1. Introduction: Sex Differences in Neuropsychology

1.1. Sex Differences in the Healthy Brain and General Cognition

Sex differences in cognitive abilities have been a widely discussed subject ~~of interest~~ already since the 1870s (for a review see Shields, 1975). Inspired by F. J. Gall's phrenology, research mainly utilised measures of head and brain size in an attempt to explain differences in cognitive capacities (cf. Cornel, 2014; Shields, 1975). Already early on, it was discovered that men had larger crania and brains compared to women. Researchers such as Romanes (1887) proposed that the comparatively smaller brains of women must be directly responsible for their intellectual inferiority and increased emotionality (see also Fee, 1979). In her 1975 review, Shields concluded that many researchers at that time lacked the necessary impartiality to investigate the topic of sex differences, as they aimed "to discover the particular physiological determinants of female inadequacy" (p. 740). Over time, as new methods to acquire and analyse (neuro-)psychological data were introduced, several researchers pointed out that those presumed cognitive sex differences were inherently grounded in stereotypical gender roles, and that men and women are more alike than previously assumed (Broverman et al., 1972; Sherman, 1967; Woolley, 1914).

Even so, the view that the brains and cognitive abilities of men and women are fundamentally different (also referred to as the "gender differences hypothesis") remained relatively common throughout both the minds of the general population, as well as the scientific community (Hyde, 2005). However, contrary to popular conceptions of psychological sex differences, numerous meta-analyses and meta-syntheses demonstrated that if any gender differences are detectable in cognitive tests, they often are negligibly small (Hirnstein et al., 2019; Hyde, 2005; Zell et al., 2015). Hyde (2005 & 2014) found that in most cognitive tasks, women and men achieved equal performances. The strongest and most robust difference in cognitive tasks that Zell et al.'s (2015) meta-synthesis identified was better performance of men in mental rotation tasks. Voyer et al.'s (2016) meta-analysis identified a significant, albeit small male advantage in visuospatial working memory tasks. A few studies found a small female advantage in certain language tasks, such as verbal fluency, but this effect was not consistently found across other tests in the language domain (Hyde, 2014 & 2016; Sommer et al., 2004). Since most existing differences tended to be small in magnitude, this led researchers to coin the "gender similarities hypothesis", stating that men and women are similar in most, but not all, psychological domains (Hyde, 2005; Zell et al., 2015).

With the advent of neuroimaging in the 1990s, new possibilities emerged for the research of sex differences. Nevertheless, there still is no consensus on the exact neural mechanisms underlying those cognitive sex differences. Several structural magnetic resonance imaging (MRI) studies and meta-analyses thereof confirmed that the volume of the crania and brain lobes are generally larger in men than in women (Allen et al., 2003; Eliot et al., 2021; Goldstein et al., 2001), with some studies reporting a difference in total brain volume of up to 8-11% (Filipek et al., 1994; Goldstein et al., 2001; Swaab & Hofman, 1984). A study by Allen et al. (2002) found that while the gross volumes of brain lobes differ between the sexes, the proportional

sizes of those regions to the total brain volume are nearly identical. Further, it has been reported that certain brain structures differ in (relative) size between the sexes. Some examples include larger volumes in the amygdala, putamen and globus pallidus in males, and larger volumes in the hippocampus and caudate nucleus in females (Cosgrove et al., 2007; Giedd et al., 1996a & 1996b). However, such findings are not uncontroversial, as sex differences in the volume of brain structures may disappear when correcting for total brain volume and/or intracranial volume (Choleris et al., 2018; Eliot et al., 2021; Tan et al., 2016).

Numerous studies also report that women have thicker cortices, as well as a higher grey-to-white matter ratio across cortical structures – even after correcting for the difference in total brain volume (Cosgrove et al., 2007; Sacher et al., 2013; Sowell et al., 2006). This effect was found to be especially robust in the inferior parietal and posterior temporal lobes (Sowell et al., 2006; Cosgrove et al., 2007). Generally, men were found to have a higher percentage of white matter (WM) and cerebrospinal fluid (Gur et al., 1999), whereas women were found to have 4-7% more grey matter (GM) than men (Eliot et al., 2021; Leonard et al., 2008; Ritchie et al., 2018). This difference is especially pronounced in the four lobes, the cingulate gyrus, and insula (Allen, et al., 2003; Goldstein et al., 2001; Gur et al., 1999). Nevertheless, differences in grey-to-white matter ration have also been reported to disappear after correcting for total brain volume (Eliot et al., 2021; Leonard et al., 2008; Jäncke et al., 2014).

Some researchers consider sexual dimorphism to be stronger in the WM than in the grey matter (Allen et al., 2003). Even though men have a higher proportion of cortical WM, women have larger corpora callosa in proportion to their total WM volume (Allen et al., 2003; Gur et al., 1999; Dubb et al., 2003; Ingalhalikar et al., 2013). Further, multiple studies have found that the corpora callosa of men and women differ in shape: Splenia are larger and more bulbous in women, whereas men have more tubular-shaped splenia, as well as larger genua (Allen et al., 1991; Dubb et al., 2003). Allen et al. (2003) proposed that WM tracts might be less sexually dimorphic than other WM components, such as glial cells and blood vessels.

Studies employing diffusion tensor imaging (DTI) to investigate the architecture of WM and its fibre tracts found that over all age ranges, men tend to have increased measures of fractional anisotropy and decreased mean diffusivity, compared to women (source). Higher measures of fractional anisotropy are thought to reflect increased axonal diameter, fibre bundle density and myelination, while the inverse relation holds for mean diffusivity (Boespflug et al., 2011; Zasler & Kaplan, 2017). In a similar vein to the reports of women having larger corpora callosa in proportion to the rest of their WM, Kanaan et al. (2012) were able to show that the corpus callosum in women has higher functional anisotropy than in men. They interpreted this finding as women's corpora callosa exhibiting greater efficiency.

DTI may not only be used to study isolated fibre tracts, but also to study the structural connectome of brain networks. Studies have found that women have a greater local brain network efficiency (Yan et al., 2011), as well as increased cortical connectivity (Gong et al., 2009) – independent of total brain volume. A large-scale DTI study investigating sex-differences in the structural connectome by Ingalhalikar et al. (2013) found a higher proportion of

intrahemispheric WM tracts in men and a higher ratio of interhemispheric connections, especially via the corpus callosum, in women. Based on these differences in the ratio of inter- and intrahemispheric connections, they argue that men exhibit a greater hemispheric asymmetry than women do, and further, that these differences in hemispheric asymmetry may give rise to sex differences in cognitive abilities (Grabowska, 2016; Kovalev et al., 2003; see Hirnstein et al., 2019 for a review).

Generally, hemispheric asymmetries in the functional connectivity of the brain, which are also referred to as functional cerebral asymmetries (FCAs) or functional lateralisation, are regarded a fundamental principle of brain organisation. FCAs are relative differences in neural functions and cognitive processes between the two hemispheres, typically with one hemisphere playing a "dominant" role for a given cognitive domain (Hausmann, 2016; Hirnstein et al., 2019). Therefore, FCAs can be thought of as an instance of functional specialisation within the brain (Gotts et al., 2013). Well-known examples are the left lateralisation of language and the right lateralisation of visuospatial processing (Hausmann, 2016; Hirnstein et al., 2019; Ocklenburg & Güntürkün, 2012).

A number of studies have compared FCAs between the sexes for different modalities and tasks and found lower levels of FCAs in women compared to men (Hiscock et al., 1995, 1999 & 2001; Liu et al., 2009; Voyer, 1996). This means that cognitive representations and brain activation patterns tend to be more bilateral and symmetrical in women, while they are largely restricted to one hemisphere in men – or in other words that in female brains there is a less strict separation of functions between the hemispheres (source).

Ingalhalikar et al. (2013) argues that those differences in FCAs are related to the different ratios of inter- and intrahemispheric connections between the sexes: Male brains possess increased FCAs with more pronounced intrahemispheric connections, whereas female brains have stronger interhemispheric connectivity and thus, process information more symmetrically. Further, they proposed that male brains are structured in a way that facilitates spatial processing and coordinated motor action, while female brains promote attention, memory, and verbal abilities.

While so far there is not enough research to determine if anatomical WM asymmetries and functional lateralisation are really related in such a way (for reviews see Corballis & Häberling, 2017; Ocklenburg & Güntürkün, 2012), many researchers argue that differences both in brain organisation and in cognition may be caused, or at least influenced, by sex hormones (e.g., Cosgrove et al., 2007; Grabowska, 2016; Hirnstein et al., 2019; Kimura & Hampson, 1994).

Sex hormones, such as oestradiol, progesterone, and testosterone, have been shown to be able to alter neuronal excitability (Rupprecht, 2003) and there is great evidence that FCAs fluctuate throughout the menstrual cycle due to the varying levels of those hormones (e.g., Bibawi et al., 1995; Hausmann et al., 2002; Hausmann, 2005; Wisniewski, 1998). Hausmann and Güntürkün (2000) established that FCAs are stable over time in men, as well as in post-menopausal women. Further, they found evidence that high levels of progesterone during the midluteal phase may

down-regulate interhemispheric interactions and thus, further decrease FCAs, whereas higher levels of FCAs were found during the menses. Other studies found similar patterns for oestradiol (Bibawi et al., 1995; Mead & Hampson, 1997).

[Ending/Transition]

1.2. Sex Differences in Stroke

Vascular diseases, such as stroke and ischemic heart diseases, currently constitute the second leading cause of death worldwide and are one of the leading causes of disability, especially in the elderly population (Bonkhoff et al., 2021; Feigin et al., 2014; Katan & Luft, 2018). The Lancet's Global Burden of Disease review for the year 2019 reported 12.2 million global incident cases of stroke: 62.4% of those strokes were ischaemias/infarcts, while the remaining 37.6% were haemorrhages. They further identified stroke to be the second-leading cause of death, accounting for a total of 6.55 million global deaths, and one of the top leading causes of long-term disabilities as measured by disease-adjusted life years. Women suffered more often from strokes (6.44 million incident cases, 56.4 million prevalent cases) compared to men (5.79 million incident strokes, 45.0 million prevalent cases) (Feigin et al., 2021). Most likely, this can at least be partially attributed to the higher life expectancy of women (Giroud et al., 2017; Bonkhoff et al., 2021).

A meta-analysis by Gargano et al. (2009) concluded that women are on average 4 years older than men are when suffering their first ischemic strokes. Since increased age is positively correlated with stroke risk and negatively correlated with functional outcomes, elderly women suffer the largest burden of stroke-induced disability and death (Appelros et al., 2009; Gibson, 2013; Reeves et al., 2008; Silva et al., 2010). Multiple studies have found that in the chronic post-stroke phase women are more likely to have significantly decreased quality of life, including impaired locomotor function and mental abilities, compared to men (Gibson, 2013; Reeves et al., 2008, Sturm et al., 2004) – the effects of which can even persist up to 5 years after initial stroke onset (Fukuda et al., 2009). Importantly, the increased stroke severity in women remains significant even after adjusting for age differences at stroke onset and does not arise from differences in lesion size (Bonkhoff et al., 2021; Dehlendorff et al., 2015; Silva et al., 2010).

In a large-scale study, Bonkhoff et al. (2021) investigated sex differences in first-ever acute ischaemic strokes and found that in both sexes the majority of lesions occurred in left and right hemispheric territories supplied by the middle cerebral artery (MCA) and to a lesser extent in regions supplied by the posterior cerebral artery (PCA). Further, they found that cortical lesions to the pre- and postcentral gyri, the supramarginal gyrus and parietal regions explained higher stroke severity, independent of hemisphere. Likewise, subcortical lesions to the thalamus, basal ganglia (BG) and certain white matter tracts, such as the inferior occipitofrontal fasciculus, superior longitudinal fasciculus, corticospinal tract, and anterior thalamic radiation, also explained higher stroke severity. This is generally in line with the findings of Wu et al. (2015), who also identified lesions in similar regions to be directly correlated with increased stroke severity and long-term disability. Especially lesions to the insula, operculum, and putamen in the right hemisphere were found to be likely responsible for more severe long-term disability, irrespective of the size of the lesion. For the left hemisphere, however, lesion volume is a significant factor affecting stroke severity, given age and sex of the patient.

Further, Bonkhoff et al. (2021) detected no differences in lesion volume between men and women but found that more regions contributed to stroke severity in women and thus, that

similar lesion patterns elicit more severe strokes in women, compared to men. The most robust sex differences were strictly left lateralised, meaning that women are more vulnerable to the effects of a left hemispheric stroke, especially to regions supplied by the PCA, such as the hippocampus, thalamus, or precuneus. Interestingly, those sex-specific effects were not present when comparing men and women below the age of 52, which is the median age of menopause onset (McKinley et al., 1992), suggesting that sex hormones play an important role in the neuropathology of stroke.

Many researchers believe that (neuro)biological sex differences, such as sex chromosomes or sex steroid hormones that contribute to different responses to cerebral ischemia (Bonkhoff et al., 2021; Bushnell et al., 2018; Gibson, 2013). Rodent models have well established that female brains sustain less injuries after experimental ischaemic stroke compared to male brains, which is attributed to the neuroprotective properties of sex steroid hormones, such as oestradiol and progesterone (Gibson et al., 2013; Liu et al., 2010; Wise et al., 2001). These hormones, taken together with testosterone, are also referred to as "neuroactive steroids" or "neuro-steroids", as they can be synthesised within the brain and are able to alter neuronal excitability (Rupprecht, 2003).

Testosterone, the primary male sex steroid, is considered to increase sensitivity to ischaemic strokes, as it has been demonstrated to promote inflammatory effects on cerebral blood vessels and impede cerebral blood flow by constricting vasculature. Conversely, oestrogens have consistently been shown to exhibit neuroprotective effects, such as inhibiting cerebrovascular inflammation, suppressing cell death mechanisms, stimulating the formation of new blood vessels, and improving cerebral blood flow (Krause et al., 2006; Manwani et al., 2014; Suzuki et al., 2009).

There is some experimental evidence in animal models that showed that acute administration of oestradiol reduces infarct size and tissue damage, as well as improves post-infarct blood flow (Gibson et al., 2009; Liu & Yang, 2013; McCullough et al., 2001; Suzuki et al, 2009). Interestingly, oestradiol administration also reduces injury in male animals, suggesting that its neuroprotective effects are independent of sex (Bushnell et al., 2018; Manwani et al., 2014). However, clinical trials in humans have not been successful so far (Gibson et al., 2013; Henderson & Lobo, 2012).

The fact that oestradiol, the primary female sex steroid, has strong neuroprotective properties, may seem counterintuitive considering the increased vulnerability of women to the effects of stroke. Women, compared to men, have a lower incidence of stroke throughout most of their lives – up until the menopause-induced decrease in oestrogen levels, at which point they become disproportionately sensitive to stroke. Taken together with the fact that increased age facilitates chronic low-grade inflammations in the brain through a natural loss of endogenous anti-inflammatory substances, the additional loss of the neuroprotective properties provided by oestradiol and the higher age of women when suffering their first stroke, increases the risks imposed by stroke for women (Bushnell et al., 2018; Koellhoffer & McCullough, 2012; Manwani & McCullough, 2012; Sohrabji et al., 2017).

There is also some evidence that sex differences in stroke sensitivity are not purely mediated by the different sex steroids, which fluctuate through life, but also by sex chromosomes. Studies have shown that in cells derived from neonatal populations, male-derived (XY) cells are more vulnerable to ischaemic injuries than female-derived (XX) cells – even in low hormonal concentrations (Koellhoffer & McCullough, 2012; Li et al., 2005; Liu et al., 2008). The same effects have also been demonstrated in aged mice: At low sex steroid levels, animals with XX chromosomes had larger infarcts, higher inflammatory responses, and more severe neurological deficits. However, the detrimental effect of a second X chromosome only emerged after reproductive maturation. Therefore, it seems likely that (ischemic) strokes are affected by a complex interaction of aging, sex-specific neuro-steroids, and sex chromosomes (Bushnell et al., 2018; Manwani et al., 2014; McCullough et al., 2016).

1.3. Visuospatial Neglect

Stroke can cause a number of ensuing neuropsychological conditions, as even small focal lesions can significantly disrupt the brain network's overall connectivity and thus, its functionality (Carrera & Tononi, 2014; Griffis et al., 2019). One syndrome that commonly occurs during the acute stage after predominantly right hemispheric stroke is visuospatial neglect, though it may also be caused by other forms of unilateral brain injury (Karnath & Rorden, 2012; Li & Malhotra, 2015; Stone et al., 1993). Neglect is often described as a supramodal disorder of spatial attention with a "heterogenous collection of symptoms" (Corbetta et al., 2005; Karnath & Rorden, 2012). The core symptoms include a pathological spatial bias towards the ipsilesional (i.e., typically right) side of space, affecting both gaze direction and exploration. This manifests as sustained and spontaneous deviation of the head- and eye-position towards the ipsilesional side at rest, as well as during goal-directed behaviour, and it persists even in complete darkness (Becker & Karnath, 2010; Karnath, 2012; Karnath & Fetter, 1995). At the same time, patients have difficulties in orienting towards the contralesional side and will typically ignore information located there (Becker & Karnath, 2010; Corbetta & Shulman, 2011; Karnath, 2015; Karnath & Rorden, 2012). Even though neglect is considered a basal disorder, meaning that the symptoms do not merely emerge in higher-order cognitive tasks, the spatial biases are not due to underlying paralysis or sensory deficits (Heilman & Valenstein, 1979; Karnath, 2012).

While there is no consensus on the exact prevalence of neglect, estimates of about 30% in the acute phase after stroke seem likely (e.g.: Bowen et al., 1999; Corbetta, 2014; Hammerbeck et al., 2019; but see also Ten Brink et al., 2017 or Stone et al., 1993 for more extreme estimates). In a large-scale observational study comprising more than 80,000 stroke patients from the United Kingdom, Hammerbeck et al. (2019) established that neglect is associated with higher age at stroke onset (on average 3 years), with more severe strokes, greater disability, and mortality. Further, they discovered a sex difference in acute neglect incidence, with women exhibiting a prevalence of 33% versus 27% in men. Recovery rates for the core symptoms during the post-acute phase are relatively high at 70-80% (Demeyere & Gillebert, 2019), making the prevalence rates of chronic neglect considerably lower than for acute neglect. Current estimates for chronic neglect prevalence vary from 8-12% (Jehkonen et al., 2000) to up to 17% (Esposito et al., 2021). Still, neglect is commonly considered to be a negative predictor for functional outcome in stroke recovery (Jehkonen et al., 2000 & 2007; Wee & Hopman, 2008; Wu et al., 2015).

Typically, the behavioural core symptoms of neglect manifest with reference to the patient's egocentre, i.e., relative to their own body centre (Corbetta & Shulman, 2011; Karnath & Rorden, 2012). However, the behavioural deficits may also occur in an allocentric reference frame: Patients with allocentric neglect ignore the left side of an object (rather than the overall space), irrespective of the object's location relative to the patient (Li et al., 2014). Although some authors argue that ego- and allocentric neglect can dissociate (Demeyere & Gillebert, 2019; Hillis et al., 2005), others report significant interactions: As many neglect patients suffer from a

combination of both types, the presentation of stimuli in the (egocentric) contralesional space may result in a more severe allocentric bias (Li et al., 2014; Rorden et al., 2012; Yue et al., 2012).

Further, those behavioural core symptoms do not necessarily only affect vision, but may also affect other modalities, such as audition, olfaction, motion, and even memory (Bisiach & Luzatti, 1978; Beschin et al., 1997; Karnath, 2012). Though the symptoms may be alleviated or overcome for a short period of time, this requires top-down (e.g., verbal request) or bottom-up (e.g., visual cues) input, as often times patients are not aware of their deficit (Karnath, 2012). Given the great heterogeneity of clinical symptoms, it is common that many patients show neglect in a particular diagnostic test, but no sign of it in another test (Vaessen et al., 2016; Verdon et al., 2010). Therefore, a combination of multiple tests is commonly utilised to diagnose neglect (for more details see Section 2.2. Behavioural Data).

The heterogeneity of clinical symptoms is also reflected in the neuroanatomy of neglect: Most often, the syndrome manifests after right unilateral brain damage in the territory of the middle cerebral artery (MCA) (Li & Malhotra, 2015). The right hemispheric perisylvian network, including the temporo-parietal junction (TPJ), inferior parietal lobule (IPL), superior and middle temporal cortex, insula, and ventrolateral prefrontal cortex (vlPFC), seems to underlie spatial orientation and it has been proposed that its disruption likely contributes to the core neglect deficits (Bartolomeo et al. 2007; Corbetta et al., 2005; Karnath, 2012; Karnath & Rorden, 2012). Other notable cortical regions that have been implicated in neglect are the posterior parietal cortex, inferior frontal cortex, angular gyrus, supramarginal gyrus (Buxbaum et al., 2004; Corbetta & Shulman, 2011; He et al., 2007; Hillis et al., 2005; Verdon et al., 2010). However, there is still an ongoing debate surrounding the exact neurological correlates of neglect with many studies reporting contradictory findings, especially regarding the role of the temporal and parietal cortices in the syndrome (Bartolomeo et al., 2007; Karnath et al., 2001).

Further, lesions to certain subcortical regions, such as the thalamus and the basal ganglia (BG), have also been shown to be associated with neglect – however, it is hypothesised that not the lesion to those regions themselves causes neglect, but rather that the disorder emerges from the long-range effects of reduced functionality in the perisylvian network (He et al., 2007; Karnath, 2012; Karnath & Niemeier, 2002).

The idea that the spatial-attentional processes whose disruption underlie neglect might emerge from damage to large networks rather than single brain areas has already been discussed for a long time (Bartolomeo et al., 2007; Corbetta, 2014; Mesulam, 1981; Saxena et al., 2022; Vaessen et al., 2016). Several studies in animal models have demonstrated that severe experimental neglect could only be induced when disrupting WM connections between the parietal and frontal lobes, whereas the ablation of either of those cortices or a combined ablation resulted in little, if any, neglect symptoms (Burcham et al., 1997; Gaffan & Hornak, 1997; Reep et al., 2004).

Interestingly, this is in line with the results obtained from fibre-tracking studies in neglect patients. It has been established that the WM fibres connecting the perisylvian network,

specifically the superior longitudinal fasciculus (SLF), arcuate fasciculus (AF), the inferior fronto-occipital fasciculus (IFOF) and the superior fronto-occipital fasciculus (SFOF) have been shown to be particularly vulnerable to causing neglect after being damaged (Chechlacz et al., 2010; He et al., 2007; Karnath et al., 2009; Urbanski et al., 2010). It also has been shown that neglect severity is greater when lesions reach deep into the WM, compared to cortical lesions of a similar size (Corbetta, 2014).

Studies investigating both structural connectivity utilising DTI, as well as functional connectivity using functional MRI (fMRI) confirmed that disconnections in the fronto-parietal network contribute to the development of chronic neglect and specifically, subcortical damage to the SLF was identified to be the best predictor of neglect. Damage to the IFOF, AF, and dorsolateral thalamus were also found to contribute to neglect severity, though not as strongly and consistently as SLF disconnections (Bartolomeo et al., 2007; He et al., 2007; Thiebaut de Schotten et al., 2014; Urbanski et al., 2010; Vaessen et al., 2016).

In line with this, Saxena et al. (2022) analysed disconnections following acute stroke and found neglect to commonly emerge from intrahemispheric fronto-parietal disconnections. Moreover, they found neglect arising from those disconnections to manifest with greater severity than from focal lesions in any of the cortical regions commonly associated with neglect, such as the right perisylvian network, which is in accordance with Corbetta's (2014) findings. Further, Saxena et al. detected a strong association of neglect severity with disconnections involving the (middle) temporal cortex, as well as disconnections involving the BG – specifically, the putamen – which fits the results of Karnath & Niemeier's (2002) lesion analysis study.

While the majority of those results were obtained from patients who suffered from an infarct in the territory of the MCA, Bird et al. (2006) described similar associations in patients with PCA-infarction: In those patients, intrahemispheric disconnections of the WM tracts between the parahippocampal gyrus and the angular gyrus was significantly correlated with neglect severity, whereas damage to those individual regions was found to not be sufficient for manifesting neglect. Further, they found that lesions to the splenium of the corpus callosum subsequently damaged interhemispheric WM fibres and in turn, also increased neglect severity (see also Bozzali et al., 2012).

Griffis et al. (2019 & 2021) developed a technique to assess brain network dysfunction after stroke based on an indirect measure of structural disconnections – without the need for acquiring DTI images (see Chapter 3: Data Analysis for details). They were able to replicate the findings obtained in seminal studies in the past (see above), in that they also found neglect severity to be primarily linked to disconnections of the SLF, and to a lesser extent of the AF, in the right hemisphere. Moreover, they found that those direction disconnections typically associated with neglect further disrupt connections between the inferior frontal junction and all lobes of the right hemisphere. Those findings are consistent with the results by He et al. (2007) and support the notion that neglect may arise from long-range interference in the function of the attentional network.

While it still has not been fully resolved, why lesions in the WM increase neglect severity compared to lesions in the GM, Bartolomeo et al. (2007) hypothesise that it likely is due to diaschisis – the neurophysiological changes that occur distant to a focal brain lesion (Carrera & Tononi, 2014). They argue that the same lesion volume may cause more dysfunction if it occurs in WM tracts compared to cortical GM, due to the disrupted connections to larger cortical areas. This could lead to altered functioning of several cortical areas or even a whole brain network, which is harder to functionally compensate for through neuroplasticity than in the case of focal GM lesions (c.f., Catani & Ffytche, 2005; Duffau, 2005).

[ending/transition]

1.4. Motivation

Sex differences in psychology, neuroanatomy and stroke pathophysiology have received a lot more attention in research than when those topics were first introduced. To the best of our knowledge, only sex differences in the incidence of neglect and performance in commonly used diagnostic tests have been studied so far, whereas potential sex differences in the neural underpinnings of neglect have not received any attention in research thus far.

[...]

Firstly, we want to investigate if we can find any sex differences in the clinical and demographic data of our patient sample, which would be in in line with the previous research on sex differences in the pathophysiology in stroke (c.f., Bonkhoff et al., 2021; Hammerbeck et al., 2019).

Secondly, we want to test if classical voxel-based lesion-behaviour can reveal any differences in the relation between focal lesions and neglect severity between men and women.

Thirdly, we want to investigate if the sex differences in hemispheric asymmetry and brain connectivity (as described e.g., by Ingalhalikar et al., 2013; more) also result in differences in WM disconnectivity after stroke. To this end, we will use Griffis et al.'s (2021) indirect method of assessing different disconnectivity measures based on lesion data, rather than assessing them directly using DTI.

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