, 2008; McManus, 2002; Papadatou-Pastou et al., 2020; Pfeifer et al.,

2022). This quota is observed independently of ethnicity (Papadatou-Pastou et al., 2020), nationality (Dawson, 1977; Perelle & Ehrman, 1994), and history (Bradshaw & Rogers, 1996; Llaurens et al., 2009), with the majority of the population being considered right-handers (Salmaso & Longoni, 1985). Nevertheless, there are observable variations in the handedness-ratio within different conditions – for example, a larger percentile of men than women are observed to be left-handed (e.g., Bryden, 1977; McManus, 2002; Papadatou-Pastou et al., 2020; Shimizu and Endo, 1983). Furthermore, differences in behavioural and cognitive abilities have been observed across different handedness groups, in studies measuring memory (Peters & Murphy, 1992; Propper et al., 2005), religious and spiritual belief (e.g., Barnett and Corballis, 2002; Christman, 2008), intelligence (e.g., Luders et al., 2007), creativity (e.g., Nicholls et al., 2010; Van der Feen et al., 2020), and physical performance (e.g., Grouios et al., 2000; Grouios et al., 2002; Gualdi-Russo et al., 2019; Loffing et al., 2012; Loffing & Hagemann, 2016; Raymond et al., 1996). Findings of cognitive and physical differences across handedness groups increase scientific, as well as general every-day interest in the neural mechanisms that affect handedness (Peters & Murphy, 1992). The topic is of interest as it clearly implies the existence of asymmetric lateralization in the brain (Marcori et al., 2019), and understanding handedness should therefore lead to a better understanding of lateralization in general (McManus, 2019).

### ***1.2.1 Assessing Hand Preference and Performance: Questionnaires and Task Trials***

There should be noted that defining handedness as a scientific term has proven itself to be a challenging task. Firstly, handedness can be denoted as both hand *preference* and hand *performance* (Ocklenburg and Güntürkün, 2018b), representing an individual's subjective preference for using a specific hand for manual activities, or an individual's objectively superior hand for performing manual activities, respectively. In the large range of studies covering handedness, this distinction is often not considered, and the term 'handedness' is used as a single continuous variable measure, measuring unspecified aspects of the term. Secondly, the categorisation of handedness varies significantly between studies (Hampson & Sankar, 2012), making it difficult to definitively quantify handedness in the population according to a dichotomous differentiation. Handedness is considered according to either a directional preference, separating blatantly between left- versus right-handedness (Witelson, 1989), or a consistency preference, separating between always right and mixed-handed (MH) (Habib et al., 1991; Witelson, 1985). As pointed out by Salmaso and Longoni (1985), since handedness is a continuous variable (Van der Feen et al., 2020), defining it is somewhat



arbitrary, and creating handedness groups by parting the continuum is highly dependent on a subjective choice of criterion. This further complicates the process of studying the causative reasons behind handedness asymmetry. Both the vague and varying definitions of handedness, as well as the shifting categorisation of handedness groups affects the methods used for measuring handedness on an objective scale.

The collective literature of handedness-research encompasses multiple different approaches for measuring handedness to assess a differentiation between different handedness groups. The most common and, arguably, most intuitive way of measuring handedness has long been assessing which hand is used or preferred when writing or drawing (e.g., Dorion et al. 2000; Salmaso & Longoni, 1985). This method is widely popular as it is relatively straightforward, quick, and affordable. Additionally, writing or drawing is a dexterity-related skill that clearly reflects the right-hand preference prevalent in the population. However, it should be noted that this population-asymmetry observation is often a measure of observed or self-reported hand-preference when writing or drawing. Hand preference is often quantifiably measured with questionnaires, allowing the subjects to state the hand they prefer to use for the given tasks and activities (e.g., Annett, 1970; Bryden, 1977; Crovitz & Zener, 1962; Steenhuis & Bryden, 1989). The most widely used handedness questionnaire is the Edinburgh Handedness Inventory (EHI), also often called the Edinburgh Handedness Questionnaire (EHQ) (Oldfield, 1971). This questionnaire asks subjects to specify which hand they prefer to use when performing a given activity. For instance, what hand the subject uses to write or opening the lid of a box. The answers are quantified and scored as a laterality quotient (LQ) for all ten items, ranging from -100 to +100, categorising the participants as left-handers or right-handers, respectively. Subsequently, alternative coding schemes have been proposed as well (Annett, 2001; Geschwind and Behan, 1982; Luders et al., 2010a). On some occasions, it is less relevant to measure handedness using a questionnaire, as asking the subjects to perform practical activities might be more viable (Bryden et al., 2007; Laland et al., 1995). For instance, many studies ask participants to perform activities covering the items listed in the EHI. Hand performance is also usually measured practically, as this assesses objective differences in the dexterity between the left- and right hand of participants. Practical performance of hand activities is often considered to provide more reliable results than those of questionnaires (Bryden et al., 2007; Laland et al., 1995; Lezak, 2012; Luders et al., 2010a). Tasks like ‘the pegboard task’, which involves participants moving rows of pegs between rows on a board, are normally used to measure handedness in practice (Annett et al., 1970). Other practical measuring methods include ‘the circle-marking task’ (Tapley & Bryden,

1985), grip strength tasks (Provins & Magliaro, 1993) and ‘the rapid finger-tapping’ task (Peters & Durdging, 1978; Peters & Servos, 1989).

### ***1.2.2 Issues When Measuring Handedness***

Complications in defining and measuring handedness objectively and consistently creates difficulties when attempts are made to explain handedness asymmetry (Ruck & Schoenemann, 2021). In order to reliably investigate the relationship between hand preference and cerebral organization, it is important to consider the possible moderation effects that affect both the participants of the study, as well as the characteristics of the study. When searching through the literature, there are observable different characteristics of handedness-studies which have shown to have significant effect on the prevalence of left-handedness across studies (Papadatou-Pastou et al., 2020; Luders et al., 2010a). When measuring handedness, specifically, how researchers define handedness lateralization and subsequently measure handedness scores, has shown to be critical for the categorisation and grouping of participants (Papadatou-Pastou et al., 2020; Westerhausen & Papadatou-Pastou, 2022).

Categorising groups according to hand preference dictates the partition of the continuous variable that is obtained with the handedness questionnaire (Christman, 2018). Handedness is often considered a binary trait, which can be measured according to a set handedness-quotient, dividing between left- or right-handedness (Büsch et al., 2010). In other cases, the categorisation depends on the degree of handedness lateralization, distinguishing between consistent and non-consistent left- and right-handers (Prichard et al., 2013). Consequently, variations of the different classification schemes are utilized across different studies, most often using either the right-, mixed-, and left-handed classification, the right-left handedness classification, or the right- non-right handedness classification. Directional classification of handedness has historically been the instrument of choice for research examining hand preference, and by this means comparing right- and left-handed individuals (Prichard et al., 2013). In more recent years, however, the focus has shifted from comparing direction of handedness, to looking at the degree of handedness (Papadatou-Pastou et al., 2020; Prichard et al., 2013). An issue that arises when there exist multiple different ways of measuring the same variable, is that individuals can be considered left-handed in one study whilst at the same time be considered MH in another study, or even right-handed based, for instance, only on the fact that the participant writes or draws with their right hand. By contrast, other authors consider individuals to be right-handed only if they perform all items of a questionnaire using their right hand (e.g., Annett, 1967; Geschwind and Behan, 1982).

The quantity within handedness groups varies significantly across studies, depending on the cut-off values used for categorisation. A meta-analysis by Papadatou-Pastou et al. (2020) showed that classification of handedness categories has a clear moderation effect, with the quantity of left-handers being highest in studies using a non-right-right classification (16.57%). The number of left-handers were lower when using the right-left classification (10.16%), and lowest for studies using a right-mixed-left classification (9.49%). Evidently, when the criteria for left-handedness categorization becomes stricter, the occurrence of left-handedness in studies drops. Nonetheless, the frequently observed 1:10 ratio of left- versus right-handers is still evident, independently of the classification used.

The structure and formulation of the questionnaires can determine the way participants interpret and answer the questions, and subsequently affect the distribution (Bryden, 1977). Still, which and how many items that should be included in a questionnaire is not universally agreed upon and varies across studies. Writing is one of the most common items to be included in questionnaires of hand preference, and often, classification of handedness is based purely on whether the participant write with their left or right hand. However, writing does not necessarily represent an individual's general hand preference across other activities – only their preference when it comes to writing. Writing is also more likely to be shifted towards right-handedness than most other items often included in handedness questionnaires (Hampson & Sankar, 2012; Kushner, 2013; Levy, 1974; Marcori et al., 2019). Salmaso and Longoni (1985) points out that the items 'writing' and 'drawing' show consistently superior right-hand preference among participants than do other items. The authors posit that the skewed preference across the items is due to writing and drawing being activities that are traditionally more subjected to social pressure. It is, however, possible to imagine that other forms of environmental influences might shift handedness towards the left as well. Inclusion of items that cover such activities might produce more left-hand preference data. Evidently, Salmaso and Longoni (1985) showed that a larger percentile of the subjects was right-hand dominant for writing (93.1%). However, on other items, this percentile was significantly reduced, proving more variation in hand-preference across different fine-motor activities than the traditional divide between right- and left-handers normally indicates. For instance, subjects preferring their left hand for holding a broom or a cricket bat was as high as 21.4% and 16.8%, respectively. These findings emphasizes that the quality of questionnaire items varies, and that some activities might be a better indication for handedness than others. As concluded by Salmaso and Longoni, percentages of left-handed individuals are not easily comparable as their group-placement might be based on a range of different evaluation

methods. Therefore, comparisons between studies using different questionnaires and quotas for handedness might not be reliable. Furthermore, the authors stress how variation in number and kind of items used in questionnaires reduces the validity of questionnaires as a measure of handedness across studies. Variations in hand-dominance across different activities points to the possibility that handedness has developed in accordance with environmental necessity and fitness. Understanding the origin of the asymmetry in hand-preference bias might therefore direct us towards a more appropriate way of objectively measuring handedness.

### ***1.2.3 Nature or Nurture: The Origin and Ontogeny of Handedness***

Whilst there is clear evidence for the actual asymmetry of handedness in the population, the origin of this divide is unclear and much discussed in the literature (Hardie & Wright, 2014). Multiple authors have attempted to explain handedness asymmetry by studying sex (e.g., Breedlove and Hampson, 2002; Davis & Annett, 1994; Geschwind & Galaburda, 1985; Hampson & Sankar, 2012; Luetjens, & Weinbauer, 2012; MacLusky & Naftolin, 1981; McManus & Bryden, 1991; Papadatou-Pastou et al., 2008; Papadatou-Pastou et al., 2020; Witelson, 1991), twins- and siblings (e.g., Annett, 2001; Davis & Annett, 1994; Jordan, 1911; McManus & Bryden, 1992; Pfeifer et al., 2022; Reiss, 1996; Sicotte et al., 1999), culture (e.g., Hung et al., 1985; Jung & Jung, 2009; Kushner, 2013; Laland, 2008; Laland et al., 1995; Levy, 1974; Marcori et al., 2019; Porac et al., 1990; Teng et al., 1976; Xu & Zheng, 2017), prenatal influences (e.g., Corballis, 2001; Hampson & Sankar, 2012; McManus & Bryden, 1992; Paracchini, 2021), and parental influences and environmental impacts affecting individuals in early stages of life (e.g., Bakan et al., 1973; Carter-Saltzman, 1980; Fox, 1985; Laland, 2008; Ocklenburg et al., 2010; Satz, 1973). A formative hypothesis regarding the neurobiological ontogenesis of handedness assumes a systematic association between the lateralization of handedness and other cognitive functions (e.g., Grimshaw and Wilson, 2013; Knecht et al., 2000; Nicholls et al., 2010; Ocklenburg et al., 2014). For instance, while a left-hemisphere dominance for language lateralization is evident across the population, irrespective of handedness (e.g., Carey & Johnstone, 2014), some people are right-hemisphere dominant for language, and this prevalence is found to be higher in left-handers than in right-handers (Carey & Johnstone, 2014). About 5-6% of right-handers have this atypical right-hemisphere language dominance, whilst about 30% of left-handers show this same lateralization pattern (Corballis, 2008; McManus, 2019). While degree of handedness does not necessarily mirror degree of language lateralization (Somers et al., 2015), Knecht et al. (2000) reported a linear relationship between the degree of handedness

and direction of language dominance. Strongly left-handed participants of this study demonstrated right-hemisphere language dominance almost seven times higher compared to the strongly right-handed participants (Knecht et al., 2000, p. 2513). Given that there appears to be a significant relationship between handedness and cognitive functions such as language and others, the neurological basis for handedness is a topic of high curiosity (Nicholls et al., 2010). Most prevalent in the handedness literature is the role of the neurological structure of the corpus callosum. Relationships between size of the corpus callosum and its subregions and different cognitive abilities have been found (Ocklenburg & Güntürkün, 2018b), further supporting the belief that callosal size and morphology might affect functionality, specifically handedness. Interest for the callosal structure in handedness research especially increased after the publication of the ground-breaking findings made by Sandra Witelson in the late 1980s.

#### ***1.2.4 Handedness and the Corpus Callosum: The Witelson Findings***

In 1985, Sandra Witelson published her pivotal article in which she reported that the corpus callosum of left-handed and ambidextrous individuals were larger compared to that of right-handers (Witelson, 1985; 1989; Witelson & Goldsmith, 1991). The results of the study showed that the corpus callosum of the left-handed and MH participants were 11% larger than the corpus callosum of right-handed participants. Witelson explained the larger amount of fibre tracts among NcRH individuals to be the result of increased interhemispheric interaction which is needed when handedness and language is represented in separate hemispheres (Aboitiz et al., 1992). This explanation was supported by Moffat et al. (1998), who, in their magnetic resonance imaging (MRI) study, investigated the relationship between speech lateralization and corpus callosum morphology of left-handed male participants. The authors found evidence for larger corpus callosum size among left-handers who also are left-hemisphere dominant for speech functions, compared to left-handers who were right-hemisphere lateralized for speech functions. The findings comparing cRH versus MH make it possible to assume that there exists a functional relationship between hand preference and callosal connectivity. Seemingly, less consistent hand preference requires more coordination through interaction between the hemispheres than do more consistent hand preference. Simply put, a stronger callosal connection in less lateralized groups such as MH, is to be predicted. As such, when attempting to explain the theoretical relationship between handedness and the corpus callosum, directional approaches appear less clear than consistency approaches. In 1989, Witelson replicated the findings of her 1985-study, further supporting the theory stating

that the corpus callosum of NcRH individuals were larger than among the cRH individuals in the post-mortem dataset. Specifically, the size-difference was significant in the isthmus substructure, located in the splenium region of the posterior corpus callosum, an area which connects the temporoparietal regions of the left and right hemispheres (Habib et al., 1991; Ocklenburg & Güntürkün, 2018a).

### ***1.2.5 Critiques Towards the Witelson Findings: Methodological Challenges When Measuring The Relationship Between Corpus Callosum Morphology and Handedness***

Whilst the findings of Witelson (1985; 1989) exposed the possible essential relationship between corpus callosum morphology and human handedness, others have failed to replicate these findings, and criticize conclusions drawn in the studies, pointing to central limitations in the methodology (e.g., Kertesz et al., 1987; O’Kusky et al., 1988; Westerhausen & Papadatou-Pastou, 2022; Zaidel et al., 1990). For instance, Witelson’s explanation for larger corpus callosum among non-right handers reflecting higher interhemispheric interaction does not explain why there is a higher prevalence of right-hemisphere dominance for language among left-handers compared to right-handers. According to Witelson’s theory, only left-handers who are left-hemisphere lateralized for language should have a larger corpus callosum than left-handers who are right-hemisphere lateralized for language (Moffat et al., 1998). However, it should be noted that Witelson (1985; 1989) did not provide any information regarding the language lateralization of the participants, and make no statements regarding left-hander’s higher right-hemisphere lateralization of language. Similar to Witelson, Luders et al. (2010a), claimed that callosal size is not necessarily related to the direction, but rather the degree of handedness lateralization. In Witelson (1985), the hand-preference of participants were collected using the Annett's Hand Preference Questionnaire, and participants were considered either right- or mixed-handed. Luders et al. (2010a) hypothesized that the size of callosal regions is dependent on the strength of lateralization, regardless of the direction of handedness. Meaning that participants who are strongly left- or right-handed are more likely to have larger callosal areas than individuals who are less strongly lateralized, like MH or ambidexters. Habib et al. (1991) questions Witelson’s assessment of subject’s handedness, and some (e.g., Westerhausen & Papadatou-Pastou, 2022) have critiqued that Witelson did not include any left-handed participants in the study, while at the same time concluding that left-handers have a larger corpus callosum than cRH.

In addition, both white and grey matter structures of the forebrain (Tamnes et al., 2013; Westlye et al., 2010) and the corpus callosum (Danielsen et al., 2020; Jäncke et al.,

1997) has shown to change throughout the lifespan. As the studies were post-mortem, the participants of Witelson (1985; 1989) were not necessarily healthy nor of young age, but non-healthy patients, whose age ranged from 25 to 65 at the time of death. As the subjects were patients who had possibly undergone medical treatment, such treatment could have some effect on neural development, although the patients suffered from peripheral cancer, which should not directly affect the central nervous system (Deprez et al. 2012; Westerhausen & Papadatou-Pastou, 2022). Furthermore, post-mortem research has its own pitfalls, possibly affecting measures of neuroanatomical structures. For instance, post-mortem deformation is the brain's tendency to shrink after death and removal from the rest of the body, and extraction and measures of neuroanatomical structures, such as the corpus callosum, might suffer from possible human errors (Lewis, 2002; Stan et al., 2006).

The many limitations of the Witelson studies highlights the pitfalls of non-definitive terminology-definitions and varied handedness assessments, and exemplifies the typical challenges present when studying handedness, especially in relation to neuroanatomical structure and function. In order to achieve a greater understanding of the relationship between handedness and the corpus callosum, the mentioned methodological challenges must be considered and accounted for, to increase scientific validity and reliability.

### **1.3 Aim of the Present Study**

The relationship between human handedness and corpus callosum morphology is, evidently, a much-discussed topic in the literature. Early findings suggest a direct relationship between corpus callosum morphology and consistency in handedness, proposing that larger callosal structures are present among MH individuals than in cRH individuals (Witelson, 1985; 1989). Witelson interpreted these findings to indicate that less-lateralized hemispheric organization for handedness is associated with stronger callosal connectivity than a strongly lateralized organization. However, a range of subsequent studies have presented varying results when attempting to study the relationship between corpus callosum morphology and handedness, either confirming (e.g., Habib et al., 1991; Denenberg et al., 1991; Clarke and Zaidel, 1994) or contradicting (e.g., Jäncke et al., 1997; Kertesz et al., 1987; Westerhausen & Papadatou-Pastou, 2022) the influential Witelson-findings. Habib et al. (1991), mentions multiple studies who were unable to replicate the findings of Witelson (1985) using MRI. The large variations in methodological approaches, including inconsistent callosal sectioning definitions, handedness assessments, and largely differing subject-pools, are to blame for inconsistent findings of callosal morphology and handedness relationship. Most importantly, a

trend in the literature is the struggle to replicate the findings of Witelson (1985; 1989). A recently published meta-analysis by Westerhausen & Papadatou-Pastou (2022) analysed the data from 24 different studies examining human handedness and corpus callosum, published between 1985 and 2020. The different studies analysed in the meta-analysis differed in handedness assessments (EHI versus the Annett's Hand Preference Questionnaire (Annett, 1970) versus handedness questionnaires by Bryden (1977)), method of data-collection (in vivo versus post-mortem), method of analysis, and number of participants. 23 of the 24 studies provided measures of total corpus callosum size, while only 16 of the 24 studies provided measures for one or more callosal subsections (for more information, see Westerhausen & Papadatou-Pastou, 2022). The authors found no significant association between corpus-callosum morphology and handedness, for neither total size nor subregions of the corpus callosum. This meta-analysis emphasises the absence of support for the original findings of Witelson (1985; 1989; Witelson & Goldsmith, 1991). Nevertheless, these papers are still referenced in the literature as a reliable foundation for handedness and corpus-callosum research (e.g., Dorion et al., 2000; Hampson & Sankar, 2012; Parker et al., 2017; Sala et al., 2017).

Consequently, the predominant aim of the present study is to attempt to conceptually replicate the historically influential Witelson findings (1985; 1989), by conducting a modified design using a significantly larger sample than was used by the original author. The study will ultimately consider the shape of the relationship between handedness, representing hand-preference according to the EHI, and callosal morphology. To answer the research questions, the present study incorporates more advanced technology in the form of structural MRI, using the *1200 Subject Data Release* dataset from The Human Connectome project (Van Essen et al., 2013), which includes information of the subject's handedness, age, and sex. Handedness will be coded following a typical classification scheme (LQ of  $>|80|$ ) to define consistent hand preference. Using structural MRI allows us to use data collected from living participants of a younger age and healthy condition, as opposed to the post-mortem data collected from patients and utilized in the original study. As previously described by multiple authors (e.g., Danielsen et al., 2020; Prendergast et al., 2015; Salat et al., 1997), lifespan changes in the corpus callosum shows a decreasing trajectory towards older age. Therefore, data collected from subjects in the age-range where mean relative callosal thickness measures reach their peak in the early twenties (Danielsen et al., 2020), was considered most applicable in the present study.



Witelson (1985; 1989) did not include consistent left-handed subjects (cLH), and the present study will conduct the primary analysis excluding cLH participants, to ensure replication. Importantly, the present study will follow suggestions made by previous authors (Westerhausen & Papadatou-Pastou, 2022), and consider total brain size as a confounding variable when measuring corpus callosum size. This will be achieved by considering the absolute measures of midsagittal corpus callosum area as well as the structure's ratio to total forebrain size (Smith, 2005). Measures and analyses of the isthmus-area of the corpus callosum in relation to handedness will be of high importance, as previous authors have highlighted this posterior callosal substructure as significantly different in size among MH subjects compared to cRH subjects (Denenberg et al., 1991; Witelson, 1989).

## 2. Material and Methods

### 2.1 Sample

To answer our research questions, we utilized a structural MR scan dataset from the Human Connectome Project (HCP); more specifically their *1200 Subject Data Release* dataset (Humanconnectome, 2017; Van Essen et al., 2013). The HCP is an open-data initiative which provides structural and functional neuroimaging data and makes it available for usage in a variation of studies. The dataset was collected by the HCP in the period of August 2012 and October 2015 and made publicly available for download. Both raw MRI data as well as tabulated data (restricted, unrestricted) of the HCP project will be utilized in the present study. Unrestricted data was downloaded on 12<sup>th</sup> of April 2021, and restricted data was downloaded on the 19<sup>th</sup> of April 2021, from the HCP website by René Westerhausen. The dataset sample contains T1-weighted imaging data from 1206 subjects, with a sex distribution of 656 women (54.4%) and 550 men (45.6%). An a priori power analysis was conducted using G\*Power3 (Faul et al., 2007). The sensitivity considering the present sample size (estimated as 600 cRH and 450 MH, i.e.,  $N = 1050$ ) is  $F = .11/d = .22$  at a test power of .95 (alpha .05), using a two-tailed test (see Raaf & Westerhausen, 2021). The 1200 Subject Data Release dataset includes only healthy participants, meaning participants with no known psychological, physical, or neurological illnesses. As a part of the 'HCP Young Adult'-project, the dataset contains only young adult participants, with a mean age of 28.84 years, and a standard deviation (*SD*) of 3.69 years. Additionally, the dataset includes behavioural data and information from each subject, including age, gender, and handedness; variables which are applied in the present study. The effect of interest in this present study is the main effect of handedness, and the

dataset contains 670 cRH, 504 MH, and 32 cLH, calculated during data collection, using the EHI.

## **2.2 Structural Magnetic Resonance Imaging Acquisition**

The data collection was done by the HCP by performing structural MR scans of the participants (Glasser et al., 2016). All HCP 3T imaging data collection was done with a Siemens Skyra “Connectome” scanner with a customized SC72 gradient insert. The relevant T1 weighted imaging sequence was acquired using the following parameters: field of view (FOV) = 224x224 mm; matrix = 320, 256 sagittal slices in a single slab. A 32-channel head coil was used for sequencing (repetition time (TR) = 2400 ms; echo time (TE) = 565 ms; inversion time (TI) = 1000 ms; flip angle (FA) = 8 degrees; band width (BW) = 210 Hz per pixel; echo spacing (ES) = 7.6 ms. The images have a 0.7 mm isotropic structural resolution.

## **2.3 Callosal Measures**

HCP provides measures of morphometric statistics generated automatically by utilizing the FreeSurfer processing pipeline, as well as functional data (Glasser et al., 2016). The data which was downloaded and utilized in the present study was EHI data (HCP variable name “Handedness”), age (“Age\_in\_Years”), sex (“Gender”), and forebrain volume (“FS\_SupraTentorial\_Vol”). Additionally, the T1-weighted images were utilized to determine the midsagittal surface of the corpus callosum, in order to quantify anatomical variations in callosal morphology between the subjects. Using the midsagittal plane, as compared to the parasagittal plane, allows us to measure regional differences across the corpus callosum, which is necessary to attempt to conceptually replicate Witelson’s parcellation scheme (1985; 1989).

Initial quality control of the structural MRI was performed by the HCP, as experienced raters evaluated the structural scans and categorized them as either excellent, good, fair, poor, or unusable according to previously established criteria vis-à-vis the tissue contrast, blurriness, and banding artifacts. Assessment of scan quality and possible neuroanatomical anomalies were performed by a radiologist. The images of all participants were re-processed by the HCP using a v3.19.0 version of the diffusion pipeline to remove noise caused by subject movement. For 1113 of the total 1206 participants in the sample, structural MR-scans were collected, as well. Furthermore, for 45 of the 1113 subjects with 3T imaging data, the data-collection was repeated, in order to secure retest reliability. For more information on the

processing of the dataset used in this thesis, see the HCP website:

<https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release>.

## **2.4 Exclusion of Participants**

Whilst the total dataset includes 1206 participants, only 1113 of these subjects have available structural MR images, which are of interest in this study. We only included participants with structural MR scans. During download, the data information of one subject failed to download and this participant was therefore excluded from the study. Additionally, standard quality control performed by the HCP on all HCP subject structural scans highlighted a group of subjects who were not eligible for inclusion in this study. The 47 subjects included under Issue code A: “Anatomical anomalies” according to HCP were excluded (see: <https://wiki.humanconnectome.org/pages/viewpage.action?pageId=88901591>). Furthermore, extraction of the corpus callosum of four participants was unsuccessful, and these participants were excluded from our study. After exclusion, the total number of subjects in the present study were 1061, with a sex distribution of 584 women (55.04%) and 477 men (44.96%). The total 1061 participants have a mean age of 28.83 years ( $SD = 3.71$  years) (See Appendix A).

## **2.5 Handedness assessment**

### ***2.5.1 The Human Connectome Sample***

The HCP assessed the hand preference of each participant using a “short form” version, of the Edinburgh Handedness Inventory (EHI) (Ruck & Schoenemann, 2021). The HCP’s variable Handedness, which is available as restricted tabulated data, is supposed to represent the EHI handedness scores of the participants. However, the variables that went into the EHI score includes merely 9 of the 10 EHI “manual” items that are available in the original questionnaire, leaving out the item “drawing”. The HCP “Handedness” score was therefore calculated using the nine “manual” questions from the EHI and including the “Hand\_Foot” question for measure of footedness, as well. Thus, the Handedness variable provided with the HCP data appears to be a mix of manual and pedal preference and cannot be unequivocally interpreted as handedness score. Because only nine of the 10 original items asking for manual preference were available within the HCP data, we adjusted the method of calculating the EHI. For the 10-item Likert scale it is suggested to count the answers

“usually” as five points and “always” as 10 points for the respective hand. The resulting difference between the right and left hand-scores (R-L) can be interpreted as the calculated LQ (Schachter, 2000). The calculated LQ ranges from -100 to 100. To achieve a comparable LQ estimate with the nine items used by HCP, two alternative approaches emerge. Firstly, one could adjust the weight per item, i.e., using the weight of 5.556 (100/18) for “usual” and 11.111 (100/9) for “always” answers. Alternatively, the weight of the item “writing” can be doubled if one assumes the missing item “drawing” is comparable to “writing”. While the first approach would yield a LQ representing the nine-item HCP-modified EHI version well, this LQ might be less comparable to the EHI LQ reported in the literature. That is, it was shown, by testing a different dataset of  $N = 99$  participants which was available to the authors, that the answers of the missing “drawing” item correlate strongly with the answers to the item “writing” (Spearman correlation: 0.895). However, it is less strongly correlated with the other eight items (between 0.290 and 0.624). Only four of the 99 participants scored differently on the two items, and none of these 4 indicated to prefer a different hand for the two activities. This finding reflects the conclusions drawn in Salmaso and Longoni (1985), which states that both “writing” and “drawing” contribute to a consistently greater right-hand preference compared to other items in the EHI. This indicates that the double weighting of “writing” might bias the resulting EHI-score less than adjusting the weights of all items to make up for the missing item “drawing”.

The subjects were classified by the HCP according to the adjusted EHI as either cRH or NcRH, including both ambidexters and left-handers. Subjects were categorized as cRH if they had a LQ of +80 or more, whilst all who scored a LQ below +80 and above -80 were considered MH. The present study includes a calculation of handedness assessments by considering the various definitions of handedness that can be found in the literature. As the handedness data collected by HCP was scored using a modified EHI questionnaire, adjustments for the assessment of handedness according to both the different methods in the literature, as well as the absent item of the questionnaire, are included in the present study.

### ***2.5.2 Assessment of Handedness Groups in the Present Study in Accordance With the Qualitative Criteria Approach***

In the present study, the classification variable, referred to as “*Witelson I*”, is based on the nine items which ask for manual preferences in the EHI questionnaire used by HCP (see Table 1). The response format used in the HCP version consisted of a 5-step Likert scale

(answer options “Always Left”, “Usually Left”, “No Preference”, “Usually Right”, and “Always Right”) which were coded from 1 to 5, so that values 1 and 2 were here counted as a “left” answer, and values 4 and 5 as a “right” answer.

**Table 1**

*Demographic characteristics of handedness scores among the subjects of **Witelson1***

Hand group	Female		Male		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%*
cRH	381	59.91	255	40.09	636	60.17
NcRH	200	47.51	221	52.50	421	39.83

*Note. \*Total percentage of dataset of 1057 according to Witelson’s classification: consistency and qualitative evaluation, including cLH participants*

### **2.5.3 Assessment of Handedness Groups in the Present Study With cLH Removed**

Witelson (1985) included no cLH in the study-sample, and thus, to increase comparability between the present study and Witelson (1985; 1989), a second classification (*Witelson2*) was introduced by additionally identifying all participants which are cLH, by defining cLH as not showing any answers larger than “3”, so that the variable codes cRH, MH, and cLH. Furthermore, the cLH groups were excluded from the analysis to replicate the study sample of Witelson (1989) (see Table 2).

**Table 2***Demographic characteristics of handedness scores among the subjects of Witelson2*

Hand group	Female		Male		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%*
cRH	381	59.91	255	40.09	636	62.29
MH	180	46.75	205	53.26	385	37.71

*Note.* \*Total percentage of dataset of 1021, with cLH participants removed

## 2.6 Data Processing

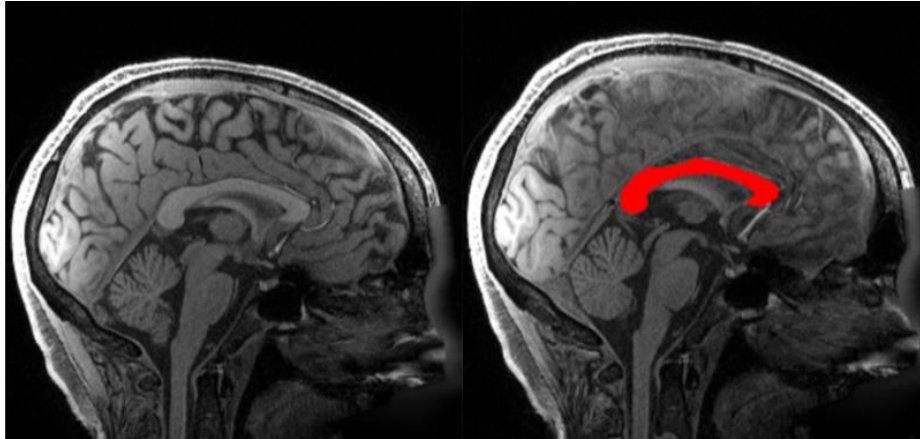
The initial part of the pre-processing of the data involves identifying and creating midsagittal slides of the corpus callosum, using automatic segmentation. Cropping of external facial and cranial features such as nose and neck was performed by the HCP before the data was introduced to the present study. The corpus callosum was extracted from T1-weighted files, a process which was conducted semi-automatically using the Linux environment *CCSeg*. The corpus callosum segmentation was carried out in the midsagittal plane of the structural MRIs, making it possible to create a visualisation of the structure. The segmentation algorithm used is based on a template initialization which is refined with mathematical morphology operations (Adamson et al., 2014; Székely et al., 1995).

The second pre-processing step involved necessary manual corrections of the automatic initial extraction, with the aim of extracting the total area of the midsagittal corpus callosum. The *CCSegThickness* pipeline software version 2.0 downloaded from <https://www.nitrc.org/projects/ccsegthickness> was used to manually correct and export the segmentation of the midsagittal corpus callosum. The toolbox comprises an end-to-end pipeline for callosal thickness analysis in T1-weighted MR image data consisting of the components of the midsagittal plane extraction, corpus callosum segmentation, a tool for quality control and possible manual editing, and a thickness profile generator (Adamson et al., 2014). Where the segmentation was not successful the “—seg-no-1k” modifier was removed. The segmentation of the corpus callosum was inspected by the authors, and, if needed, manual corrections was made to the segmentations. The authors were blinded to the hand preference of the subject during this procedure. The subsequent post-processing procedure is introduced

to detect and remove anterior pericallosal veins from the segmentation. Such corrections were needed if excess voxels surpassing the lines of the callosal structure were included, or if there were an absence of voxels in regions comprising the corpus callosum (see Figure 2). If neural abnormalities in the images were detected, the subjects were removed from the study.

## Figure 2

*Corpus callosum segmentation from an image in the midsagittal plane*

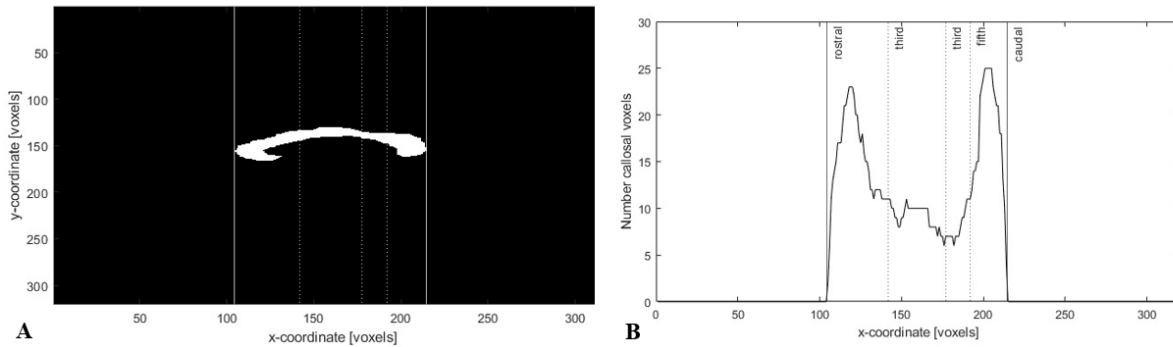


*Note.* Automatic segmentation followed by manual corrections of the automatic initial extraction, if necessary. Image is presented in a posterior- to – anterior direction. Facial and cranial features removed by the HCP, to avoid possible subject identification.

Finally, rotation of the corpus callosum was done using an in-house toolbox programmed in Matlab (see Westerhausen et al., 2016) in order to align the rostrum and the splenium of the corpus callosum along a straight line. The very endpoint of the rostrum in the anterior corpus callosum of each image was individually manually determined by one author to be the posterior-most voxel area of the in-bend anterior half of the structure, while the splenium was determined as the most ventral voxel in the posterior half of the region. The line between each identified point was rotated and the corpus callosum oriented along a horizontal line using the toolbox. This procedure was performed in order to create a consistent measure point for each section of the corpus callosum of each subject. Witelson (1989; Witelson & Goldsmith; 1991) found differences in subregional structures between handedness groups, with significant size differences appearing in the isthmus. Therefore, measures of subregions were conducted to analyse potential size-differences across the callosal substructures (see Figure 3). Finally, the corpus callosum segmentation is extracted and exported for further analysis.

**Figure 3**

*Measure of callosal subregional areas.*



*Note.* The vertical lines across both images show the partition: Solid lines show start and end of the corpus callosum, while dotted lines mark thirds and posterior fifth. **Figure 3A** presents the callosal outline after rotation. **Figure 3B** shows the number of voxels per column of the image matrix. The subregional area is depicted as the area below the curve between the respective lines. The isthmus area is located between the second third and the fifth line.

## 2.7 Statistical Analysis

All analyses were done using RStudio version 4.1.2. Variables mentioned are available for further clarity in Appendix B. Following our preregistration, four separate two-way between-groups analyses of variance (ANOVA) were performed to assess the difference in the midsagittal surface area of the corpus callosum across members of the different handedness groups. Each analysis was performed multiple times using the different handedness classifications *Witelson1* and *Witelson2* (see Appendix B). For the primary analysis performed, the dependent variable is the total size of the corpus callosum on the midsagittal surface area, assessed from structural T1-weighted MRI images. Using absolute measures of the midsagittal surface area allows us to attempt replication of the methodology of Witelson (1989), as this study did not include the ratio between the corpus callosum and total brain size. The independent variables were the categorical variables of Handedness as assessed in *Witelson1* (cRH vs. NcRH), as well as the Sex of the participants (Female vs. Male). An alpha threshold of 5% was adapted, and the effect size measure Cohen's *d*, reflecting the standardised mean difference of corpus callosum size, was calculated for each analysis. Additionally, the analysis was performed using the *Witelson2* handedness assessment classification (cRH vs. MH).

The second analysis considered the ratio between the size of the midsagittal callosal surface area and total forebrain volume. Forebrain volume was chosen based on justifications



by Jäncke et al. (1997) and gathered from T1- weighted images using the supratentorial volume (FS\_SupraTentorial\_Vol) provided by the HCP. Total forebrain volume was calculated by excluding neural regions that is not deemed a part of the supratentorial volume, meaning subcortical structures and the cerebellum. Determination of 2D representation of forebrain volume was done by raising the forebrain volume to the power of  $2/3$ , to convert it into an area equivalent value, making the numerator and denominator into the same unit. Ratios were then multiplied with 1000 to achieve a more convenient scaling for visualisation. Calculation of the interaction effect was done using the ratio of brain size and corpus callosum. The ratio was treated as a dependent variable, whilst the variables Sex and Handedness as assessed in *Witelson1* (cRH vs. NcRH) were used as independent variables. The analysis was also performed, following the same procedure, but using the *Witelson2* handedness assessment classification (cRH vs. MH).

Previous authors have questioned whether the size difference observed in the corpus callosum, reflects a subregional, rather than global effect (see Westerhausen and Papadatou-Pastou, 2022). In some studies, larger, significant size-differences in this posterior corpus callosum region have been highlighted (Denenberg et al., 1991). Particularly, Witelson (1989; Witelson & Goldsmith, 1991) noted that the isthmus region in the corpus callosum of NcRH participants was larger compared to that of the other subjects. Therefore, an analysis of variance to study the effect of both handedness and sex on the size of the isthmus was performed. In the same fashion as the primary analysis of midsagittal callosal surface area, analyses of the absolute isthmus measures were performed using the different handedness classifications *Witelson1* and *Witelson2*. The dependent variable is absolute measures of the isthmus subregion of the corpus callosum. The independent variables are the categorical variables of handedness as assessed in *Witelson1* (cRH vs. NcRH), as well as the Sex of the participants (Female vs. Male). Additionally, the analysis was performed using the *Witelson2* handedness assessment classification (cRH vs. MH).

To consider for the possible confounding effect of brain size, analyses of the ratio between isthmus callosal substructure area and forebrain volume were conducted. Forebrain volume was calculated similarly for isthmus ratio as for corpus callosum ratio measures. Ratios were then multiplied with 1000 to achieve a more convenient scaling for visualisation. Calculation of the interaction effect was done using the ratio of total forebrain volume measures and isthmus callosal substructure area measures. The ratio was treated as a dependent variable, whilst the variables Sex and Handedness as assessed in *Witelson1* (cRH

vs. NcRH) were used as independent variables. The analysis was also performed using the *Witelson2* handedness assessment classification (cRH vs. MH).

## **2.8 Ethical Considerations and Data Protection**

The research-project was internally ethically evaluated and accepted by ‘the Department of Psychology’s internal research ethics committee’ on January 20<sup>th</sup> (Reference number: 18092856). The dataset used is considered open access data, including all imaging data and most of the behavioural data. This means that the data is available to those who register an account at ConnectomeDB and agree to the *Open Access Data Use Terms*. As stated by the HCP, released data are not considered de-identified as combining certain restricted data might increase the possibility of subject-identification (Van Essen et al., 2013). The variable “handedness” is considered restricted data, but using only one restricted form of data avoids combining data that would make it possible to easily identify study subjects. We accordingly thought that approval from the Norsk Senter for Forskningsdata (NSD), to assure our storage and processing, was in line with Norwegian legislation (Ref. 724068).

## **3. Results**

### **3.1 Analysis of Midsagittal Surface Area Using Qualitative Criteria for Handedness Assessments: Including the Groups of cRH and NcRH**

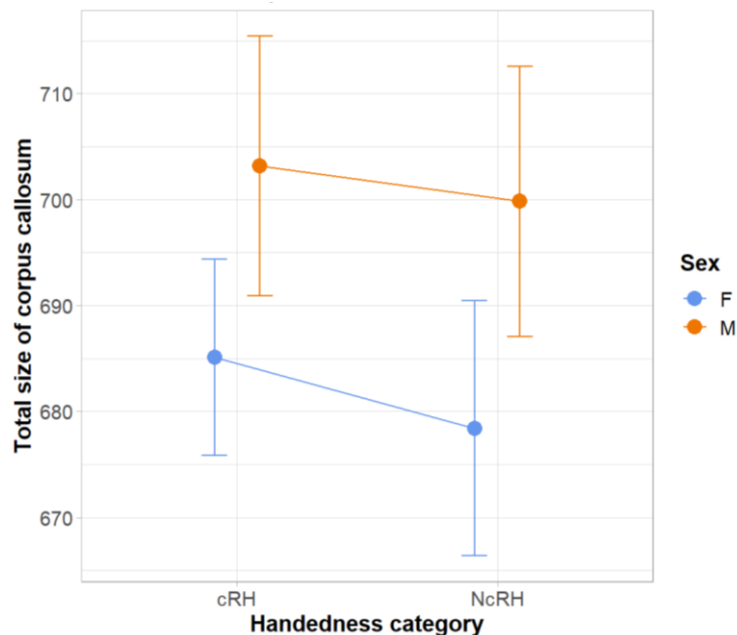
Four separate one-way between-groups ANOVAs was performed in order to investigate differences between the handedness groups of cRH and NcRH, as assessed in *Witelson* (1985;1989), and sex (female vs. male), including both main effect and the interaction effect.

#### **3.1.1 Total Midsagittal Surface Area of the Corpus Callosum**

The ANOVA of the absolute midsagittal corpus callosum area showed no significance of the main effect of Handedness ( $F(1, 1053) = .717, p = .397, \eta^2 < .001$ ) with cRH having a mean ( $\pm$  standard deviation) of  $692.4 (\pm 95.3) \text{ mm}^2$  and NcRH having a mean of  $689.7 (\pm 92.2) \text{ mm}^2$  (see Figure 4). The ANOVA yielded a significant main effect of Sex ( $F(1, 1053) = 11.056, p = .001$ ) with an effect size of  $\eta^2 = .0104$ , indicating the corpus callosum to be larger in men (mean area:  $701.62 \pm 97.8 \text{ mm}^2$ ) than in women ( $682.8 \pm 90.1 \text{ mm}^2$ ). Finally, the interaction of Sex and Handedness was also not significant ( $F(1, 1053) = .0801, p = .78, \eta^2 < .001$ ).

**Figure 4**

*Analysis of total midsagittal surface area of the corpus callosum*



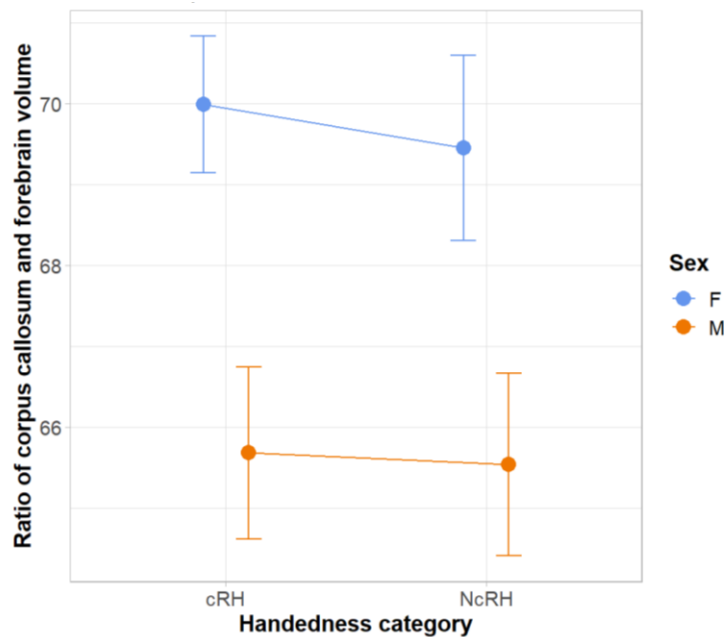
*Note.* The figure displays no significant interaction-effect of Handedness (cRH vs. NcRH) and Sex (F vs. M) on the total midsagittal surface area of the corpus callosum (mm<sup>2</sup>). As depicted in the plot, there is no present main effect of Handedness. There is an observable difference between cRH and NcRH, but this difference is not significant. There is a significant main effect of Sex on corpus callosum size, as men (M) were observed to have a larger callosal area than women (F), independent of Handedness. Error bars represent the 95% confidence limits.

### **3.1.2 Ratio of Total Callosum Area and Forebrain Volume**

For the sake of calculations for the analysis of the ratio, the measures of mean values and standard deviations of Handedness and Sex were multiplied by 1000. The ANOVA of the ratio of midsagittal corpus callosum area showed no significance of the main effect of Handedness ( $F(1, 1053) = .41, p = .522, \eta^2 < .001$ ) with cRH having a mean of  $68.27 (\pm 8.74)$  mm<sup>2</sup> and NcRH having a mean of  $67.40 (\pm 8.59)$  mm<sup>2</sup> (see Figure 5). The ANOVA yielded a significant main effect of Sex ( $F(1, 1053) = 59.17, p < .001$ ) with an effect size of  $\eta^2 = .053$  indicating the corpus callosum to be larger in women ( $69.8 \pm 8.3$  mm<sup>2</sup>) than in men ( $65.6 \pm 8.58$  mm<sup>2</sup>). Finally, the interaction of Sex and Handedness was also not significant ( $F(1, 1053) = .136, p = .71, \eta^2 < .001$ ).

**Figure 5**

*Analysis of the ratio of midsagittal callosal surface area and forebrain volume*



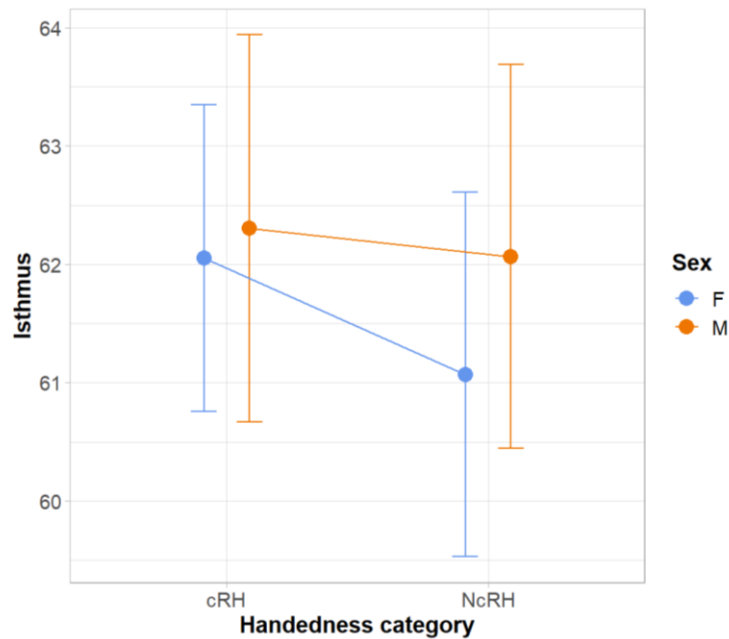
*Note.* The figure displays no significant interaction-effect between Handedness (cRH vs. NcRH) and Sex (F vs. M) on the ratio of the midsagittal callosal surface area and forebrain volume ( $\text{mm}^2$ ). As depicted in the plot, there is no main effect of Handedness. There is an observable difference between cRH and NcRH, but this difference is not significant. There is a significant main effect of Sex on corpus callosum size, as women were observed to have a larger callosal area than men, when counting for total forebrain volume size, independent of Handedness. Error bars represent the 95% confidence limits.

### **3.1.3 Isthmus**

The ANOVA of the absolute isthmus area showed no significance of the main effect of Handedness ( $F(1, 1053) = .59, p = .44, \eta^2 < .001$ ) with cRH having a mean of  $62.15 (\pm 13.02)$   $\text{mm}^2$  and NcRH having a mean of  $61.59 (\pm 11.68)$   $\text{mm}^2$  (see Figure 6). The ANOVA yielded no significant main effect of Sex ( $F(1, 1053) = .62, p = .43$ ) with an effect size of  $\eta^2 < .001$ . The size of the isthmus could be considered larger in women ( $61.71 \pm 12.28$   $\text{mm}^2$ ) than in men ( $61.19 \pm 12.78$   $\text{mm}^2$ ), but this observation is not significant. Finally, the interaction of Sex and Handedness was also not significant ( $F(1, 1053) = .22, p = .64, \eta^2 < .001$ ).

**Figure 6**

*Analysis of absolute isthmus callosal substructure area measures*



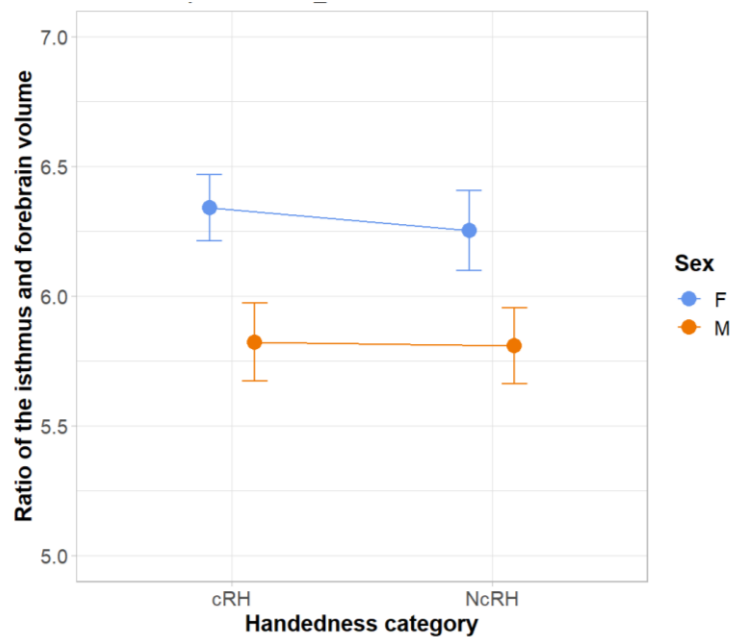
*Note.* The figure displays no significant interaction between Handedness (cRH vs. NcRH) and Sex (F vs. M) on the absolute measures of the isthmus (mm<sup>2</sup>). As depicted in the plot, there is no main effect of Handedness. There is an observable difference between cRH and NcRH, but this difference is not significant. Likewise, there is no significant main effect of Sex on isthmus size, but women were observed to have larger isthmus callosal substructure volume than men, independent of Handedness. Error bars represent the 95% confidence limits.

### **3.1.4 Ratio of Isthmus and Total Forebrain Volume**

For the sake of calculations for the analysis of the ratio, the measures of mean values and standard deviations of Handedness and Sex were multiplied by 1000. The ANOVA of the ratio of isthmus area and adjusted forebrain volume showed no significance of the main effect of Handedness ( $F(1, 1053) = .44, p = .506, \eta^2 < .001$ ) with cRH having a mean of  $6.134 (\pm 1.27) \text{ mm}^2$  and NcRH having a mean of  $6.021 (\pm 1.13) \text{ mm}^2$  (see Figure 7). The ANOVA yielded a significant main effect of Sex ( $F(1, 1053) = 40.43, p = .000$ ) with an effect size of  $\eta^2 = .037$ , with the mean relative size of the isthmus in women being larger ( $6.311 \pm 1.21 \text{ mm}^2$ ) than in men ( $5.82 \pm 1.16 \text{ mm}^2$ ). Finally, the interaction of Sex and Handedness was also not significant ( $F(1, 1053) = .243, p = .63, \eta^2 < .001$ ).

**Figure 7**

*Analysis of the ratio of isthmus callosal substructure area and forebrain volume*



*Note.* The figure displays no significant interaction between Handedness (cRH vs. NcRH) and Sex (F vs. M) on the ratio of isthmus callosal substructure area and total forebrain volume ( $\text{mm}^2$ ). As visible in the plot, there is no main effect of Handedness. There is an observable difference between cRH and NcRH, but this difference is not significant. There is a significant main effect of Sex, as women were observed to have a larger isthmus callosal substructure area than men, when considering total forebrain volume, independent of Handedness. Error bars represent the 95% confidence limits.

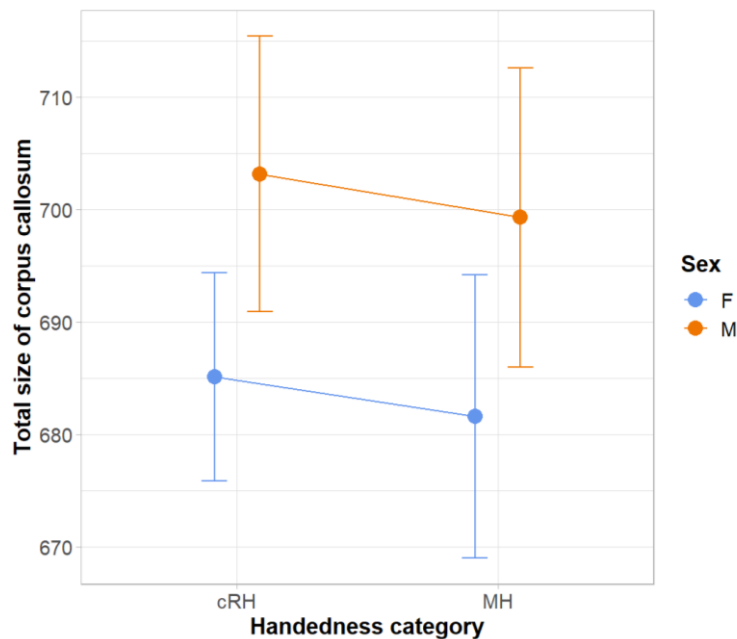
### **3.2 Analysis of Midsagittal Surface Excluding cLH: Including the Groups of cRH and MH**

#### **3.2.1 Total Midsagittal Surface Area of the Corpus Callosum**

The ANOVA of the absolute midsagittal corpus callosum area showed no significance of the main effect of Handedness ( $F(1, 1017) = .368, p = .544, \eta^2 < .001$ ) with cRH having a mean of  $692.4 (\pm 95.3) \text{ mm}^2$  and MH having a mean of  $691 (\pm 92.1) \text{ mm}^2$  (see Figure 8). The ANOVA yielded a significant main effect of Sex ( $F(1, 1017) = 8.565, p = .004$ ) with an effect size of  $\eta^2 = .008$ , indicating the corpus callosum to be larger in men (mean area:  $701.45 \pm 97.8 \text{ mm}^2$ ) than in women ( $684 \pm 90.03 \text{ mm}^2$ ). Finally, the interaction of Sex and Handedness was also not significant ( $F(1, 1017) = .001, p = .98, \eta^2 < .001$ ).

**Figure 8**

*Analysis of total midsagittal surface area of the corpus callosum*



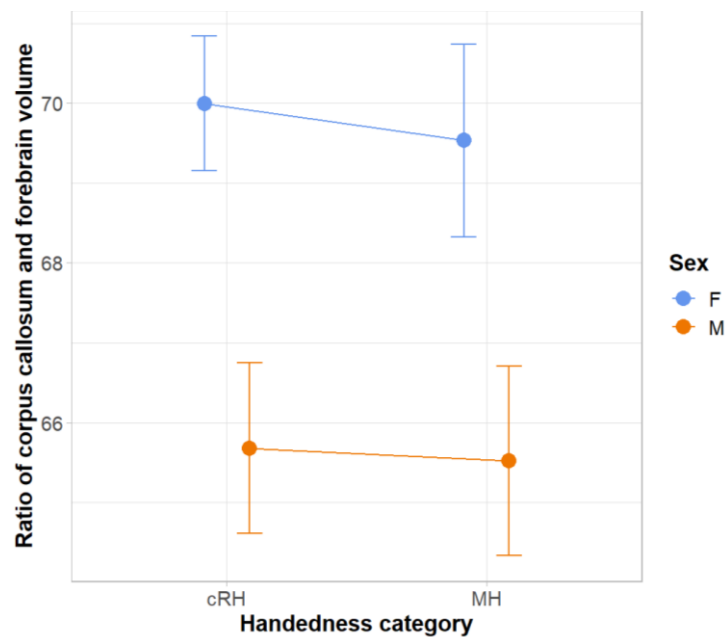
*Note.* The figure displays no significant interaction-effect between Handedness (cRH vs. MH) and Sex (F vs. M) on the total midsagittal surface area of the corpus callosum (mm<sup>2</sup>). As depicted in the plot, there is no main effect of the Handedness categories. There is an observable difference between cRH and NcRH, but this difference is not significant. There is a significant main effect of Sex on corpus callosum size, as men were observed to have a larger callosal midsagittal surface area than women, independent of the Handedness. Error bars represent the 95% confidence limits.

### **3.2.2 Ratio of total callosum area and forebrain volume**

The ANOVA of the relative midsagittal corpus callosum area showed no significance of the main effect of Handedness ( $F(1, 1017) = .32, p = .57, \eta^2 < .001$ ) with cRH having a mean of  $68.27 (\pm 8.74)$  mm<sup>2</sup> and MH having a mean of  $67.4 (\pm 8.65)$  mm<sup>2</sup> (see Figure 9). The ANOVA yielded a significant main effect of Sex ( $F(1, 1017) = 57.07, p < .001$ ) with an effect size of  $\eta^2 = .052$  indicating the corpus callosum to be larger in women ( $69.84 \pm 8.32$  mm<sup>2</sup>) than in men ( $65.61 \pm 8.62$  mm<sup>2</sup>). Finally, the interaction of Sex and Handedness was also not significant ( $F(1, 1053) = .07, p = .79, \eta^2 < .001$ ).

**Figure 9**

*Analysis of the ratio of midsagittal callosal surface area and forebrain volume*



*Note.* The figure displays the interaction-effect between Handedness (cRH vs. MH) and Sex (F vs. M) on the ratio of the midsagittal callosal surface area and forebrain volume ( $\text{mm}^2$ ). As depicted in the plot, there is no main effect of Handedness. There is an observable difference between cRH and NcRH, but this difference is not significant. There is a significant main effect of Sex, however, as women were observed to have a larger callosal area than men, when considering total brain size, irrespective of Handedness. Error bars represent the 95% confidence limits.

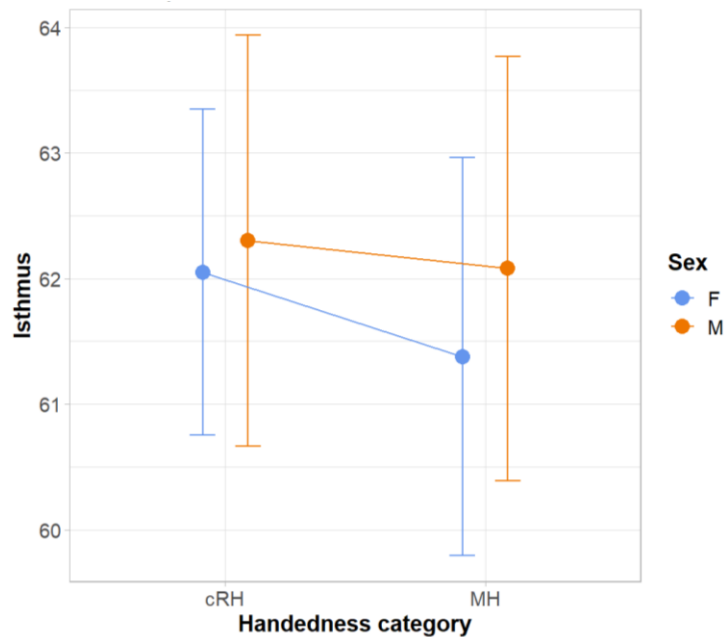
### **3.2.3 Isthmus**

The ANOVA of the absolute isthmus area presented no significance of the main effect of Handedness ( $F(1, 1017) = .30, p = .59, \eta^2 < .001$ ) with cRH having a mean of  $62.15 (\pm 13.03) \text{ mm}^2$  and MH having a mean of  $61.75 (\pm 11.59) \text{ mm}^2$  ( see Figure 10). The ANOVA yielded no significant main effect of Sex ( $F(1, 1017) = .34, p = .56$ ) with an effect size of  $\eta^2 < .001$ . The size of the isthmus could be considered larger in men ( $62.20 \pm 12.81 \text{ mm}^2$ ) than in women ( $61.84 \pm 12.24 \text{ mm}^2$ ), but this observation is not significant. Finally, the interaction of Sex and Handedness was also not significant ( $F(1, 1017) = .078, p = .78, \eta^2 < .001$ ).



**Figure 10**

*Analysis of absolute isthmus callosal substructure area*



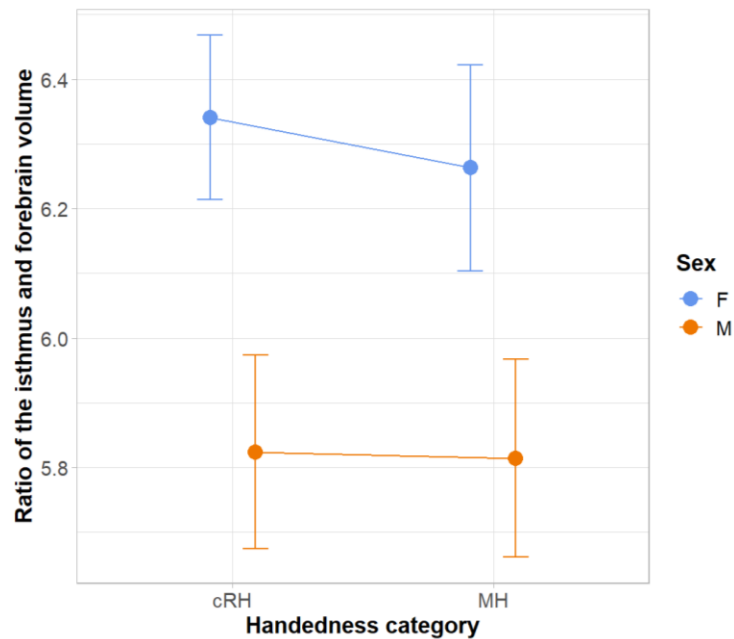
*Note.* The figure displays no significant interaction between Handedness (cRH vs. MH) and Sex (F vs. M) on the absolute measures of the isthmus (mm<sup>2</sup>). As depicted in the plot, there is no main effect of Handedness groups. Likewise, there is no significant main effect of Sex on isthmus size. Men were observed to have larger isthmus callosal substructure volume than women, independent of Handedness, but this observation is not significant. Error bars represent the 95% confidence limits.

### **3.2.4 Ratio of Isthmus and Total Forebrain Volume**

For the sake of calculations, the measures of mean values and standard deviations of Handedness and Sex were multiplied by 1000. The ANOVA of the ratio of isthmus area and adjusted forebrain volume produced no significance of the main effect of Handedness ( $F(1, 1017) = .317, p = .574, \eta^2 < .001$ ) with cRH having a mean of  $6.134 (\pm 1.27) \text{ mm}^2$  and MH having a mean of  $6.024 (\pm 1.12) \text{ mm}^2$  (see Figure 11). The ANOVA yielded a significant main effect of Sex ( $F(1, 1017) = 38.74, p = .000$ ) with an effect size of  $\eta^2 = .037$ , with the mean relative size of the isthmus in women being larger ( $6.316 \pm 1.208 \text{ mm}^2$ ) than in men ( $5.82 \pm 1.169 \text{ mm}^2$ ). Finally, the interaction of Sex and Handedness was also not significant ( $F(1, 1017) = .19, p = .662, \eta^2 < .001$ ).

**Figure 11**

*Analysis of the ratio of isthmus callosal substructure area and forebrain volume*



*Note.* The figure displays the interaction between Handedness (cRH vs. MH) and Sex (F vs. M) on the ratio of isthmus callosal substructure area and total forebrain volume (mm<sup>2</sup>). There is no main effect of Handedness categories. There is, however, a significant main effect of Sex, as women were observed to have larger isthmus callosal substructure area than men, when considering total forebrain volume, independent of Handedness. Error bars represent the 95% confidence limits.

## 4. Discussion

The results illustrate that the present study fails to replicate the findings of Witelson (1985; 1989) using a larger dataset and structural MRI. There were no detected significant relationship between corpus callosum morphology, and the variables Handedness, assessed with EHI, and Sex. For the present approach, we followed the procedure as described in the pre-registration of the study. Evidently, this increases the severity of the findings as it follows pre-planning (Lakens, 2022).

### 4.1 The Relationship Between Handedness and Callosal Morphology

The role of the corpus callosum in interhemispheric integration of information has been a topic of scientific interest for decades (Christman, 2018; Gazzaniga, 2005; Ocklenburg & Güntürkün, 2018a; Ocklenburg & Güntürkün, 2018b). Its possible functional effect on cognitive development has been conferred, and it is assumed that lateralization is almost completely dependent on the existence of the corpus callosum (Gazzaniga, 2000). Ever since

the publications of Witelson (1985; 1989), the corpus callosum has been assumed to play an essential role in the development of human handedness. The Witelson-findings reinforced the notion that individuals who deviated from consistent right-handedness do so because their corpus callosum is significantly larger than that of cRH. Subsequent studies have confirmed that there is a dissimilarity in the morphology and size of the corpus callosum of individuals who are considered ambidextrous or left-handed (e.g., Habib et al., 1991; Denenberg et al., 1991; Clarke and Zaidel, 1994). A recently published meta-analysis by Westerhausen and Papadatou-Pastou (2022) was, however, not able to confirm Witelson's influential findings, as their results did not reveal any significant difference in callosal morphology across handedness groups. Hence, the aim of the present study was to attempt a replication of Witelson's (1985; 1989) findings by reproducing the approach towards studying the interaction between corpus callosum morphology and handedness. We approached this goal by investigating the EHI scores and structural MRI data of  $N > 1000$  participants, collected by the HCP. Based on the original studies and previous literature, we predicted a directional hypothesis stating that NcRH/MH have a larger midsagittal corpus callosum area than cRH, both before and after correcting for relative callosal size to forebrain volume. Whilst the present study aimed to replicate Witelson (1985; 1989), the goal was ultimately to optimise the methodological approach to increase the validity and reliability of the findings.

Subsequently, while Witelson originally assessed the handedness of the subjects according to Annett's Hand Preference Questionnaire (Annett, 1970), the cRH, MH, and cLH subjects in our dataset were assessed with the EHI (Oldfield, 1971) and following a typical classification scheme ( $LQ > |80|$  to define consistent hand preference). A major challenge in handedness research is the assessment of hand preference, as there is no chosen method or quotient for measuring the variable that is agreed upon within the literature. Comparability between studies might be diminished if various researchers measure different aspects of a function, such as handedness (Salmaso & Longoni, 1985). As has been pointed out by earlier authors (Salmaso & Longoni, 1985), questionnaires are often criticised for their low validity, compared to performance tests. The Annett's Hand Preference Questionnaire used by Witelson (1985; 1989) has been questioned for its reduced dependability, especially regarding the validity of the items included in the questionnaire (Dragovic & Hammond, 2007). Handedness data in the present study was collected by the HCP using the EHI questionnaire. Handedness assessed using the EHI is expected to increase the overall validity of handedness measure. As the EHI performs relatively well regarding both validity and reliability (Ransil et

al., 1994), and as the questionnaire is renowned within the research field, using it allows for easier replication possibilities for future studies.

Additionally, defining handedness further complicates the issue, as it depends on whether one evaluates handedness according to degree or direction. The method chosen to define handedness can have significant implications for the sample distribution, since subjects categorised in one group might not be categorised in the same group, if the classification methods differ across studies. To illustrate, when assessing the participants of the present study according to both qualitative definition of Witelson (Witelson, 1985) and the quantitative definition of Habib et al. (1991), 277 out of 1057 participants (26.2%) were classified differently by the two criteria. In Witelson (1989), the participants of the study were classified as either cRH or NcRH. This classification was done by performing a qualitative analysis of the items within the questionnaire, as opposed to using the overall score of the questionnaire. cRH included participants who confirmed a right-hand preference on all items, as well as subjects who were mostly right-handed, but had a left-hand preference on certain items. NcRH preference included subjects who noted a preference on at least one of the twelve tasks, regardless of hand preference for the item “writing”. Using the nine handedness-items used by HCP, the same principle was applied to the present study by classifying all individuals who indicated left-hand preference for at least one task as NcRH/MH. The remaining individuals who answered most items with “no preference” were also classified as NcRH. Subjects who were classified as cLH were excluded from the study, in order to ensure replication of the original studies.

The analyses presented no significant main effect of handedness groups on callosal morphology. The effect size for the analysis of the absolute corpus callosum midsagittal surface areas, comparing cRH and MH, was small ( $d = .02$ ). For the relative measures of callosal size, the effect size was  $d = .10$ . Compared to the original study of Witelson (1985), which produced an effect size of  $d = -.55$ , the present study offered little evidence for any significant effect of either handedness group. This difference between the current and the original study is to be expected when comparing the sample size of each study, with Witelson (1985) having a sample size of  $N = 42$ , compared to our sample of  $N = 1021$ . For the analysis of handedness measures excluding cLH subjects, our effect size was small ( $d = .03$ ) compared to the original study which produced an effect size of  $d = -.86$  (Witelson, 1989). The significantly small effect sizes of the present study support the conclusions one can draw from our results; there is no significant difference between cRH and NcRH/MH subjects on the morphology of the midsagittal corpus callosum surface area. Evidently, these findings support

the conclusions drawn in the meta-analysis of Westerhausen & Papadatou-Pastou (2022) and rejects the conclusions of Witelson (1985; 1989). Compared to the small effect sizes of handedness groups on callosal morphology in the present study, Skumlien et al. (2018) reported significant main effects of age for both absolute and relative callosal area measures, when comparing younger and older participants ( $d = .69$  for absolute area,  $d = .75$  for relative area). Evidently, aging appears to have a much larger effect on callosal morphology than handedness. Yet, attributing functional consequences of either variable is difficult.

As the current analyses demonstrate such small effect of handedness on callosal size, we can exclude the large population-effect sizes suggested by Witelson, and we were unable to confirm the original findings in terms of effect size and statistical significance. As multiple studies have shown significant differences in callosal morphology across handedness groups (e.g., Burke & Yeo, 1994; Habib et al., 2010; Westerhausen et al., 2004), possible moderation effects of confounding variables should be considered. Notably, Witelson (1985; 1989) demonstrated clear significant interaction effects of sex and hand preference on callosal morphology. The possible moderator effect of sex was counted for in the present study, but the results present no significant interaction effects of handedness and sex across analyses of neither total, nor relative measures of callosal morphology. These findings support the results of the meta-analysis of Westerhausen and Papadatou-Pastou (2022), which found no evidence for a significant interaction of sex and handedness when examining total corpus callosum morphology. While these findings contradict Witelson (1985; 1989), interaction effects of sex and hand preference have been observed in a range of studies (e.g., Clarke & Zaidel, 1994; Habib et al., 1991; Witelson, 1989; Witelson & Goldsmith, 1991), many of which have examined the possibility that observed interpersonal differences in callosal morphology, is a result of dissimilarities within corpus callosum subregions (e.g., Jäncke et al., 1997; Westerhausen et al., 2004; Westerhausen et al., 2016).

#### **4.2 Subregional Analyses**

In her 1989 study, Witelson observed that the detected callosal differences occurred in the posterior subregion of the corpus callosum, the region classified as the isthmus area. Specifically, the isthmus of the posterior corpus callosum was significantly larger among NcRH than cRH men, but not women; a finding Witelson attributed to the assumption that women have less clear lateralization than men. Subsequent studies have produced similar results of such interaction effects (e.g., Habib et al., 1991). For instance, Denenberg et al. (1991), replicated the findings of Witelson (1989), demonstrating larger isthmal size among

NcRH men. Meanwhile, Clarke and Zaidel (1994) observed a different interaction effect between hand preference and sex on the isthmus area. They found that cRH women had a larger isthmus area than cRH men. Notably, the authors found no effect of sex on isthmus size for the MH group, which is not in line with the findings of Witelson (1989). Burke and Yeo (1994) found another interaction effect between sex and handedness, reporting that stronger right-hand preference predicted larger posterior callosal size in men but reduced total callosal size in women. Evidently, the literature provides different views on how the interaction between sex and hand preference affects the isthmus. Nonetheless, there is evidence for overall interaction effects. Following the approach made by Witelson (1989), the present study compared the absolute and relative measures of the isthmus of cRH and NcRH/MH men and women. Consequently, the results demonstrate no significant interaction effect of handedness and sex on the isthmus region, neither for absolute nor relative measures of the isthmus.

Besides finding an interaction effect on isthmal size, Witelson (1989) further reported significant main effects of handedness on the callosal subsection as well. Overall, NcRH participants demonstrated a larger isthmus size than cRH, a finding that was supported by Luders et al. (2010a), who detected thicker isthmus size among left-handers. Likewise to the analyses of total callosal size, no significant main effect of handedness was detected on isthmus size in the present study. These findings contradict Witelson (1989), but support the results presented in Steinmetz et al. (1992), who discovered no effect of handedness on size measures of the isthmus. For absolute measures of the isthmus, using the quantitative handedness criteria, the effect size of handedness was  $d = .045$ , whilst the effect size using the qualitative handedness criteria was  $d = .032$ . For the relative measures, the effect size of handedness was  $d = .032$ , and  $d = .009$ . for the quantitative and qualitative criteria, respectively. The results indicate that possible observed callosal size-differences should not be attributed to the isthmus of the posterior third area of the corpus callosum.

The observed non-significant interaction- and main effects of the present study somewhat opposes the previous literature (e.g., Clarke & Zaidel, 1994; Denenberg et al., 1991; Witelson, 1989). Even though there exist studies of subregional effect, these studies are relatively rare, and callosal regions are often defined after arbitrary criteria, as an objective division of subregions is yet to be agreed upon (Westerhausen & Papadatou-Pastou, 2022). Therefore, the present study, using a large dataset, contribute to the overall understanding of the effect of handedness on both total callosal size and subregional callosal sections. Importantly, as the present study discarded any interaction effect of sex and handedness, and

any main effect of handedness, the findings further illustrate how the attention must be directed towards the possible confounding effect of sex, and the importance of counting for proportionality.

### 4.3 Observed Main Effects of Sex

A fundamental challenge for neuroscientific research in general, and laterality research specifically, is the case of proportionality between callosal size and total brain volume. As evidence supports, there is clear relationship between total brain size and the size of neuroanatomical structures such as the corpus callosum (Jäncke et al., 1997). Evidently, when analysing relative measures, Witelson (1989) demonstrated larger isthmal size among women than men, regardless of hand preference, thus illustrating the substantial effect of counting for total brain size. For the sake of replication, proportionality was taken into consideration in the present study by including measures of the ratio of total forebrain volume on total callosal size and the size of the isthmus subregion. For both absolute and relative measures of total callosal area, there was a main effect of sex. For the absolute measures, men were observed to have a larger callosal size than women, irrespective of handedness. This observation was inverted, however, when measuring the relative callosal size, as the result demonstrated larger callosal areas among women, then men. The effect size of absolute measures of the corpus callosum was small, with analysis including cLH producing an effect of  $d = .201$ , and analysis excluding cLH producing an effect of  $d = .186$ . For the relative callosal measures, however, the effect size was larger, with both analyses including and excluding cLH producing an effect of  $d = .50$ . For absolute measures of isthmus size, no significant main effect of sex was detected. Overall, the analyses of relative measures produced significant main effects of sex, with the mean relative size of the total corpus callosum and the isthmus being larger in women than in men on almost all measures. Similarly to the effect size of total callosal area measures, the effect size of absolute measures of the isthmus was small, with analysis including cLH producing an effect of  $d = .042$ , and analysis excluding cLH producing an effect of  $d = .092$ . For the relative measures of the isthmus, however, the effect size was larger, with analyses including cLH producing an effect of  $d = .41$ , and analysis excluding cLH producing an effect of  $d = .42$ .

While significant effects of sex on absolute isthmus measures were detected, relatively small effect sizes overall indicate that the observed effect cannot be explained by the measures included in this study. For all analyses except the measure of absolute isthmus size, there is a significant main effect of sex, which support previous findings (Clarke & Zaidel,

1994; Steinmetz et al., 1992; Westerhausen et al., 2004; Witelson, 1989). However, throughout the present study, no significant interaction-effect between handedness and sex was demonstrated. These results indicate that observed variations in callosal morphology cannot explain the higher prevalence of left-handed men in the populations. A suggestion made by Steinmetz et al., (1992; 1995) illustrate that observed sex effects, but absent sex-handedness interaction effects, may reflect sex-specific differences in the interhemispheric connectivity and functional organization of the temporoparietal cortex. Evidently, Ojemann et al. (1989) speculated that observed sex effects may be due to greater interhemispheric sharing of language functions between left and right posterior brain areas in women, which could explain stronger interhemispheric connections via the fibers of the isthmus.

Statements regarding sex differences are often viewed as controversial, as findings varies considerably across studies (Aboitiz et al., 1992; Clarke & Zaidel, 1994; Luders et al., 2010b). It is hypothesised that significant sex differences in the literature often reflects methodological differences between studies, rather than actual differences between the sexes (van der Knaap & van der Ham, 2011). Importantly, while relative measures of callosal measures should be included when measuring possible effects of sex, this is not always the case (Westerhausen and Papadatou-Pastou, 2022). Our findings, as well as other's (e.g., Steinmetz et al., 1992; 1995), confirm a significantly larger isthmus size for women than men, for relative measures of the callosal structure and substructures. Typically, it is assumed that larger callosal mean area reflects more interhemispheric connections, as claimed by Witelson (1989) and the excitatory model. However, this assumption is not necessarily supported by the current field of laterality research, nor the present study (Bloom & Hynd, 2005). Based on combined morphological and histological analyses (Hou & Pakkenberg, 2012; Riise & Pakkenberg, 2011), the midsagittal area appears to be a good predictor of callosal quantity of myelinated axons (Westerhausen & Papadatou-Pastou, 2022), but callosal anatomy is also influenced by factors such as fibre thickness, packing density, or myelination (Steinmetz et al., 1992; 1995). Discrepancies in these factors may obstruct formation of structural-functional correlations based on large anatomic measurements. Notably, according to Aboitiz et al (1992), fibre density in the corpus callosum does not differ between sexes, nor does it change with midsagittal callosal area. As such, inconsistencies within the literature is prevalent, and there is a need for further research on interhemispheric connectivity and possible confounding factors occurring on axon-level. Still, Westerhausen et al. (2004) found significant effects of sex and handedness on alterations in molecular diffusion and size of the corpus callosum. In light of such findings, discrepancies in macro- and microstructure of



callosal pathways can be assumed to be related to both handedness and sex. In which degree the interaction of these factors directly affect callosal morphology is yet to be decided. Based on the present study, the main effect of handedness, and the effect of handedness' interaction with sex, is not significantly related to corpus callosum morphology.

#### **4.4 Limitations and Directions for Future Studies**

While the present study was able to assess handedness scores qualitatively according to the degree of handedness, measures comparing handedness assessed according to direction versus consistency were absent. In her studies, Witelson emphasizes the relevance of consistency rather than the direction of hand preference (Witelson & Goldsmith, 1991). Classification of direction of handedness is determined by assessing the overall items of a questionnaire, hand preference on behaviour, and comparing left- versus right-handers (Prichard et al., 2013). By contrast, assessing handedness according to a consistency approach, measuring the degree of handedness, is done by implementing a cut-off LQ (e.g.,  $LQ > 80$  (Habib et al., 1991)), or by performing a qualitative analysis of the response pattern in the handedness questionnaire (Westerhausen & Papadatou-Pastou, 2022). In the present study, handedness was measured according to the degree of handedness, in order to replicate the approach suggested by Witelson (1989). While consistency of handedness has been suggested to be a more powerful and appropriate way to classify handedness than direction (Prichard et al., 2013), comparing the approach with measures of direction might provide interesting differences to achieve more understanding regarding the relationship between handedness and morphology of the callosal structure. Prichard et al., 2013 found that degree of handedness measures showed a systematic effect on episodic memory retrieval and cognitive flexibility, specifically, but it is possible that measures of handedness direction rather than degree will produce significant effects when measuring other domains, such as callosal morphology. Future studies should implement such a comparison as a way to establish a preferred approach for measures of the relationship between corpus callosum morphology and handedness. Furthermore, we were unable to measure the LQ of handedness as a continuous variable, by considering the shape of the relationship between handedness and callosal morphology. Handedness is commonly viewed as a dichotomous variable, by classifying scores using binary categories, such as left-handedness or right-handedness. However, Annett (1970) suggested that hand preference is distributed as a continuous variable. In the present approach, we included categories from the EHI LQ, rather than use it as continuous measures of hand preference. It can be argued that variance in the data is

reduced by creating binary categories out of a variable that ranges from -100 to 100. Also, the current approach intentionally excluded cLH subjects, in order to ensure replication of the original studies. While this ensured replication, the findings will not be applicable for left-handers. Inclusion of left-handed participants should be included in future studies in order to represent and measure the full spectre of handedness.

The fact that handedness data was assessed with a self-report questionnaire, should be considered a limitation, as well. As concluded by previous authors, questionnaires produce a lower reliability when measuring handedness than when asking participants to perform practical activities to measure (Bryden et al., 2007; Laland et al., 1995; Lezak, 2012; Luders et al., 2010a). As stated by Luders et al., (2010a), future studies might benefit from implementing observational measures to account for the low dependability of questionnaires. Furthermore, the HCP utilized a modified version of the EHI, removing the item and adding the item “Hand\_Foot”. Consequently, this had to be adjusted for, by excluding “Hand\_Foot” and adding the values of the item “Writing” twice, assuming that the missing item “Drawing” is comparable to “Writing”. As a result, the adjustment of the modified EHI should be considered a limitation, as it fails to fully represent the assessment questionnaire and to coincide with preceding studies that utilize the original EHI in its complete form. Additionally, we were not able to look at a performance definition as the data available from HCP has been shown to have low reliability (Ruck & Schoenemann, 2021). Accordingly, any analysis based on this dataset would not have produced reliable results.

It is possible to assume that the lack of age-variation within the HCP dataset used in the present study, could be classified as a limitation. The subjects included in the dataset are of roughly the same age (22-35 years), limiting the possibility to compare callosal structure of cRH, NcRH, and MH of different age groups. Considering that Witelson (1989) and others (e.g., Hepper et al., 2005; Provins, 1992; Witelson & Nowakowski, 1991) concluded that callosal axon-size differences in quite early, even prenatal, life-stages is the determinant of handedness asymmetry, it might be of interest for future studies to perform a longitudinal approach to replicate Witelson’s findings. Notably, as pointed out by Danielsen et al. (2020), the size of the corpus callosum changes throughout the lifespan, and the different regions of the corpus callosum increases and decreases in size at different paces and stages of life, with the isthmus and genu reaching their peak values first (Prendergast et al., 2015). Furthermore, it has been suggested that individual and sex differences are dependent on developmental trajectory throughout the lifespan, which displays a longer callosal development period for

women (Salat et al., 1997). Evidently, age can be considered a determinant for fibre size across and within the regions of the corpus callosum (Danielsen et al., 2020). These findings indicate that interindividual subregional size differences affected by handedness might occur at different life stages. Dismissing other age groups can have repercussions for callosal subdivision and applicability of the study results, as we can merely draw conclusions regarding young adults. As Witelson's (1985) subjects had a mean age of 49.1 ( $\pm 3.63$ ) years, deficiencies between the results of Witelson (1985; 1989) and the results of the present study might be somewhat affected by the different mean ages. Future studies on corpus callosum morphology should therefore seek to include data from samples including subjects from a large age-range, in order to compare systematic interindividual differences for hand preference on callosal size.

The results of the current study weakens the fundamentality of Witelson's (1985; 1989) findings, allowing for research on the relationship of callosal morphology and hand preference to be viewed in a new light. Therefore, it is of interest that future studies research the possible confounding effects of other functions that might affect interindividual differences in hand preference. For instance, after qualitatively analysing musicians, Christman (1993) presented evidence for how handedness may be related to preferences for certain motor tasks, stating that non-consistent handers were more likely to play instruments that require temporally integrated bimanual motor actions (Prichard et al., 2013). One can hypothesize that people who engage in certain activities might have to adjust their handedness preference according to the demands of the activities. For instance, right-handers who frequently play classic computer games might show improved or above average dexterity in their left hand, as this typically is needed to move in-game characters using the W-, A-, S, and D-buttons located on the left-side of traditional keyboards. Similar shifts might also be observable among individuals who play certain instruments that force handedness shift (e.g., Christman, 1993). Evidence supporting this possibility comes from research on hand preference among athletes, which shows that cRH and NcRH individuals perform differently at various sports, depending on the task-demands of the activity (e.g., Loffing et al., 2012; Loffing & Hagemann, 2016; Raymond et al., 1996), with many studies finding a higher percentage of left-handers among high-achieving athletes (e.g., Loffing, 2017; Raymond et al., 1996). As such, future studies should investigate the effective development and interindividual differences in the callosal motor pathways. Furthermore, investigating the effect of changed hand preference as a result of practice or forced shift, on the callosal

structure and its subsections, could provide further insight into which callosal subregions that have a significant relationship with handedness.

Additionally, as supported by the findings of the current study, handedness might not be directly affected by callosal morphology, or vice versa. Investigating the interaction effect of handedness and various cognitive processes, could expose possible confounders that affects the respective either handedness or the corpus callosum, or both. For example, a left-hemisphere dominance for language lateralization is evident across the population, independent of handedness, but the occurrence of right-hemisphere dominance for language is more prevalent among left-handers than right-handers (e.g., Carey & Johnstone, 2014; Knecht et al., 2000). In their 2015 study, Somers et al. found that subjects with strong left-hand preference showed the highest prevalence for atypical language lateralization, including bilateral, moderate, and strong right-hemispheric lateralization. Meanwhile, Knecht et al. (2000) found that stronger right-handedness was negatively correlated with the frequency of right-hemisphere language dominance, reporting a linear relationship between the degree of handedness and direction of language dominance. Evidently, stronger left-handedness exhibited a relatively stronger positive relationship with the frequency of right-hemisphere language dominance. Strongly left-handed participants of this study demonstrated right-hemisphere language dominance almost seven times higher compared to the strongly right-handed participants (Knecht et al., 2000, p. 2513). Neither the present study, nor Witelson (1985; 1989) performed any analysis of language lateralization among subjects, but the possible confounding effect of language asymmetry has been much postulated and should still be of interest for future research.

Authors who seeks to research callosal morphology should recognize that measuring the callosal structure can be considered a limitation in itself. In the literature, the measure of the corpus callosum has been performed in various ways, including post-mortem (e.g., Witelson 1985; 1989), MRI (e.g., Clarke & Zaidel, 1994; Ojemann, 1983; Ojemann et al., 1989), or diffusion tensor imaging (DTI) (e.g., Westerhausen et al., 2004). Whilst Witelson (1985; 1989) chose a post-mortem approach, the present study strayed away from this methodology by utilizing structural MRI data of live subjects. By choosing this approach, possible issues surrounding post-mortem methods, such as post-mortem deformation and human error relating to such methods, can be excluded (Lewis, 2002; Stan et al., 2006). However, as is relevant for the current study, studies measuring the relationship between corpus callosum morphology and functional lateralization do so based on the assumption that

callosal size directly corresponds to the quantity of interhemispheric connections (Bloom & Hynd, 2005). While this assumption is generally accepted, it is not necessarily the case. Measures of callosal fibres through DTI should therefore be an important addition to future research. DTI allows for multidimensional scans of axon networks (van der Knaap & van der Ham, 2011). Such imaging methods make it possible to measure the size and density of fibres, as well as conducting fibre tractography, to connect fibres to their corresponding cortical regions and establish neural connectivity (Häberling et al., 2011; Mooshagian, 2008). Additionally, utilizing DTI could aid in the accreditation of the assumption that larger callosal size equal a larger number of interhemispheric connections. Westerhausen et al. (2004), performed a measure of the effects of handedness and sex on macro- and microstructure of the corpus callosum and its subregions, by combining diffusion tensor MRI and high-resolution MRI. The study revealed significant alterations in the molecular diffusion, as well as callosal size, in regard to sex and handedness, and demonstrated that DTI produces information of interhemispheric connectivity on a more accurate level than anatomical measures, such as post-mortem and structural MRI methods. In addition, Skumlien et al. (2018) suggested that measures of functional connectivity of interhemispheric neuronal activity and quality/speed of interhemispheric interaction should be implemented in research of callosal functioning, stating that such methods are “better suited to detect individual differences in dynamic aspects of hemispheric cooperation” (Skumlien et al., 2018, p. 13). Combining these recommended methods could improve the overall validity of measures of functional connectivity and callosal morphology, establishing further understanding of the relationship between axon quantity, myelination, and callosal size, and functional interhemispheric integration.

## **5. Conclusion**

The present study aimed to conceptually replicate the findings of Witelson (1985; 1989), by revising the methodological approach in order to increase the scientific reliability and validity of the findings. The goal was to see whether NcRH/MH subjects had a significantly larger callosal area than cRH. Additionally, measures of the subregional isthmus area of the posterior third of the corpus callosum was measured, as Witelson (1989) emphasized significant hand and sex effects on the morphology of this region. The findings of the present study revealed no significant effect of handedness on callosal morphology, consequently rejecting the previous notions declared by Witelson. As the conclusions drawn by Witelson have long been considered a reliable foundation for research on the relationship

between the corpus callosum and asymmetric functions, such as handedness, the present study provides a renewed view on the role the callosal structure plays in regard to handedness asymmetry, by declining the long-standing notions of the original studies. Additionally, our findings support the conclusions drawn in Westerhausen and Papadatou-Pastou (2022), that the original findings have been deemed non-reliable by later research. Following the suggestions of the aforementioned meta-analysis, the current analysis evaluated sex differences and brain size effect in accordance with handedness measures, demonstrating the non-existent significant interaction effect of these functions on callosal morphology. Furthermore, central limitations and complications in handedness research, and the accompanying literature, have been presented and discussed, with the objective of highlighting pitfalls that reduces the reliability of previous assumptions. As such, the present study suggests that future studies avoid inferring differences in callosal connectivity to handedness, without controlling for limitations that obstruct the accuracy of the measures.

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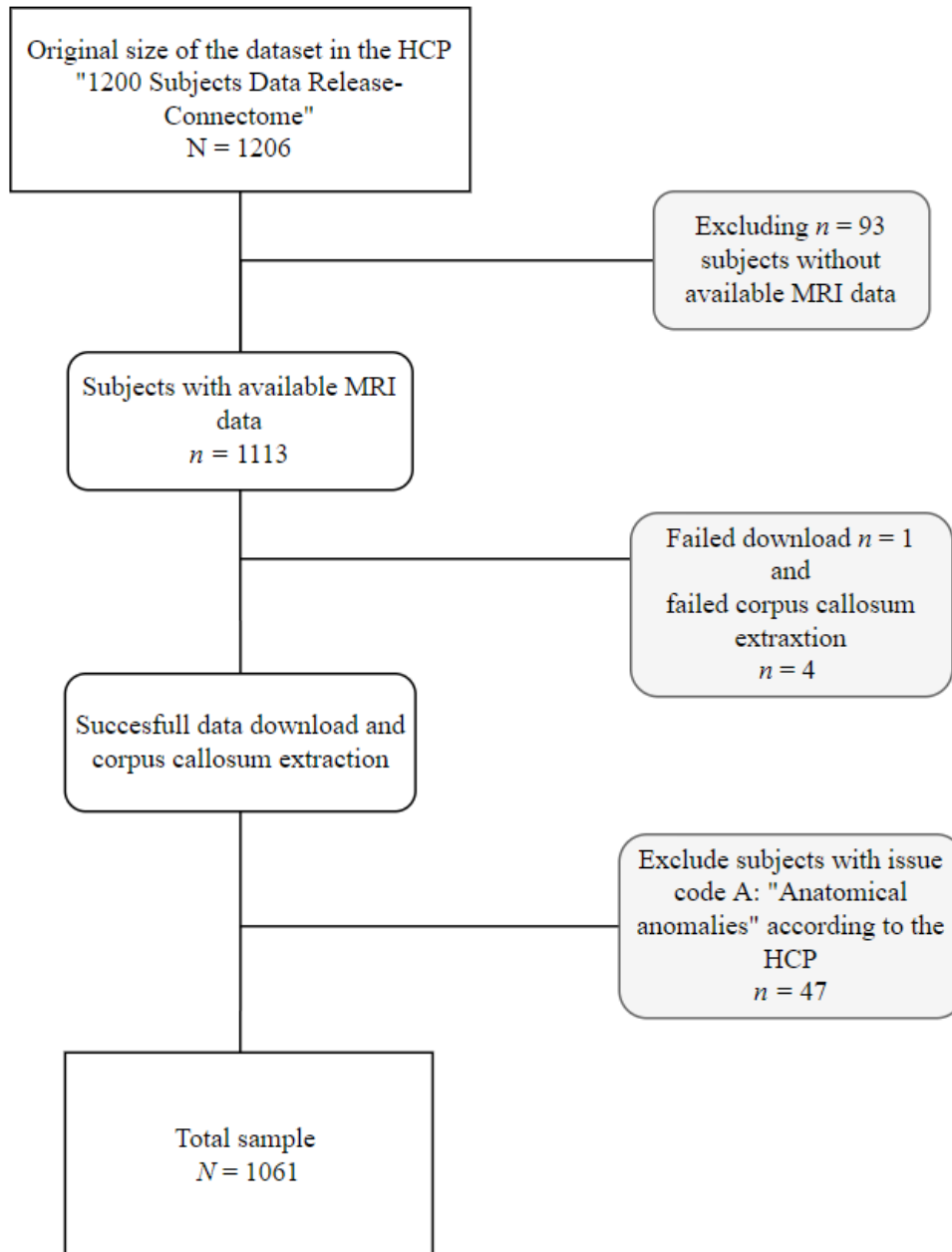
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## 7. Appendix

### Appendix A

Exclusion criteria for subjects in the dataset used in the present study:



## Appendix B

### Script for the present study

```
#####  
##SCRIPT FOR THE PRIMARY HYPOTHESIS  
#####  
library(haven)  
library(car)  
  
## Loading required package: carData  
  
library(ggplot2)  
  
# HCP_CC_DATA_w_Handedness is the dataset including all handedness computations based on different criteria  
# Make sure that the directory is the (PLACEHOLDER: add zip-file containing the HCP_CC_DATA_w_Handedness dataset)  
setwd("/PLACEHOLDER: must be adjusted to local directory structure/")  
HCP_CC_DATA_w_Handedness <- read.csv("HCP_CC_DATA_w_Handedness.csv", sep = ",", dec = ",")  
SubjectID_Exclude <- read.csv("Excl_ID.csv") #excluding individuals who do not meet the requirements according to HCP - EXCLUDED ID-NUMBERS MUST BE PLACED IN A FOLDER NAMED Excl_ID.csv.  
  
library(tidyverse)  
  
## -- Attaching packages ----- tidyverse 1.3.1 --  
  
## v tibble 3.1.7      v dplyr  1.0.9  
## v tidyr  1.2.0      v stringr 1.4.0  
## v readr  2.1.2      v forcats 0.5.1  
## v purrr  0.3.4  
  
## -- Conflicts ----- tidyverse_conflicts() --  
## x dplyr::filter() masks stats::filter()  
## x dplyr::lag()    masks stats::lag()  
## x dplyr::recode() masks car::recode()  
## x purrr::some()  masks car::some()  
  
# Rename column "Gender" to "Sex"  
names(HCP_CC_DATA_w_Handedness)[names(HCP_CC_DATA_w_Handedness) == "Gender"] <- "Sex"  
  
#Witelson 1: as described one "left" leads to NcrH classification  
HCP_CC_DATA_w_Handedness$Witelson1 = (HCP_CC_DATA_w_Handedness$Hand_Writing < 3) | (HCP_CC_DATA_w_Handedness$Hand_Scissors < 3) | (HCP_CC_DATA_w_Handedness$Hand_Throwing < 3) | (HCP_CC_DATA_w_Handedness$Hand_Toothbrush < 3) | (HCP_CC_DATA_w_Handedness$Hand_Knife < 3) | (HCP_CC_DATA_w_Handedness$Hand_Spoon < 3) | (HCP_CC_DATA_w_Handedness$Hand_Broom < 3) | (HCP_CC_DATA_w_Handedness$Hand_Match < 3) | (HCP_CC_DATA_w_Handedness$Hand_Box < 3)
```

```

#Counts the number of "3" answers per participant
temp.var.count3s = (HCP_CC_DATA_w_Handedness$Hand_Writing == 3) + (HCP_CC_DATA_w_Handedness
$Hand_Scissors == 3) + (HCP_CC_DATA_w_Handedness$Hand_Throwing == 3) + (HCP_CC_DATA_w_Hand
edness$Hand_Toothbrush == 3) + (HCP_CC_DATA_w_Handedness$Hand_Knife == 3) + (HCP_CC_DATA_w_
Handedness$Hand_Spoon == 3) + (HCP_CC_DATA_w_Handedness$Hand_Broom == 3)+ (HCP_CC_DATA_w_Ha
ndedness$Hand_Match == 3) + (HCP_CC_DATA_w_Handedness$Hand_Box == 3)

#set these participants to "TRUE", i.e. NcRH
HCP_CC_DATA_w_Handedness$Witelson1[which(temp.var.count3s>4)] = TRUE

#make factor
HCP_CC_DATA_w_Handedness$Witelson1 = as.factor(HCP_CC_DATA_w_Handedness$Witelson1)
levels(HCP_CC_DATA_w_Handedness$Witelson1) = c("cRH", "NcRH")

#provide summary
tabl.witelson1 = table(HCP_CC_DATA_w_Handedness$Witelson1)

# ADDING WITELSON 2 CLASSIFICATION

#Temp var: "No preference" leading to NcLH classification
temp.var.id.NcLH = (HCP_CC_DATA_w_Handedness$Hand_Writing > 3) | (HCP_CC_DATA_w_Handedness$
Hand_Scissors > 3) | (HCP_CC_DATA_w_Handedness$Hand_Throwing > 3) | (HCP_CC_DATA_w_Handedn
ess$Hand_Toothbrush > 3) | (HCP_CC_DATA_w_Handedness$Hand_Knife > 3) | (HCP_CC_DATA_w_Hande
dness$Hand_Spoon > 3) | (HCP_CC_DATA_w_Handedness$Hand_Broom > 3) | (HCP_CC_DATA_w_Handedne
ss$Hand_Match > 3) | (HCP_CC_DATA_w_Handedness$Hand_Box > 3)

#set the participants "TRUE", i.e. NcLH, which have 5 or more "3s" (see previous chunk)
temp.var.id.NcLH[which(temp.var.count3s>4)] = TRUE

#Witelson 2: take Witelton1 but add cLH
HCP_CC_DATA_w_Handedness$Witelson2 = as.numeric(HCP_CC_DATA_w_Handedness$Witelson1)
HCP_CC_DATA_w_Handedness$Witelson2[which(temp.var.id.NcLH == FALSE)] = 3
HCP_CC_DATA_w_Handedness$Witelson2 = as.factor(HCP_CC_DATA_w_Handedness$Witelson2)
levels(HCP_CC_DATA_w_Handedness$Witelson2) = c("cRH", "MH", "cLH")
tabl.Witelson2 = table(HCP_CC_DATA_w_Handedness$Witelson2)

#remove subject with Issue code A: "Anatomical anomalies" according to HCP (info retrieved
11.01.2022, from
#https://wiki.humanconnectome.org/pages/viewpage.action?pageId=88901591)
count_n_removed = 0

```

```

for (idx in seq_along(SubjectID_Exclude$ID)){
  if ( length(which(HCP_CC_DATA_w_Handedness$SubjectID == SubjectID_Exclude$ID[idx])) == 1)
  {
    count_n_removed = count_n_removed +1 #counts the number of sbj removed
    HCP_CC_DATA_w_Handedness = HCP_CC_DATA_w_Handedness[which(!HCP_CC_DATA_w_Handedness$SubjectID == SubjectID_Exclude$ID[idx]),]
  }
}

## Factorize variables from HCP_CC_DATA_w_Handedness HCP_CC_DATA_w_Handedness
HCP_CC_DATA_w_Handedness$Witelson1 = as.factor(HCP_CC_DATA_w_Handedness$Witelson1)
HCP_CC_DATA_w_Handedness$Sex = as.factor(HCP_CC_DATA_w_Handedness$Sex)
options(contrasts = c("contr.helmert", "contr.poly"))

#Exclude NAs
HCP_CC_DATA_w_Handedness = na.omit(HCP_CC_DATA_w_Handedness) #omits (effectively removes) a
LL rows where "NA" is present in any column

##Calculate CC/forebrain ratio
#Must use as.numeric on $totalsize and $isthmus as they are considered character values and
not numeric values
HCP_CC_DATA_w_Handedness$CCFBV_ratio = as.numeric(HCP_CC_DATA_w_Handedness$totalsize)/((HCP
_CC_DATA_w_Handedness$FS_SupraTentorial_Vol)^(2/3))*1000
HCP_CC_DATA_w_Handedness$isthmusFBV_ratio = as.numeric(HCP_CC_DATA_w_Handedness$isthmus)/((
HCP_CC_DATA_w_Handedness$FS_SupraTentorial_Vol)^(2/3))*1000
#HCP_CC_DATA_w_Handedness$isthmusFBV_ratio = as.numeric(HCP_CC_DATA_w_Handedness$isthmus)/((
(HCP_CC_DATA_w_Handedness$FS_SupraTentorial_Vol)^(2/3))

##=====
##  Witelson1 Anovas
##=====

##=====
# Anova for raw data
##=====
#DV: total area
crf.lm2 <- lm(totalsize ~ Sex * Witelson1, data = HCP_CC_DATA_w_Handedness)
anova_raw = Anova(crf.lm2, type = 3) #RW: if you commit the output to a variable ...
anova_raw$`Sum Sq`[2] #RW: you can access the components of the table like this, here Sum S
q Sex

## [1] 97032.83

```

```

anova_raw_totalsss = sum(anova_raw$`Sum Sq`[2:5]) #RW: total some of squares = sum of all Sum Sq without intercept

#or we store it in the ANOVA output!
anova_raw$efz = NaN #create column of NaN as place holder
anova_raw

## Anova Table (Type III tests)
##
## Response: totalsize
##
##           Sum Sq   Df   F value  Pr(>F)  efz
## (Intercept) 476236801   1 54263.7787 0.00000  NaN
## Sex          97033     1   11.0562 0.00091  NaN
## Witelson1    6296     1    0.7174 0.39720  NaN
## Sex:Witelson1  703     1    0.0801 0.77728  NaN
## Residuals   9241475 1053                NaN

#Finding the effect size of the variables:
anova_raw$efz[2] = anova_raw$`Sum Sq`[2]/anova_raw_totalsss #... finding efz for variable Sex
anova_raw$efz[3] = anova_raw$`Sum Sq`[3]/anova_raw_totalsss #... finding efz for variable Witelson1
anova_raw$efz[4] = anova_raw$`Sum Sq`[4]/anova_raw_totalsss #... finding efz for variable Sex:Witelson1
anova_raw$efz[5] = anova_raw$`Sum Sq`[5]/anova_raw_totalsss #... finding efz for variable Residuals

#Type "anova_raw" and you see the results
anova_raw

## Anova Table (Type III tests)
##
## Response: totalsize
##
##           Sum Sq   Df   F value  Pr(>F)   efz
## (Intercept) 476236801   1 54263.7787 0.00000   NaN
## Sex          97033     1   11.0562 0.00091 0.01038
## Witelson1    6296     1    0.7174 0.39720 0.00067
## Sex:Witelson1  703     1    0.0801 0.77728 0.00008
## Residuals   9241475 1053                0.98887

#exploring means
HCP_CC_DATA_w_Handedness$totalsize = as.numeric(HCP_CC_DATA_w_Handedness$totalsize) # <- This should be done once, causes many errors if not

mean_M = mean(HCP_CC_DATA_w_Handedness$totalsize[which(HCP_CC_DATA_w_Handedness$Sex == 'M')])

```

```

sd_M = sd(HCP_CC_DATA_w_Handedness$totalsize[which(HCP_CC_DATA_w_Handedness$Sex == 'M')])
mean_F = mean(HCP_CC_DATA_w_Handedness$totalsize[which(HCP_CC_DATA_w_Handedness$Sex == 'F')
])
sd_F = sd(HCP_CC_DATA_w_Handedness$totalsize[which(HCP_CC_DATA_w_Handedness$Sex == 'F')])

mean_cRH = mean(HCP_CC_DATA_w_Handedness$totalsize[which(HCP_CC_DATA_w_Handedness$Witelson1
== 'cRH')])
sd_cRH = sd(HCP_CC_DATA_w_Handedness$totalsize[which(HCP_CC_DATA_w_Handedness$Witelson1 ==
'cRH')])
mean_NcRH = mean(HCP_CC_DATA_w_Handedness$totalsize[which(HCP_CC_DATA_w_Handedness$Witelson
1 == 'NcRH')])
sd_NcRH = sd(HCP_CC_DATA_w_Handedness$totalsize[which(HCP_CC_DATA_w_Handedness$Witelson1 ==
'NcRH')])

###=====
# Anova for ratio of Corpus Callosum and Forebrain volume (brain size)
###=====

#DV: ratio
# Calculating interaction effect using the the ratio of Corpus Callosum and brain size
#(CCFBV_ratio) as dependent variable, and Sex and handedness (Sex*Witelson1) as independent
variables
CCanova <- lm(CCFBV_ratio ~ Sex * Witelton1, data = HCP_CC_DATA_w_Handedness)
Anova(CCanova, type = 3)

## Anova Table (Type III tests)
##
## Response: CCFBV_ratio
##          Sum Sq   Df  F value    Pr(>F)
## (Intercept) 4558411    1 63938.6078 < 2.2e-16 ***
## Sex          4218     1   59.1674 3.316e-14 ***
## Witelton1     29     1    0.4100  0.5221
## Sex:Witelton1  10     1    0.1357  0.7127
## Residuals    75072 1053
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

anova_ratio = Anova(CCanova, type = 3) #RW: if you commit the output to a variable ...
anova_ratio$`Sum Sq`[2] #RW: you can access the components of the table like this, here Sum
Sq Sex

## [1] 4218.255

```

```

anova_ratio_totalsss = sum(anova_ratio$`Sum Sq`[2:5]) #RW: total some of squares = sum of all Sum Sq without intercept

anova_ratio$efz = NaN #create column of NaN as place holder
anova_ratio

## Anova Table (Type III tests)
##
## Response: CCFBV_ratio
##           Sum Sq   Df   F value  Pr(>F)  efz
## (Intercept) 4558411   1 63938.6078 0.00000  NaN
## Sex          4218     1   59.1674 0.00000  NaN
## Witelson1    29      1    0.4100 0.52213  NaN
## Sex:Witelson1 10     1    0.1357 0.71266  NaN
## Residuals   75072 1053                NaN

#Finding the effect size of the variables:
anova_ratio$efz[2] = anova_ratio$`Sum Sq`[2]/anova_ratio_totalsss #... finding efz for variable Sex
anova_ratio$efz[3] = anova_ratio$`Sum Sq`[3]/anova_ratio_totalsss #... finding efz for variable Witelson1
anova_ratio$efz[4] = anova_ratio$`Sum Sq`[4]/anova_ratio_totalsss #... finding efz for variable Sex:Witelson1
anova_ratio$efz[5] = anova_ratio$`Sum Sq`[5]/anova_ratio_totalsss #... finding efz for variable Residuals

#Type "anova_ratio" and you see the results
anova_ratio

## Anova Table (Type III tests)
##
## Response: CCFBV_ratio
##           Sum Sq   Df   F value  Pr(>F)   efz
## (Intercept) 4558411   1 63938.6078 0.00000   NaN
## Sex          4218     1   59.1674 0.00000 0.05317
## Witelson1    29      1    0.4100 0.52213 0.00037
## Sex:Witelson1 10     1    0.1357 0.71266 0.00012
## Residuals   75072 1053                0.94634

#exploring means
Ratio_mean_M = mean(HCP_CC_DATA_w_Handedness$CCFBV_ratio[which(HCP_CC_DATA_w_Handedness$Sex == 'M')])
Ratio_sd_M = sd(HCP_CC_DATA_w_Handedness$CCFBV_ratio[which(HCP_CC_DATA_w_Handedness$Sex == 'M')])
Ratio_mean_F = mean(HCP_CC_DATA_w_Handedness$CCFBV_ratio[which(HCP_CC_DATA_w_Handedness$Sex == 'F')])

```

```

Ratio_sd_F = sd(HCP_CC_DATA_w_Handedness$CCFBV_ratio[which(HCP_CC_DATA_w_Handedness$Sex ==
'F')])

Ratio_mean_cRH = mean(HCP_CC_DATA_w_Handedness$CCFBV_ratio[which(HCP_CC_DATA_w_Handedness$Witelson1 == 'cRH')])
Ratio_sd_cRH = sd(HCP_CC_DATA_w_Handedness$CCFBV_ratio[which(HCP_CC_DATA_w_Handedness$Witelson1 == 'cRH')])
Ratio_mean_NcRH = mean(HCP_CC_DATA_w_Handedness$CCFBV_ratio[which(HCP_CC_DATA_w_Handedness$Witelson1 == 'NcRH')])
Ratio_sd_NcRH = sd(HCP_CC_DATA_w_Handedness$CCFBV_ratio[which(HCP_CC_DATA_w_Handedness$Witelson1 == 'NcRH')])

##=====
# Anova for raw Isthmus data
##=====
#DV: Isthmus
crf.lm2 <- lm(isthmus ~ Sex * Witelson1, data = HCP_CC_DATA_w_Handedness)
anova_isthmus_raw = Anova(crf.lm2, type = 3) #RW: if you commit the output to a variable ..
.
anova_isthmus_raw$`Sum Sq`[2] #RW: you can access the components of the table like this, here Sum Sq Sex

## [1] 97.08651

anova_isthmus_raw_totalss = sum(anova_isthmus_raw$`Sum Sq`[2:5]) #RW: total some of squares
= sum of all Sum Sq without intercept

#or we store it in the ANOVA output!
anova_isthmus_raw$efz = NaN #create column of NaN as place holder
anova_isthmus_raw

## Anova Table (Type III tests)
##
## Response: isthmus
##
##          Sum Sq   Df    F value    Pr(>F)   efz
## (Intercept) 3811174    1 24338.5812 0.00000  NaN
## Sex          97      1    0.6200 0.43122  NaN
## Witelson1   93      1    0.5914 0.44206  NaN
## Sex:Witelson1 35      1    0.2220 0.63764  NaN
## Residuals 164889 1053                NaN

#Finding the effect size of the variables:
anova_isthmus_raw$efz[2] = anova_isthmus_raw$`Sum Sq`[2]/anova_isthmus_raw_totalss #... finding efz for variable Sex

```



```

anova_isthmus_raw$efz[3] =anova_isthmus_raw$`Sum Sq`[3]/anova_isthmus_raw_totals$ #... finding efz for variable Witelson1
anova_isthmus_raw$efz[4] =anova_isthmus_raw$`Sum Sq`[4]/anova_isthmus_raw_totals$ #... finding efz for variable Sex:Witelson1
anova_isthmus_raw$efz[5] =anova_isthmus_raw$`Sum Sq`[5]/anova_isthmus_raw_totals$ #... finding efz for variable Residuals

#Type "anova_raw" and you see the results
anova_isthmus_raw

## Anova Table (Type III tests)
##
## Response: isthmus
##
##           Sum Sq   Df   F value  Pr(>F)    efz
## (Intercept) 3811174   1 24338.5812 0.00000   NaN
## Sex           97     1    0.6200 0.43122 0.00059
## Witelson1     93     1    0.5914 0.44206 0.00056
## Sex:Witelson1  35     1    0.2220 0.63764 0.00021
## Residuals   164889 1053                0.99864

HCP_CC_DATA_w_Handedness$isthmus = as.numeric(HCP_CC_DATA_w_Handedness$isthmus) # <- This should be done once, causes many errors if not

#exploring means
IsthmusRaw_mean_M = mean(HCP_CC_DATA_w_Handedness$isthmus[which(HCP_CC_DATA_w_Handedness$Sex == 'M')])
IsthmusRaw_sd_M = sd(HCP_CC_DATA_w_Handedness$isthmus[which(HCP_CC_DATA_w_Handedness$Sex == 'M')])
IsthmusRaw_mean_F = mean(HCP_CC_DATA_w_Handedness$isthmus[which(HCP_CC_DATA_w_Handedness$Sex == 'F')])
IsthmusRaw_sd_F = sd(HCP_CC_DATA_w_Handedness$isthmus[which(HCP_CC_DATA_w_Handedness$Sex == 'F')])

IsthmusRaw_mean_cRH = mean(HCP_CC_DATA_w_Handedness$isthmus[which(HCP_CC_DATA_w_Handedness$Witelson1 == 'cRH')])
IsthmusRaw_sd_cRH = sd(HCP_CC_DATA_w_Handedness$isthmus[which(HCP_CC_DATA_w_Handedness$Witelson1 == 'cRH')])
IsthmusRaw_mean_NcRH = mean(HCP_CC_DATA_w_Handedness$isthmus[which(HCP_CC_DATA_w_Handedness$Witelson1 == 'NcRH')])
IsthmusRaw_sd_NcRH = sd(HCP_CC_DATA_w_Handedness$isthmus[which(HCP_CC_DATA_w_Handedness$Witelson1 == 'NcRH')])

##=====
# Anova for the ratio between isthmus and forebrain volume

```

```

##=====##

## NB! Calculate ratio between isthmus and totalsize! Call it "isthmusFBV_ratio"

#DV: isthmusFBV_ratio
# Calculating interaction effect using the the ratio of the isthmus and brain size
#(isthmusFBV_ratio) as dependent variable, and Sex and handedness (Sex*Witelson1) as indepe
ndent variables
CCanova <- lm(isthmusFBV_ratio ~ Sex * Witelson1, data = HCP_CC_DATA_w_Handedness)
Anova(CCanova, type = 3)

## Anova Table (Type III tests)
##
## Response: isthmusFBV_ratio
##
##          Sum Sq   Df   F value    Pr(>F)
## (Intercept) 36528   1 25705.7944 < 2.2e-16 ***
## Sex          57     1   40.4298 3.032e-10 ***
## Witelson1    1     1    0.4425  0.5061
## Sex:Witelson1 0     1    0.2344  0.6284
## Residuals   1496 1053
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

anova_isthmus_ratio = Anova(CCanova, type = 3) #RW: if you commit the output to a variable
...
anova_isthmus_ratio$`Sum Sq`[2] #RW: you can access the components of the table like this,
here Sum Sq Sex

## [1] 57.45056

anova_isthmus_ratio_totalss = sum(anova_isthmus_ratio$`Sum Sq`[2:5]) #RW: total some of squ
ares = sum of all Sum Sq without intercept

anova_isthmus_ratio$efz = NaN #create column of NaN as place holder
anova_isthmus_ratio

## Anova Table (Type III tests)
##
## Response: isthmusFBV_ratio
##
##          Sum Sq   Df   F value    Pr(>F)  efz
## (Intercept) 36528   1 25705.7944 0.00000 NaN
## Sex          57     1   40.4298 0.00000 NaN
## Witelson1    1     1    0.4425 0.50608 NaN
## Sex:Witelson1 0     1    0.2344 0.62837 NaN
## Residuals   1496 1053                NaN

```

```

#Finding the effect size of the variables:
anova_isthmus_ratio$efz[2] =anova_isthmus_ratio$`Sum Sq`[2]/anova_isthmus_ratio_totalss #..
. finding efz for variable Sex
anova_isthmus_ratio$efz[3] =anova_isthmus_ratio$`Sum Sq`[3]/anova_isthmus_ratio_totalss #..
. finding efz for variable Witelson1
anova_isthmus_ratio$efz[4] =anova_isthmus_ratio$`Sum Sq`[4]/anova_isthmus_ratio_totalss #..
. finding efz for variable Sex:Witelson1
anova_isthmus_ratio$efz[5] =anova_isthmus_ratio$`Sum Sq`[5]/anova_isthmus_ratio_totalss #..
. finding efz for variable Residuals

#Type "anova_ratio" and you see the results
anova_isthmus_ratio

## Anova Table (Type III tests)
##
## Response: isthmusFBV_ratio
##
##           Sum Sq   Df    F value  Pr(>F)    efz
## (Intercept)  36528    1 25705.7944 0.00000   NaN
## Sex           57      1   40.4298 0.00000 0.03695
## Witelson1     1      1    0.4425 0.50608 0.00040
## Sex:Witelson1  0      1    0.2344 0.62837 0.00021
## Residuals   1496 1053                0.96243

#exploring means
IsthmusRatio_mean_M = mean(HCP_CC_DATA_w_Handedness$isthmusFBV_ratio[which(HCP_CC_DATA_w_Ha
ndedness$Sex == 'M')])
IsthmusRatio_sd_M = sd(HCP_CC_DATA_w_Handedness$isthmusFBV_ratio[which(HCP_CC_DATA_w_Handed
ness$Sex == 'M')])
IsthmusRatio_mean_F = mean(HCP_CC_DATA_w_Handedness$isthmusFBV_ratio[which(HCP_CC_DATA_w_Ha
ndedness$Sex == 'F')])
IsthmusRatio_sd_F = sd(HCP_CC_DATA_w_Handedness$isthmusFBV_ratio[which(HCP_CC_DATA_w_Handed
ness$Sex == 'F')])

IsthmusRatio_mean_cRH = mean(HCP_CC_DATA_w_Handedness$isthmusFBV_ratio[which(HCP_CC_DATA_w_
Handedness$Witelson1 == 'cRH')])
IsthmusRatio_sd_cRH = sd(HCP_CC_DATA_w_Handedness$isthmusFBV_ratio[which(HCP_CC_DATA_w_Hand
edness$Witelson1 == 'cRH')])
IsthmusRatio_mean_NcRH = mean(HCP_CC_DATA_w_Handedness$isthmusFBV_ratio[which(HCP_CC_DATA_w
_Handedness$Witelson1 == 'NcRH')])
IsthmusRatio_sd_NcRH = sd(HCP_CC_DATA_w_Handedness$isthmusFBV_ratio[which(HCP_CC_DATA_w_Han
dedness$Witelson1 == 'NcRH')])

##=====##
##Anovas for Witelson2
##=====##

```

```

W2Dataset<-HCP_CC_DATA_w_Handedness

## Factorize variables from W2Dataset
W2Dataset$Witelson2 = as.factor(W2Dataset$Witelson2)
W2Dataset$Sex = as.factor(W2Dataset$Sex)
#options(contrasts = c("contr.helmert", "contr.poly"))
#Exclude cLH
W2Dataset = W2Dataset[which(!W2Dataset$Witelson2 == "cLH"),] #selects all which are not (!)
"cLH"

##=====
# Anova for raw data
##=====
#DV: total area
crf.lm2.w2 <- lm(totalsize ~ Sex * Witelson2, data = W2Dataset)
anova_raw_w2 = Anova(crf.lm2.w2, type = 3) #RW: if you commit the output to a variable ...
anova_raw_w2$`Sum Sq`[2] #RW: you can access the components of the table like this, here Sum
Sq Sex

## [1] 75362.37

anova_raw_w2_totalss = sum(anova_raw_w2$`Sum Sq`[2:5]) #RW: total some of squares = sum of
all Sum Sq without intercept

#or we store it in the ANOVA output!
anova_raw_w2$efz = NaN #create column of NaN as place holder
anova_raw_w2

## Anova Table (Type III tests)
##
## Response: totalsize
##
##           Sum Sq   Df  F value  Pr(>F)  efz
## (Intercept) 451612606    1 51324.5249 0.00000 NaN
## Sex          75362      1    8.5647 0.00350 NaN
## Witelson2    3236      1    0.3678 0.54436 NaN
## Sex:Witelson2      8      1    0.0009 0.97669 NaN
## Residuals  8948744 1017                NaN

#Finding the effect size of the variables:
anova_raw_w2$efz[2] =anova_raw_w2$`Sum Sq`[2]/anova_raw_w2_totalss #... finding efz for var
iable Sex
anova_raw_w2$efz[3] =anova_raw_w2$`Sum Sq`[3]/anova_raw_w2_totalss #... finding efz for var
iable Witelson2
anova_raw_w2$efz[4] =anova_raw_w2$`Sum Sq`[4]/anova_raw_w2_totalss #... finding efz for var
iable Sex:Witelson2

```

```

anova_raw_w2$efz[5] = anova_raw_w2$`Sum Sq`[5]/anova_raw_w2_totalss #... finding efz for variable Residuals

#Type "anova_raw" and you see the results
anova_raw_w2

## Anova Table (Type III tests)
##
## Response: totalsize
##
##          Sum Sq  Df    F value  Pr(>F)    efz
## (Intercept) 451612606    1 51324.5249 0.00000    NaN
## Sex          75362     1    8.5647 0.00350 0.00835
## Witelson2    3236     1    0.3678 0.54436 0.00036
## Sex:Witelson2      8     1    0.0009 0.97669 0.00000
## Residuals 8948744 1017                    0.99129

#exploring means
W2Dataset$totalsize = as.numeric(W2Dataset$totalsize) # <- This should be done once, cause
s many errors if not

mean_w2_M = mean(W2Dataset$totalsize[which(W2Dataset$Sex == 'M')])
sd_w2_M = sd(W2Dataset$totalsize[which(W2Dataset$Sex == 'M')])
mean_w2_F = mean(W2Dataset$totalsize[which(W2Dataset$Sex == 'F')])
sd_w2_F = sd(W2Dataset$totalsize[which(W2Dataset$Sex == 'F')])

mean_w2_cRH = mean(W2Dataset$totalsize[which(W2Dataset$Witelson2 == 'cRH')])
sd_w2_cRH = sd(W2Dataset$totalsize[which(W2Dataset$Witelson2 == 'cRH')])
mean_w2_MH = mean(W2Dataset$totalsize[which(W2Dataset$Witelson2 == 'MH')])
sd_w2_MH = sd(W2Dataset$totalsize[which(W2Dataset$Witelson2 == 'MH')])

##=====
# Anova for ratio of Corpus Callosum and Forebrain volume (brain size)
##=====

#DV: ratio
# Calculating interaction effect using the the ratio of Corpus Callosum and brain size
#(CCFBV_ratio) as dependent variable, and Sex and handedness (Sex*Witelson2) as independent
variables
CCanova_w2 <- lm(CCFBV_ratio ~ Sex * Witelson2, data = W2Dataset)
#Anova(CCanova_w2, type = 3)
anova_ratio_w2 = Anova(CCanova_w2, type = 3) #RW: if you commit the output to a variable ..
.

```

```

anova_ratio_w2$`Sum Sq`[2] #RW: you can access the components of the table like this, here
Sum Sq Sex

## [1] 4087.597

anova_ratio_w2_totalss = sum(anova_ratio$`Sum Sq`[2:5]) #RW: total some of squares = sum of
all Sum Sq without intercept

anova_ratio_w2$efz = NaN #create column of NaN as place holder
anova_ratio_w2

## Anova Table (Type III tests)
##
## Response: CCFBV_ratio
##
##          Sum Sq   Df   F value  Pr(>F)  efz
## (Intercept) 4316439   1 60268.2608 0.00000  NaN
## Sex          4088    1   57.0731 0.00000  NaN
## Witelson2    23     1    0.3194 0.57212  NaN
## Sex:Witelson2  5     1    0.0725 0.78784  NaN
## Residuals   72838 1017                NaN

#Finding the effect size of the variables:
anova_ratio_w2$efz[2] =anova_ratio_w2$`Sum Sq`[2]/anova_ratio_w2_totalss #... finding efz f
or variable Sex
anova_ratio_w2$efz[3] =anova_ratio_w2$`Sum Sq`[3]/anova_ratio_w2_totalss #... finding efz f
or variable Witelson2
anova_ratio_w2$efz[4] =anova_ratio_w2$`Sum Sq`[4]/anova_ratio_w2_totalss #... finding efz f
or variable Sex:Witelson2
anova_ratio_w2$efz[5] =anova_ratio_w2$`Sum Sq`[5]/anova_ratio_w2_totalss #... finding efz f
or variable Residuals

#Type "anova_ratio" and you see the results
anova_ratio_w2

## Anova Table (Type III tests)
##
## Response: CCFBV_ratio
##
##          Sum Sq   Df   F value  Pr(>F)   efz
## (Intercept) 4316439   1 60268.2608 0.00000   NaN
## Sex          4088    1   57.0731 0.00000 0.05153
## Witelson2    23     1    0.3194 0.57212 0.00029
## Sex:Witelson2  5     1    0.0725 0.78784 0.00007
## Residuals   72838 1017                0.91817

#exploring means
Ratio_mean_w2_M = mean(W2Dataset$CCFBV_ratio[which(W2Dataset$Sex == 'M')])

```

```

Ratio_sd_w2_M = sd(W2Dataset$CCFBV_ratio[which(W2Dataset$Sex == 'M')])
Ratio_mean_w2_F = mean(W2Dataset$CCFBV_ratio[which(W2Dataset$Sex == 'F')])
Ratio_sd_w2_F = sd(W2Dataset$CCFBV_ratio[which(W2Dataset$Sex == 'F')])

Ratio_mean_w2_cRH = mean(W2Dataset$CCFBV_ratio[which(W2Dataset$Witelson2 == 'cRH')])
Ratio_sd_w2_cRH = sd(W2Dataset$CCFBV_ratio[which(W2Dataset$Witelson2 == 'cRH')])
Ratio_mean_w2_MH = mean(W2Dataset$CCFBV_ratio[which(W2Dataset$Witelson2 == 'MH')])
Ratio_sd_w2_MH = sd(W2Dataset$CCFBV_ratio[which(W2Dataset$Witelson2 == 'MH')])

##=====
# Anova for raw Isthmus data
##=====
#DV: Isthmus
crf.lm2.w2 <- lm(isthmus ~ Sex * Witelson2, data = W2Dataset)
anova_isthmus_raw_w2 = Anova(crf.lm2.w2, type = 3) #RW: if you commit the output to a variable ...
anova_isthmus_raw_w2$`Sum Sq`[2] #RW: you can access the components of the table like this, here Sum Sq Sex

## [1] 53.62766

anova_isthmus_raw_w2_totalss = sum(anova_isthmus_raw_w2$`Sum Sq`[2:5]) #RW: total sum of squares = sum of all Sum Sq without intercept

#or we store it in the ANOVA output!
anova_isthmus_raw_w2$efz = NaN #create column of NaN as place holder
anova_isthmus_raw_w2

## Anova Table (Type III tests)
##
## Response: isthmus
##
##           Sum Sq   Df  F value  Pr(>F)  efz
## (Intercept) 3616692    1 23095.1662 0.00000  NaN
## Sex           54      1    0.3425 0.55855  NaN
## Witelson2     47      1    0.3011 0.58328  NaN
## Sex:Witelson2  12      1    0.0770 0.78144  NaN
## Residuals   159262 1017                NaN

#Finding the effect size of the variables:
anova_isthmus_raw_w2$efz[2] = anova_isthmus_raw_w2$`Sum Sq`[2]/anova_isthmus_raw_w2_totalss
#... finding efz for variable Sex
anova_isthmus_raw_w2$efz[3] = anova_isthmus_raw_w2$`Sum Sq`[3]/anova_isthmus_raw_w2_totalss
#... finding efz for variable Witelson2
anova_isthmus_raw_w2$efz[4] = anova_isthmus_raw_w2$`Sum Sq`[4]/anova_isthmus_raw_w2_totalss

```

```

#... finding efz for variable Sex:Witelson2
anova_isthmus_raw_w2$efz[5] =anova_isthmus_raw_w2$`Sum Sq`[5]/anova_isthmus_raw_w2_totallss
#... finding efz for variable Residuals

#Type "anova_raw" and you see the results
anova_isthmus_raw_w2

## Anova Table (Type III tests)
##
## Response: isthmus
##
##           Sum Sq   Df   F value  Pr(>F)    efz
## (Intercept) 3616692   1 23095.1662 0.00000   NaN
## Sex           54     1    0.3425 0.55855 0.00034
## Witelson2    47     1    0.3011 0.58328 0.00030
## Sex:Witelson2 12     1    0.0770 0.78144 0.00008
## Residuals   159262 1017                0.99929

W2Dataset$isthmus = as.numeric(W2Dataset$isthmus) # <- This should be done once, causes many errors if not

#exploring means
IsthmusRaw_mean_w2_M = mean(W2Dataset$isthmus[which(W2Dataset$Sex == 'M')])
IsthmusRaw_sd_w2_M = sd(W2Dataset$isthmus[which(W2Dataset$Sex == 'M')])
IsthmusRaw_mean_w2_F = mean(W2Dataset$isthmus[which(W2Dataset$Sex == 'F')])
IsthmusRaw_sd_w2_F = sd(W2Dataset$isthmus[which(W2Dataset$Sex == 'F')])

IsthmusRaw_mean_w2_cRH = mean(W2Dataset$isthmus[which(W2Dataset$Witelson2 == 'cRH')])
IsthmusRaw_sd_w2_cRH = sd(W2Dataset$isthmus[which(W2Dataset$Witelson2 == 'cRH')])
IsthmusRaw_mean_w2_MH = mean(W2Dataset$isthmus[which(W2Dataset$Witelson2 == 'MH')])
IsthmusRaw_sd_w2_MH = sd(W2Dataset$isthmus[which(W2Dataset$Witelson2 == 'MH')])

##=====
# Anova for the ratio between isthmus and forebrain volume
##=====

## NB! Calculate ratio between isthmus and totalsize! Call it "isthmusFBV_ratio"

#DV: isthmusFBV_ratio
# Calculating interaction effect using the the ratio of the isthmus and brain size
#(isthmusFBV_ratio) as dependent variable, and Sex and handedness (Sex*Witelson2) as independent variables
CCanova_w2 <- lm(isthmusFBV_ratio ~ Sex * Witelson2, data = W2Dataset)
Anova(CCanova_w2, type = 3)

```



```

## Anova Table (Type III tests)
##
## Response: isthmusFBV_ratio
##           Sum Sq  Df    F value    Pr(>F)
## (Intercept) 34610   1 24387.6124 < 2.2e-16 ***
## Sex          55     1   38.7377 7.076e-10 ***
## Witelson2    0     1    0.3171  0.5735
## Sex:Witelson2  0     1    0.1912  0.6620
## Residuals   1443 1017
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

anova_isthmus_ratio_w2 = Anova(CCanova_w2, type = 3) #RW: if you commit the output to a variable ...
anova_isthmus_ratio_w2$`Sum Sq`[2] #RW: you can access the components of the table like this, here Sum Sq Sex

## [1] 54.9757

anova_isthmus_ratio_w2_totalss = sum(anova_isthmus_ratio_w2$`Sum Sq`[2:5]) #RW: total some of squares = sum of all Sum Sq without intercept

anova_isthmus_ratio_w2$efz = NaN #create column of NaN as place holder
anova_isthmus_ratio_w2

## Anova Table (Type III tests)
##
## Response: isthmusFBV_ratio
##           Sum Sq  Df    F value    Pr(>F)  efz
## (Intercept) 34610   1 24387.6124 0.00000 NaN
## Sex          55     1   38.7377 0.00000 NaN
## Witelson2    0     1    0.3171 0.57351 NaN
## Sex:Witelson2  0     1    0.1912 0.66200 NaN
## Residuals   1443 1017                NaN

#Finding the effect size of the variables:
anova_isthmus_ratio_w2$efz[2] =anova_isthmus_ratio_w2$`Sum Sq`[2]/anova_isthmus_ratio_w2_totalss #... finding efz for variable Sex
anova_isthmus_ratio_w2$efz[3] =anova_isthmus_ratio_w2$`Sum Sq`[3]/anova_isthmus_ratio_w2_totalss #... finding efz for variable Witelson2
anova_isthmus_ratio_w2$efz[4] =anova_isthmus_ratio_w2$`Sum Sq`[4]/anova_isthmus_ratio_w2_totalss #... finding efz for variable Sex:Witelson2
anova_isthmus_ratio_w2$efz[5] =anova_isthmus_ratio_w2$`Sum Sq`[5]/anova_isthmus_ratio_w2_totalss #... finding efz for variable Residuals

```

```

#Type "anova_ratio" and you see the results
anova_isthmus_ratio_w2

## Anova Table (Type III tests)
##
## Response: isthmusFBV_ratio
##           Sum Sq   Df   F value   Pr(>F)     efz
## (Intercept)  34610    1 24387.6124 0.00000    NaN
## Sex           55     1   38.7377 0.00000  0.03667
## Witelson2     0     1    0.3171 0.57351  0.00030
## Sex:Witelson2  0     1    0.1912 0.66200  0.00018
## Residuals    1443 1017                0.96284

#exploring means
IsthmusRatio_mean_w2_M = mean(W2Dataset$isthmusFBV_ratio[which(W2Dataset$Sex == 'M')])
IsthmusRatio_sd_w2_M = sd(W2Dataset$isthmusFBV_ratio[which(W2Dataset$Sex == 'M')])
IsthmusRatio_mean_w2_F = mean(W2Dataset$isthmusFBV_ratio[which(W2Dataset$Sex == 'F')])
IsthmusRatio_sd_w2_F = sd(W2Dataset$isthmusFBV_ratio[which(W2Dataset$Sex == 'F')])

IsthmusRatio_mean_w2_cRH = mean(W2Dataset$isthmusFBV_ratio[which(W2Dataset$Witelson2 == 'cRH')])
IsthmusRatio_sd_w2_cRH = sd(W2Dataset$isthmusFBV_ratio[which(W2Dataset$Witelson2 == 'cRH')])
IsthmusRatio_mean_w2_MH = mean(W2Dataset$isthmusFBV_ratio[which(W2Dataset$Witelson2 == 'MH')])
IsthmusRatio_sd_w2_MH = sd(W2Dataset$isthmusFBV_ratio[which(W2Dataset$Witelson2 == 'MH')])

##=====
# Creating plots using Witelson1
##=====

library(tidyr)
library(rstatix)

##
## Attaching package: 'rstatix'

## The following object is masked from 'package:stats':
##
##   filter

##=====
#FIRST ANALYSIS: Interaction plot for dependable variable totalsize
Data4plot = HCP_CC_DATA_w_Handedness %>% group_by(Witelson1, Sex) %>%

```

```

get_summary_stats(totalsize, type = "full")

#Plotting interaction as Line plot based on means
ggplot(Data4plot, aes(x=Witelson1, y=mean, colour=Sex)) +
  geom_errorbar(aes(ymin=mean-ci, ymax=mean+ci),
               width=.20,
               position=position_dodge(width=.35)) +
  geom_point(size = 4,
             position=position_dodge(width=.35)) +
  geom_line(aes(x=as.numeric(Witelson1)),
            position=position_dodge(width=.35)) +
  scale_color_manual(values=c("cornflowerblue", "darkorange2"))+
  ggtitle("Witelson1 first analysis: totalsize of CC") +
  xlab("Handedness category") +
  ylab("Total size of corpus callosum") +
  theme_light()+
  theme(aspect.ratio=1,
        axis.text.x = element_text(size=12),
        axis.title.x = element_text(size=14, face="bold"),
        axis.text.y = element_text(size=12),
        axis.title.y = element_text(size=14, face="bold"),
        legend.text = element_text(size = 12),
        legend.title = element_text(size=14, face="bold"))

##=====
#SECOND ANALYSIS: Interaction plot for dependable variable Corpus callosum - forebrain ratio
o CCFBV_ratio
Data4plot = HCP_CC_DATA_w_Handedness %>% group_by(Witelson1, Sex) %>%
  get_summary_stats(CCFBV_ratio, type = "full")

#Plotting interaction as Line plot based on means
ggplot(Data4plot, aes(x=Witelson1, y=mean, colour=Sex)) +
  geom_errorbar(aes(ymin=mean-ci, ymax=mean+ci),
               width=.20,
               position=position_dodge(width= .35)) +
  geom_point(size = 4,
             position=position_dodge(width=.35)) +
  geom_line(aes(x=as.numeric(Witelson1)),
            position=position_dodge(width=.35)) +
  scale_color_manual(values=c("cornflowerblue", "darkorange2"))+
  ggtitle("Second analysis: CCFBV ratio") +

```

```

xlab("Handedness category") +
ylab("Ratio of corpus callosum and forebrain volume") +
theme_light()+
theme(aspect.ratio=1,
      axis.text.x = element_text(size=12),
      axis.title.x = element_text(size=14, face="bold"),
      axis.text.y = element_text(size=12),
      axis.title.y = element_text(size=14, face="bold"),
      legend.text = element_text(size = 12),
      legend.title = element_text(size=14, face="bold"))

##=====
#THIRD ANALYSIS: Interaction plot for dependable variable isthmus
Data4plot = HCP_CC_DATA_w_Handedness %>% group_by(Witelson1, Sex) %>%
  get_summary_stats(isthmus, type = "full")

#Plotting interaction as line plot based on means
ggplot(Data4plot, aes(x=Witelson1, y=mean, colour=Sex)) +
  geom_errorbar(aes(ymin=mean-ci, ymax=mean+ci),
               width=.20,
               position=position_dodge(width=.35)) +
  geom_point(size = 4,
             position=position_dodge(width=.35)) +
  geom_line(aes(x=as.numeric(Witelson1)),
            position=position_dodge(width=.35)) +
  scale_color_manual(values=c("cornflowerblue", "darkorange2"))+
  ggtitle("Third analysis: isthmus") +
  xlab("Handedness category") +
  ylab("Isthmus") +
  theme_light()+
  theme(aspect.ratio=1,
        axis.text.x = element_text(size=12),
        axis.title.x = element_text(size=14, face="bold"),
        axis.text.y = element_text(size=12),
        axis.title.y = element_text(size=14, face="bold"),
        legend.text = element_text(size = 12),
        legend.title = element_text(size=14, face="bold"))

##=====
#FOURTH ANALYSIS: Interaction plot for dependable variable isthmus-forebrain ratio
Data4plot = HCP_CC_DATA_w_Handedness %>% group_by(Witelson1, Sex) %>%
  get_summary_stats(isthmusFBV_ratio, type = "full")

```

```

#Plotting interaction as Line plot based on means
ggplot(Data4plot, aes(x=Witelson1, y=mean, colour=Sex)) +
  geom_errorbar(aes(ymin=mean-ci, ymax=mean+ci),
                width=.20,
                position=position_dodge(width=.35)) +
  geom_point(size = 4,
             position=position_dodge(width=.35)) +
  geom_line(aes(x=as.numeric(Witelson1)),
            position=position_dodge(width=.35)) +
  scale_color_manual(values=c("cornflowerblue", "darkorange2"))+
  ggtitle("Fourth analysis: isthmus_forebrain ratio") +
  xlab("Handedness category") +
  ylab("Ratio of the isthmus and forebrain volume") +
  ylim(5,7)+
  theme_light()+
  theme(aspect.ratio=1,
        axis.text.x = element_text(size=12),
        axis.title.x = element_text(size=14, face="bold"),
        axis.text.y = element_text(size=12),
        axis.title.y = element_text(size=14, face="bold"),
        legend.text = element_text(size = 12),
        legend.title = element_text(size=14, face="bold"))

##=====
# Creating plots for Witelson2
##=====

library(tidyr)
library(rstatix)

##=====
#Interaction plot for dependable variable totalsize
Data4plot = W2Dataset %>% group_by(Witelson2, Sex) %>%
  get_summary_stats(totalsize, type = "full")

#Plotting interaction as Line plot based on means
ggplot(Data4plot, aes(x=Witelson2, y=mean, colour=Sex)) +
  geom_errorbar(aes(ymin=mean-ci, ymax=mean+ci),
                width=.20,
                position=position_dodge(width=.35)) +
  geom_point(size = 4,
             position=position_dodge(width=.35)) +
  geom_line(aes(x=as.numeric(Witelson2)),
            position=position_dodge(width=.35)) +

```

```

        position=position_dodge(width=.35)) +
scale_color_manual(values=c("cornflowerblue", "darkorange2"))+
ggtitle("Witelson2 first analysis: totalsize of CC") +
xlab("Handedness category") +
ylab("Total size of corpus callosum") +
theme_light()+
theme(aspect.ratio=1,
      axis.text.x = element_text(size=12),
      axis.title.x = element_text(size=14, face="bold"),
      axis.text.y = element_text(size=12),
      axis.title.y = element_text(size=14, face="bold"),
      legend.text = element_text(size = 12),
      legend.title = element_text(size=14, face="bold"))

##=====
#Interaction plot for dependable variable Corpus callosum - forebrain ratio CCFBV_ratio
Data4plot = W2Dataset %>% group_by(Witelson2, Sex) %>%
  get_summary_stats(CCFBV_ratio, type = "full")

#Plotting interaction as Line plot based on means
ggplot(Data4plot, aes(x=Witelson2, y=mean, colour=Sex)) +
  geom_errorbar(aes(ymin=mean-ci, ymax=mean+ci),
               width=.20,
               position=position_dodge(width=.35)) +
  geom_point(size = 4,
             position=position_dodge(width=.35)) +
  geom_line(aes(x=as.numeric(Witelson2)),
            position=position_dodge(width=.35)) +
  scale_color_manual(values=c("cornflowerblue", "darkorange2"))+
  ggtitle("Second analysis: CCFBV ratio") +
  xlab("Handedness category") +
  ylab("Ratio of corpus callosum and forebrain volume") +
  theme_light()+
  theme(aspect.ratio=1,
        axis.text.x = element_text(size=12),
        axis.title.x = element_text(size=14, face="bold"),
        axis.text.y = element_text(size=12),
        axis.title.y = element_text(size=14, face="bold"),
        legend.text = element_text(size = 12),
        legend.title = element_text(size=14, face="bold"))

##=====
#Interaction plot for dependable variable isthmus
Data4plot = W2Dataset %>% group_by(Witelson2, Sex) %>%

```

```

get_summary_stats(isthmus, type = "full")

#Plotting interaction as Line plot based on means
ggplot(Data4plot, aes(x=Witelson2, y=mean, colour=Sex)) +
  geom_errorbar(aes(ymin=mean-ci, ymax=mean+ci),
               width=.20,
               position=position_dodge(width=.35)) +
  geom_point(size = 4,
             position=position_dodge(width=.35)) +
  geom_line(aes(x=as.numeric(Witelson2)),
            position=position_dodge(width=.35)) +
  scale_color_manual(values=c("cornflowerblue", "darkorange2"))+
  ggtitle("Third analysis: isthmus") +
  xlab("Handedness category") +
  ylab("Isthmus") +
  theme_light()+
  theme(aspect.ratio=1,
        axis.text.x = element_text(size=12),
        axis.title.x = element_text(size=14, face="bold"),
        axis.text.y = element_text(size=12),
        axis.title.y = element_text(size=14, face="bold"),
        legend.text = element_text(size = 12),
        legend.title = element_text(size=14, face="bold"))

##=====
#Interaction plot for dependable variable isthmus-forebrain ratio
Data4plot = W2Dataset %>% group_by(Witelson2, Sex) %>%
  get_summary_stats(isthmusFBV_ratio, type = "full")

#Plotting interaction as Line plot based on means
ggplot(Data4plot, aes(x=Witelson2, y=mean, colour=Sex)) +
  geom_errorbar(aes(ymin=mean-ci, ymax=mean+ci),
               width=.20,
               position=position_dodge(width=.35)) +
  geom_point(size = 4,
             position=position_dodge(width=.35)) +
  geom_line(aes(x=as.numeric(Witelson2)),
            position=position_dodge(width=.35)) +
  scale_color_manual(values=c("cornflowerblue", "darkorange2"))+
  ggtitle("Fourth analysis: isthmus_forebrain ratio") +
  xlab("Handedness category") +
  ylab("Ratio of the isthmus and forebrain volume") +

```

```
theme_light()+
theme(aspect.ratio=1,
      axis.text.x = element_text(size=12),
      axis.title.x = element_text(size=14, face="bold"),
      axis.text.y = element_text(size=12),
      axis.title.y = element_text(size=14, face="bold"),
      legend.text = element_text(size = 12),
      legend.title = element_text(size=14, face="bold"))

##=====#
```