

Thesis

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Sex-Specific Lesion Patterns and Disconnectome Induced by Stroke and
Corresponding Sex Differences Associated with Acute Visuospatial Neglect

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Disclosures:

I affirm that I have written the dissertation myself and have not used any sources and aids other than those indicated.

I affirm that I have not included data generated in one of my laboratory rotations and already presented in the respective laboratory report.

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Abstract

One of the many factors affecting cognition and brain health is biological sex, and while the exact neurobiological underpinnings have not been identified so far, it has been proposed that this may be rooted in sex differences in brain connectivity. Previous research has demonstrated that women exhibit more interhemispheric white matter connections, while men have a greater proportion of intrahemispheric connections. However, it is still unclear if/how those underlying sex differences in brain connectivity affect white matter disconnections caused by focal strokes and thus, how severe stroke-induced syndromes, such as visuospatial neglect, manifest. Here we show that while men and women do not differ significantly in their lesion localisation after acute right-hemispheric stroke, they exhibit sex-specific disconnectivity patterns. We identified different clusters of voxels in women and men that contribute to neglect severity when damaged. Further, we revealed sex-specific region-to-region disconnectivity patterns, with thalamus disconnections being significantly associated with the female sex. In the predictive modelling of patient status, disconnection-based models outperformed lesion-based models, especially during the prediction of neglect diagnosis. Our findings highlight while there are sex-specific disconnectivity patterns after stroke, future studies are needed to further our understanding of the underlying mechanisms and ultimately contribute to personalised medicine.

1. Introduction

1.1. Sex Differences in Brain Connectivity

Sex differences in cognitive abilities have been a widely discussed subject since the 1870s already (for a review see Shields, 1975). The so-called “gender differences hypothesis”, which maintains that the brains and cognitive abilities of men and women¹ are fundamentally different, still remains relatively common throughout both the minds of the general population, as well as the scientific community to this date (Hyde, 2005; Hirnstein et al., 2019). However, contrary to popular conceptions of psychological sex differences, numerous meta-analyses and meta-syntheses demonstrated that if any sex differences are detectable in cognitive tests, they often are negligibly small (Choleris et al., 2018; 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 a meta-synthesis by Zell et al. (2015) 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).

Nevertheless, even small sex differences in cognition may be highly relevant for societal issues, such as discrimination against one of the sexes in a particular career path based on harmful stereotypes (Ceci et al., 2009; Hartley & Sutton, 2013; Hirnstein et al., 2019), as well as for clinical applications and personalised medical care (Choleris et al., 2018; Ritchie et al., 2018). Still, there is no consensus regarding the exact neurobiological mechanisms underlying cognitive sex differences, but a complex interaction of nature and nurture has been proposed (Hirnstein et al., 2019; Miller & Halpern, 2014). A particularly influential theory proposes that cognitive sex differences may arise from differences in brain connectivity and hemispheric asymmetry (Ingalhalikar et al., 2013; Pletzer, 2014; see Hirnstein et al., 2019 for a review).

A large-scale diffusion tensor imaging (DTI) study by Ingalhalikar et al. (2013) investigating sex-differences in the structural connectome of the healthy human brain found a higher proportion of intrahemispheric white matter (WM) tracts in men, and a higher ratio of interhemispheric connections, especially via the corpus callosum, in women. In other words, men exhibit a stronger hemispheric asymmetry. These differences in the ratio of inter- and intrahemispheric

¹ Sex (i.e., the biological component) and gender (i.e., the psychosocial manifestation) of human masculinity and femininity are entangled, though not identical. For the purposes of the present study, we employ the term “sex” rather than “gender” or the more recently proposed compound label “sex/gender (s/g)”, as we had no access to the patients’ self-identities, but only to their medical records (for overviews/guidelines on sex/gender research in the neurosciences see Jordan-Young & Rumiati, 2012; Springer et al., 2012).

connections grew more pronounced throughout development from childhood and adolescence to (young) adulthood. Further, they found men to have significantly stronger intrahemispheric connections between the four lobes (e.g., between the right frontal and right temporal lobes) and increased connectivity within the respective lobes, compared to women. Moreover, they concluded that male brains possess enhanced modularity, meaning that their brains can clearly be delineated into sub-networks that emphasise local short-range connectivity within the lobes.

Those findings of male brains being optimised for intrahemispheric connections and female brains for interhemispheric connections are in line with anatomical studies establishing that men possess a higher proportion of cortical WM, whereas women have larger corpora callosa in proportion to their total WM volume (Allen et al., 1991; Allen et al., 2003; Dubb et al., 2003; Gur et al., 1999; Ingalhalikar et al., 2013). Other DTI studies investigating the architecture of cortical WM fibre tracts supported those findings, by establishing that men tend to have increased axonal diameters, fibre bundle density and myelination (as inferred from fractional anisotropy), whereas those parameters were higher in the corpus callosum in women (Boespflug et al., 2011; Kanaan et al., 2012; Zasler & Kaplan, 2017).

Some researchers even claim that the increased interhemispheric connectivity, especially via the corpus callosum, makes female brains more efficient on a global level, compared to male brains, which are organized in a more modular manner (Gong et al., 2009; Gur et al., 1999; Ingalhalikar et al., 2013; Yan et al., 2011). Based on this, it is argued that those sex differences in structural hemispheric asymmetry may give rise to differences in functional lateralisation (Grabowska, 2017; Ingalhalikar et al., 2013; Kovalev et al., 2003; see Hirnstein et al., 2019 for a review).

Generally, functional lateralisation can be understood as hemispheric asymmetries in the functional connectivity of the brain, and it refers to relative differences in the neural functions and cognitive processes between the two hemispheres with one hemisphere typically playing a “dominant” role for a given cognitive domain (Hausmann, 2016; Hirnstein et al., 2019). Therefore, functional lateralisation is considered to be an instance of functional specialization within the brain (Gotts et al., 2013). Well-known examples are the left lateralisation of language and the right lateralisation of visuospatial attention (Hausmann, 2016; Hirnstein et al., 2019; Jia et al., 2022; Ocklenburg & Güntürkün, 2012).

A number of studies have compared functional lateralisation between the sexes for different modalities and tasks and found lower levels of lateralisation 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 tend to be restricted to one hemisphere in men – or in other words: in female brains there is a less strict separation of functions between the hemispheres. Ingalhalikar et al. (2013) argue that those differences in functional lateralisation are related to the different ratios of inter- and intrahemispheric connections between the sexes: Male brains

possess increased levels of lateralisation with more pronounced intrahemispheric connections, whereas female brains have stronger interhemispheric connectivity and thus, process information more symmetrically.

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 such differences in brain connectivity may be caused, or at least influenced, by sex hormones (e.g., Cosgrove et al., 2007; Grabowska, 2017; 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 (Hausmann, 2016; Rupperecht, 2003) and there is great evidence that functional lateralisation fluctuates throughout the menstrual cycle due to the varying levels of those hormones (e.g., Bibawi et al., 1995; Hausmann, 2005; Hausmann et al., 2002; Wisniewski, 1998). Studies have established that lateralisation is stable over time in men, as well as in post-menopausal women (e.g., Hausmann & Güntürkün, 2000). Further, there is evidence that high levels of progesterone and oestradiol during the midluteal phase may up-regulate interhemispheric interactions and thus, further decrease lateralisation, whereas increased levels of functional lateralisation were found during the menses when levels of oestradiol and progesterone are the lowest (Bibawi et al., 1995; Hausmann et al., 2002; Hausmann & Güntürkün, 2000; Mead & Hampson, 1997).

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 strokes to be the second-leading cause of death, accounting for a total of 6.55 million global deaths. Women suffered from strokes more often (6.44 million incident cases, 56.4 million prevalent cases) compared to men (5.79 million incident stroke cases, 45.0 million prevalent cases; Feigin et al., 2021). Most likely, this can be at least partially attributed to the higher life expectancy of women, as stroke risk increases with age (Giroud et al., 2017; Bonkhoff et al., 2021).

A meta-analysis by Gargano et al. (2008) concluded that women are on average 4 years older than men are when suffering their first ischemic stroke. 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). These effects 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). Therefore, it seems likely that there must be some other underlying reason for the increased vulnerability to the effects of stroke in women.

A study by Barrett et al. (2007) found that in first-ever minor ischaemic strokes (i.e., strokes with small lesion size and minor severity and symptoms) men and women did not differ significantly in regards to lesion size and location or stroke severity. However, they note that their results may not be able to generalise to more severe stroke populations.

In a large-scale study, Bonkhoff et al. (2021) investigated sex differences in 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 were associated with 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 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.

Further, Bonkhoff et al. (2021) detected no differences in lesion volume between men and women but found that lesions affecting more regions were significantly associated with increased 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, contribute to different responses to cerebral ischemia (Bonkhoff et al., 2021; Bushnell et al., 2018; Gibson, 2013). For example, the primary male sex steroid testosterone 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). The fact that oestradiol 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).

Interestingly, 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). Taking everything together, it therefore 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). Typically, these 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). 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; Esposito et al., 2021; Hammerbeck et al., 2019). In a large-scale observational study comprising more than 80,000 stroke patients from the United Kingdom, Hammerbeck et al. (2019) found that neglect patients are on average 3 years older at stroke onset than patients without neglect, and that neglect is associated with more severe strokes, greater disability, and mortality. Further, they discovered a significant, but small 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. 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).

Further, the behavioural core symptoms of neglect do not necessarily only affect vision, but may also affect other modalities, such as audition, olfaction, motion, and even mental representations (Beschinn et al., 1997; Bisiach & Luzatti, 1978; 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 patients are often 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 MCA (Li & Malhotra, 2015). The right-hemispheric perisylvian network – including the temporo-parietal junction, inferior parietal lobule (IPL), superior and middle temporal cortex, insula, and ventrolateral prefrontal cortex – 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, and 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, 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 experimentally-induced neglect could only be elicited 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 magnetic resonance imaging (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 were 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, as well as to the thalamus, were not necessary or sufficient to cause neglect, but contributed to neglect severity (see also Bozzali et al., 2012).

Griffis et al. (2019 & 2021) developed a tool 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). The authors were able to replicate the findings obtained in seminal studies in the past, in that they also found neglect severity to be primarily linked to right-hemispheric disconnections of the SLF, and to a lesser extent of the AF. Moreover, they found that those 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 damage to the WM increases neglect severity, Bartolomeo et al. (2007) hypothesise that it is likely due to diaschisis – the remote neurophysiological effects altering the functionality of brain regions distant to the focal brain lesion, due to a disruption of neuronal pathways (Carrera & Tononi, 2014). They argue that the same lesion volume may cause more dysfunction if it occurs in WM tracts compared to cortical grey matter (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 (cf. Catani & Ffytche, 2005; Duffau, 2005).

1.4. Motivation

Sex differences in psychology, neuroanatomy, and stroke pathophysiology lately have received a lot more attention in research compared to when those topics were first introduced. However, to the best of our knowledge, there has been very little (if any) research investigating sex differences in lesion localisation after acute right-hemispheric stroke, or if/how sex-specific WM white matter disconnections affect neurological post-stroke syndromes, such as visuospatial neglect.

There are very few studies investigating sex differences in lesion topology (notably Barret et al., 2007; Bonkhoff et al., 2021 & 2022; Wu et al., 2015), which mainly analysed it in the context of functional correlations with stroke severity – in other words, they identified regions whose damage status contributes to stroke severity to varying degrees in men and women.

Even though visuospatial neglect is a highly lateralised syndrome that is common in survivors of right-hemispheric stroke, research has not paid much attention to sex and the previously described corresponding connectivity asymmetry as factors that might affect the manifestation of this syndrome significantly. While a difference in neglect incidence between the sexes has been established (Hammerbeck et al., 2019), studies on sex differences in neglect severity and symptoms have been inconclusive so far (Kleinman et al., 2008; Varnava & Halligan, 2007) and further, we are unaware of any study investigating sex differences in the anatomical and connectomic correlates of neglect.

It seems possible that neglect-specific differences between the sexes may (only) manifest in the stroke-induced disconnections, given that men and women differ in their underlying structural brain connectivity (Ingalhalikar et al., 2013) and that neglect has increasingly been considered to be a disconnection syndrome (Bartolomeo et al., 2007; Doricchi et al., 2008; Thiebaut de Schotten et al., 2008).

Consequently, we investigated the following questions:

- 1) Are there any differences in lesion localisations between men and women?
- 2) Are there any sex-specific patterns in stroke-induced WM disconnections?
- 3) Are there any sex differences in lesion or disconnectivity patterns associated with the severity of visuospatial neglect?
- 4) Can lesion data and disconnection data be used to predict patient status in predictive modelling?

To this end, we firstly tested if the clinical and demographic data of our patient sample were in line with the previous research on sex differences in the pathophysiology of stroke (cf. Bonkhoff et al., 2021; Hammerbeck et al., 2019). Secondly, we evaluated if there are differences in lesion localisation that can be attributed either purely to sex or to sex-specific differences underlying neglect. Thirdly, we used a recently introduced method of indirect lesion-connectome mapping (Griffis et al., 2019; for a review see Sperber et al., 2022) to assess different disconnectivity measures based on lesion data.

We examined if there are any differences in the whole-brain (voxel-wise) disconnectivity or region-to-region (parcel-wise) disconnectivity, which are due to sex or sex-specific neglect characteristics. Lastly, we utilised a supervised machine learning classifier in the form of a support vector machine (SVM) to predict the patient status (i.e., sex, neglect diagnosis, or a combination of both) based on lesion data, as well as whole-brain disconnectivity data.

2. Material & Methods

2.1. Patient Sample

This study reanalysed data from right-hemispheric stroke patients, admitted to the Centre of Neurology at the University Clinic of Tübingen and whose data had been used for previous studies conducted at the Division for Neuropsychology. All patients provided their informed consent for study participation and scientific data usage. The study was conducted in accordance with the revised guidelines from the Declaration of Helsinki and was approved by the ethics committee of the medical faculty of Tübingen University.

The inclusion criteria for the study were as follows:

- > Imaging data must have been acquired during the acute phase of the patient's stroke, i.e., within 14 days after stroke onset
- > The (normalised) imaging data must have been of sufficiently high quality and revealed a demarcated, unilateral right-hemispheric lesion
- > The patient experienced no previous strokes, traumatic insults, or brain tumours
- > The patient completed at least two out of the three diagnostic tests for visuospatial neglect during the acute phase after the patient's stroke, i.e., within 14 days after stroke onset
 - » If only two of the three tests were completed, their results must have been sufficient for a clear diagnosis, i.e., either exceeding or not meeting the threshold for pathological neglect in both tests

Following these criteria, the study included a total of 206 right-hemispheric stroke patients, comprised of 103 female and 103 male patients (see Table 1 for demographic data). Sex was assessed by the patients' medical records. Patients were assessed for primary visual field defects (i.e., hemi- or quadrantanopia) via standard neurological confrontation testing. A total of 73 patients were diagnosed with visuospatial neglect, meaning that they exceeded the defined threshold in at least 2 out of the 3 diagnostic tests (see 2.2. Behavioural Data for details, and Supplementary Tables 1a and 1b for demographic data of the neglect and non-neglect groups).

Table 1: Clinical and demographic data of the patient sample

	Total (n = 206)	Female (n = 103)	Male (n = 103)	p-value
Age (<i>years</i>)	62.6 (14.0) [26-93]	64.4 (15.4) [26-93]	60.8 (12.1) [29-83]	0.064 ^a
Patient Group (<i>Neglect, Non-Neglect</i>)	73, 133	40, 63	33, 70	0.308 ^b
Days between Stroke & Imaging	2.9 (3.1) [0-14]	2.8 (3.1) [0-14]	3.1 (3.1) [0-14]	0.580 ^a
Aetiology (<i>Infarct, Haemorrhage, Both</i>)	169, 34, 3	79, 22, 2	90, 12, 1	0.137 ^b
Lesion volume (<i>cm³</i>)	36.0 (44.8) [0.09-312.6]	34.8 (44.8) [0.16-312.6]	37.3 (43.8) [0.09-194.7]	0.688 ^a
Arterial Territory of Infarct (<i>ACA, MCA, PCA</i>)	12, 134, 22	11, 61, 7	1, 73, 15	0.003^b
Days between Stroke & Assessment	3.7 (2.6) [0-14]	4.0 (2.5) [0-14]	3.5 (2.7) [0-13]	0.195 ^a
Letter CoC	0.16 (0.27) [-0.06-0.99]	0.16 (0.27) [-0.02-0.99]	0.15 (0.27) [-0.06-0.96]	0.851 ^a
Bells CoC	0.15 (0.25) [-0.11-0.92]	0.14 (0.23) [-0.10-0.92]	0.17 (0.26) [-0.11-0.91]	0.385 ^a
Copying Errors	1.16 (1.93) [0-7]	1.13 (1.81) [0-7]	1.19 (2.04) [0-7]	0.794 ^a
Mean z-Score	0.02 (0.97) [-0.75-3.04]	0.01 (0.91) [-0.63-3.04]	0.03 (1.02) [-0.74-2.93]	0.833 ^a
Visual field defects (<i>N</i>)	32	16	16	0.849 ^b

Results are given as either number of patients or mean (standard deviation) [range]. The lesion volume was computed for the normalised lesion in MNI space. For the calculation of p-values, we first confirmed that the samples had equal variances and then either an equal variances t-test ('a', for continuous variables) or a Chi² test ('b', for categorical variables) was calculated. p-values < 0.05 are considered significant and highlighted in bold. Abbreviations: *n* – Number of patients, *ACA* – Anterior Cerebral Artery, *MCA* – Medial Cerebral Artery, *PCA* – Posterior Cerebral Artery, *CoC* – Centre of Cancellation (Rorden & Karnath, 2010)

2.2. Behavioural Data

We employed three commonly used diagnostic tests for the visuospatial neglect examination: the Letter Cancellation Task (Weintraub & Mesulam, 1985), the Bells Cancellation Test (Gauthier et al., 1989) and a copying task (Karnath & Niemeier, 2002; see Rorden & Karnath, 2010 for an overview). The patients completed those tasks as standard paper-and-pencil tests on a horizontally oriented DIN A4 (21 x 29.7cm) sheet of paper fixated at the centre of the patient's sagittal midline.

In the cancellation tests, patients are tasked with cancelling all target stimuli that are spatially distributed on the horizontally oriented sheet of paper. In the Letter Cancellation Task, the targets are 60 instances of the letter "A", which are distributed among other distractor letters, while in the Bells Test the targets are 35 bell icons distributed among other distractor symbols. Patients received no time limit for completing these tasks and were asked to confirm twice that they were content with their performance before ending the tasks.

For our analyses, we calculated the Centre of Cancellation (CoC; Rorden & Karnath, 2010) values individually for every patient. The CoC is a continuous score ranging from -1 to +1, which describes the number of missed items and their corresponding location. A score of -1 denotes a severe right-sided neglect, while a score of +1 is interpreted as severe left-sided neglect.

The individual CoC values were then compared to a cut-off value (0.083 for the letter cancellation test and 0.081 for the bells cancellation test, respectively). Any value above the cut-off was seen as pathological and interpreted as a potential indicator for visuospatial neglect (cf. Rorden & Karnath, 2010).

In the copying task, the number of errors made while copying a complex multi-object scene was counted. The scene comprises four items – a fence, a car, a house, and a tree – with two items each located in each half of the horizontally oriented sheet of paper. The omission of at least one contralateral feature of a given item was counted as 1 error point, while the omission of a whole item was counted as 2 error points. Additional error points were given, if the patient drew a contralateral feature or item on the ipsilesional side of the paper. If a patient scored at least 2 out of 8 possible error points, this was deemed pathological behaviour. If a patient exhibited pathological behaviour in at least 2 of the 3 tests, they were diagnosed with visuospatial neglect for the purposes of this study (cf. Karnath & Niemeier, 2002).

Results from all three behavioural tasks were z-scored and a mean of those scores was calculated for every patient. To ensure comparability between the male and female subsamples, we calculated the z-scores based on the entire patient sample, since the z-scores that were calculated for the subsamples did not differ significantly as assessed by a t-test.

2.3. Neuroimaging Data

We used the neuroimaging data acquired during the patients' clinical investigation at the Centre of Neurology. Therefore, we included structural images of different modalities in this study. Out of the 206 total scans, 98 were CT scans; the remaining 108 were MR scans. On average, scans were acquired 2.9 days (SD = 3.1) after stroke (see Table 1).

If images of multiple modalities were available for a patient, MR scans were preferred to delineate the patient's lesion. For patients with available MR scans, we preferentially used diffusion-weighted imaging (DWI) for scans acquired within the first two days after stroke onset ($n = 43$) and T2-weighted fluid attenuated inversion recovery (T2FLAIR) images for images acquired at a later point ($n = 65$). These scans were used to delineate the patients' lesions. For 36 patients, we used an additional scan of another modality (e.g., DWI and T1; see Supplementary Tables 2a and 2b for a full list) to improve the normalisation quality of the image.

The neuroimaging data were pre-processed using MATLAB versions R2016b and R2020a (MathWorks, Inc., Natick, USA), as well as the SPM12 toolbox (Wellcome Department of Cognitive Neurology, London, UK). Generally, we followed the guidelines to lesion-behaviour mapping as described in de Haan and Karnath (2018) and Karnath et al. (2019).

If multiple images of different modalities were available for a given patient, the corresponding images were co-registered using the SPM12 function as a first step.

Then, we used the “Clusterize Toolbox” (Clas et al., 2012; de Haan et al., 2015) for SPM to delineate each patient’s lesion semi-automatically. The toolbox’s algorithm first automatically detects potential lesions, i.e., hyper- or hypointense areas, by clustering the image. Following Clas et al. (2012), we used a default minimum cluster size of 100 voxels. The potential lesions flagged by the algorithm are then manually reviewed, selected, and modified, resulting in a binary voxel-wise lesion map.

For patients that suffered from both a haemorrhagic stroke as well as an infarct, and as a result exhibited two lesions of different intensities (e.g., hyperintense haemorrhages and hypointense infarcts in CT scans), the Clusterize algorithm was applied separately for each intensity. Afterwards, the corresponding lesion maps were added and corrected for potential overlaps using a custom MATLAB script. Every patient’s resulting lesion map was visually inspected for its good match by overlaying it on top of the anatomical scan using the MRIcron software (Rorden & Brett, 2000).

Thereafter, the “Clinical Toolbox” (Rorden et al., 2012) for SPM was used to normalise every patient’s anatomical scan, as well as the previously created lesion map, to MNI space (Montreal Neurological Institute; Collins et al., 1994) with the standard voxel size of 1mm^3 . We used this toolbox for the normalisation process rather than the standard SPM12 normalisation function, since it allowed us to normalise the scan to an age-matched template and apply lesion masks. We used either cost-function masking or enantiomorphic correction to control for the lesions during the normalisation process (cf. Karnath et al., 2019). Afterwards, we masked the extracerebral space, as well as the lateral ventricles and cerebellum to optimise the normalisation by using a custom MATLAB script. Lastly, the quality of the normalisation was manually checked for every patient’s scan by comparing the normalised brain to the template brain of the given image modality using MRIcron.

2.4. Data Analysis

2.4.1. Voxel-based Lesion-Behaviour Mapping

We first used MRICron to create descriptive lesion overlay plots for all relevant groups. Lesion overlap plots are topographies of all patients' normalised lesion maps (for an overview see de Haan & Karnath, 2018). The resulting topographies were interpreted by referencing the Brainnetome atlas (Fan et al., 2016; for more details see Section 3.3.).

Subsequently, we conducted a voxel-based lesion-behaviour mapping analysis with "NiiStat" (<https://github.com/neurolabusc/NiiStat>) to identify voxels for which damage is associated with a sex-specific pattern or a more severe behavioural deficit in the diagnostic tests. First, we used mass-univariate non-parametric Lieberman tests using the binary voxel status (i.e., 0 = undamaged, 1 = damaged) as independent variable and sex as dependent variable. This was done to investigate whether there are specific voxels that are more often lesioned in women or men, respectively. Then, we employed mass-univariate general linear models (GLMs) using the normalised behavioural score as dependent variable to identify voxels whose damage is associated with more severe neglect symptoms for the whole patient sample. Thereafter, we repeated this analysis separately for the female and male patient subsamples, to investigate if different clusters of voxels are associated with neglect severity in women and men.

We performed all tests at a one-sided significance level of $p < 0.05$ and corrected for family-wise errors by employing 5,000 permutations with maximum statistic permutation (Nichols & Holmes, 2002).

2.4.2. Whole-Brain Disconnectivity

To identify which WM tracts were damaged by the focal stroke-induced lesions, we used the "Lesion Quantification Toolkit" (LQT; Griffis et al., 2021), which provides an indirect measure of structural disconnections. Based on a patient's lesion map, the LQT creates individual WM disconnectivity topographies by identifying all fibres in a given WM tract that intersect the lesioned area. To this end, we used the HCP-842 tract-wise connectome atlas, which includes 70 WM tracts and is distributed with the LQT (Yeh et al., 2018).

More specifically, the LQT embeds the binary lesion map as a region-of-interest (ROI) into the tractography atlas and filters all fibres in a given WM tract that run through the lesioned area. These fibres are considered "disconnected streamlines", which are then compared to the total number of fibres/streamlines of their associated WM tract to estimate how severely disconnected that WM tract is. The resulting topographies describe the percentage of disconnected fibres for every WM voxel and allow the topographical assessment of a lesion's impact on whole-brain connectivity.

We additionally used "NiiStat" to investigate if damage to a specific WM voxel was significantly associated with sex or sex-specific neglect severity. As already described in Section 3.1. for the voxel-wise lesion-behaviour mapping (VLBM) analysis, we ran this analysis once using sex as

dependent variable, and once using the behavioural score as dependent variable in order to determine whether the voxels that were disconnected in men and women were similar enough to be directly compared. We then repeated the neglect severity analysis three times: for the whole patient sample, for the female patients and for the male patients, separately.

2.4.3. Region-to-Region Disconnectivity

To identify which GM regions were disconnected from each other due to the stroke-induced WM tract damage as estimated in Section 3.2., we once again employed the LQT (Griffis et al., 2021) to create parcel-wise disconnectivity matrices for every patient. This was done by combining the HCP-842 connectome atlas (Yeh et al., 2018) with a brain parcellation atlas. We chose the Brainnetome atlas (BN-246; Fan et al., 2016) as our parcellation atlas, as it was specifically developed for connectivity analyses and includes cortical ($n = 210$), as well as subcortical ($n = 36$) regions. Following Griffis et al.'s (2021) recommendations, we defined structural connections between a parcel pair as the streamlines that bilaterally end within the two parcels. This resulted in symmetric 246-by-246 disconnectivity matrices for every patient.

In order to assess if any of the disconnections differ between the male and female subsamples, we used custom MATLAB scripts employing mass-univariate non-parametric Wilcoxon rank-sum tests. For this, we loaded the symmetric 246-by-246 disconnectivity matrices into MATLAB and removed the diagonal and redundant elements below it. We also removed any ROI-to-ROI disconnections that are either (physiologically) non-existent in the patient sample or are present in less than 20% of the patient sample ($N(\text{All}) = 40$; $N(\text{F}) = 20$; $N(\text{M}) = 20$) (cf. Smaczny et al., 2021; Sperber & Karnath, 2017). After removing those data, we compared the disconnection scores between the male and female subsamples using the Wilcoxon rank-sum test. To correct for multiple comparisons, we utilised a maximum statistic permutation approach. For this, we pseudo-randomly permuted the sex labels and calculated the rank-sum test for each ROI-to-ROI connection; this procedure was repeated 50,000 times. For every permutation iteration, we saved the maximum of the absolute z-statistic, which describes how different the two group means are from each other. Then, we compared the z-statistics derived from the original sex labels to the permutation distribution. By identifying the 95th percentile of permutation-derived maximum statistics, we obtained an FWE-corrected, one-sided threshold for statistical significance at $p = 0.05$ (Nichols & Holmes, 2001).

2.4.4. Prediction of Patient Status

In an exploratory analysis, we used a supervised machine learning classifier in the form of a support vector machine (SVM), more specifically a nu-support vector classification (nu-SVC; Schölkopf et al., 2000 & 2001), to investigate if lesion-derived data can predict the patient status. The nu-SVC was implemented using custom scripts employing the “libsvm” package’s MATLAB version (Chang & Lin, 2011).

To create the instance matrix, we concatenated the vectorised voxel-wise disconnection maps of all patients, such that matrix rows comprised patients, while columns contained the associated disconnection status of all voxels. Following our previous approach, we once again excluded voxels from the analysis that were damaged in less than 5 patients. Previous research has shown that feature reduction significantly enhances model fit in lesion-deficit modelling (Kasties et al., 2021). Therefore, we used principal component analysis for dimensionality reduction: 52 components were cumulatively needed to explain more than 95% of the data's variance. Thus, our resulting instance matrix had a dimension of 206-by-52. Finally, we applied mean normalisation to scale the data, such that all values were in the range between 0 and 1.

We followed the same steps for the voxel-wise lesion maps (i.e., we also used the same exclusion criteria, applied the same concatenation and normalisation steps before performing a principal component analysis), in order to assess if disconnection maps or lesion maps held a higher predictive power. Here, 107 components were cumulatively needed to explain more than 95% of the variance, thus, resulting in a 206-by-107 instance matrix.

For labels, we used a numerical representation of either sex (1 = female, 2 = male), patient group (1 = neglect, 2 = non-neglect) or sex-specific patient group (1 = female neglect, 2 = male neglect, 3 = female non-neglect, 4 = male non-neglect). We implemented the nu-SVC with a radial basis function kernel, since previous research has demonstrated that non-linear kernels improve model performance compared to linear ones in lesion-behaviour modelling studies (Zhang et al., 2014). To ensure proper generalisation of the model, we used a nested cross-validation (CV) approach as described and implemented by Röhrig et al. (2022). In this CV approach, the outer loop served for testing the model on unseen data, whereas the inner loop was utilised to optimise the hyperparameters nu and C.

More specifically, we employed a 10-fold CV for the outer loop, with almost equally sized folds. One fold of the patient sample ($n = 20$ or 21) was utilised as the test set, while the remaining nine folds ($n = 186$ or 185) served as the training set, which were passed on to the inner loop. In the inner loop, we used a 5-fold CV with four folds serving as the training set and one fold as the validation set. To optimise the hyperparameters nu and C, we implemented a grid search algorithm ($C = 2^{-5}, 2^{-4}, \dots, 2^{15}$ and $\text{nu} = 0.01, 0.06, \dots, 0.51$), which trained every combination of different C and nu values in the specified range, before testing their performance on the validation fold. At the end of the inner loop, we averaged the prediction accuracy for every combination of C and nu values and selected the combination with the highest accuracy as our model. We then re-trained the model during the outer loop using the optimised parameters on the whole training set and tested it on the test set. With this approach, every patient's status was predicted once in the outer loop. To overcome variance-driven issues caused by different sample randomisations and thus, to generalise our model performance, we then repeated the model fitting procedure ten times, with different sample pseudo-randomisations. Finally, the predictions were averaged across the ten model repetitions for all patients. Using the averaged predictions, the final prediction accuracy in the form of precision (i.e., the number of correct predictions divided by the number of patients) was calculated.

3. Results

3.1. Clinical and Demographic Data

The average mean age at stroke onset was higher in women than in men (F: 64.4 ± 15.4 years vs M: 60.8 ± 12.1 years), exhibiting a trend towards significance (see Table 1). This finding of women being older than men when experiencing their first stroke was also present in the neglect and non-neglect groups, though lacking significance (see Supplementary Tables 1a & 1b for details).

Overall, more women in our sample were diagnosed with neglect ($n = 40$) than men were ($n = 33$) – however, this difference did not reach significance (see Table 1). Further, there was no significant difference between the sexes in performance in any of the three diagnostic tests (see Table 1 & Figure 1).

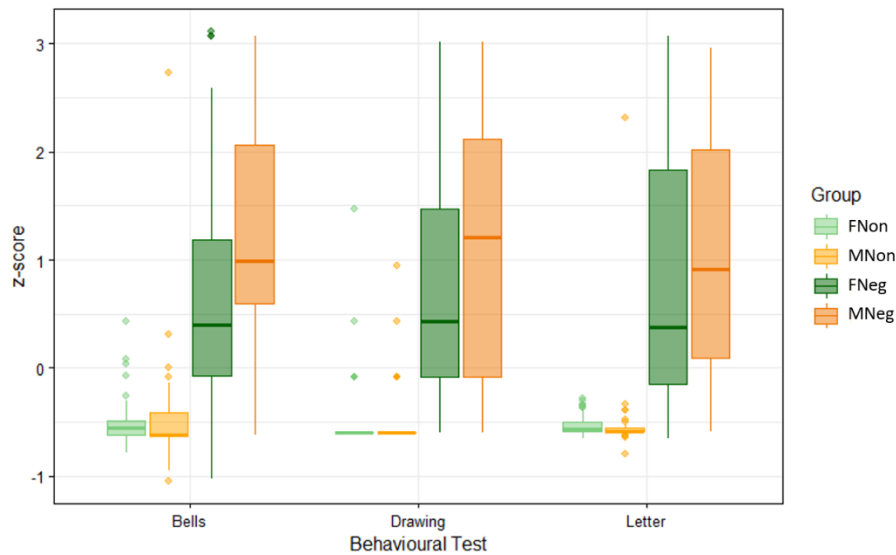


Figure 1: z-normalised performances in the three diagnostic tests for the sex-specific patient groups. Boxplots of the z-normalised behavioural scores in the Bells Cancellation Test, the copying task and the Letter Cancellation Task (see Section 2.2. for details). For the cancellation tasks, the CoC scores were z-normalised, whereas in the drawing task the raw error score was normalised. Distributions are given for the female subsample (in green) and male subsample (in orange). The scores of the neglect subsample are depicted in a darker colour than of the non-neglect subsample (of the corresponding sex), i.e., female neglect [FNeg] = dark green, female non-neglect [FNon] = light green, male neglect [MNeg] = dark orange, male non-neglect [MNon] = light orange.

Women had negligibly smaller lesions ($\mu = 34.8 \pm 44.8 \text{ cm}^3$) than men ($\mu = 37.3 \pm 43.8 \text{ cm}^3$). However, this difference was non-significant (see Table 1). This trend was also present in the neglect and non-neglect groups (see Supplementary Tables 1a & 1b for details).

Infarct was the more common cause of stroke in our sample: 169 patients suffered from an infarct, 34 from a haemorrhage and 3 patients from a combination of both. Table 1 shows a slight but non-significant trend of men suffering from more infarcts ($n = 90$) than women ($n = 79$), while women were slightly more likely of experiencing haemorrhagic strokes ($n = 24$) than their male counterparts ($n = 13$).

Of the 172 patients ($N(F) = 81$; $N(M) = 91$) that suffered from an infarct or a combination of infarct and haemorrhage, the arterial territory that was most commonly affected was the one supplied by the MCA (see Supplementary Table 3). A total of 73 male and 61 female patients experienced an infarct related to the MCA. The territories supplied by the anterior cerebral artery (ACA; including the BG) were affected by infarct in 11 female patients and 1 male patient. The PCA (including the thalamus) was the focus of infarction in 7 women and 15 men. We detected a significant difference in infarct incidence in the areas supplied by the ACA, with women being affected significantly more often than men. Further, we found a slight trend of men being affected more often by infarcts centred in regions supplied by the PCA.

3.2. Voxel-based Lesion-Behaviour Mapping

The topography of overlay plots of the patients' acute lesions can be seen in Figure 2, while the overlay plots for the neglect and non-neglect groups can be found in Supplementary Figures 1 and 2. Only voxels that have been damaged in at least 5 patients are shown, with darker/colder colours representing damage in fewer patients and brighter/warmer colours indicating damage in more patients. Visual inspection revealed that the majority of damaged voxels across all patients lays in the area of and surrounding the insula and the BG. For the female subsample, the centre is found in the BG, while for the male subsample, it is spread out more and located between the BG and the insula.

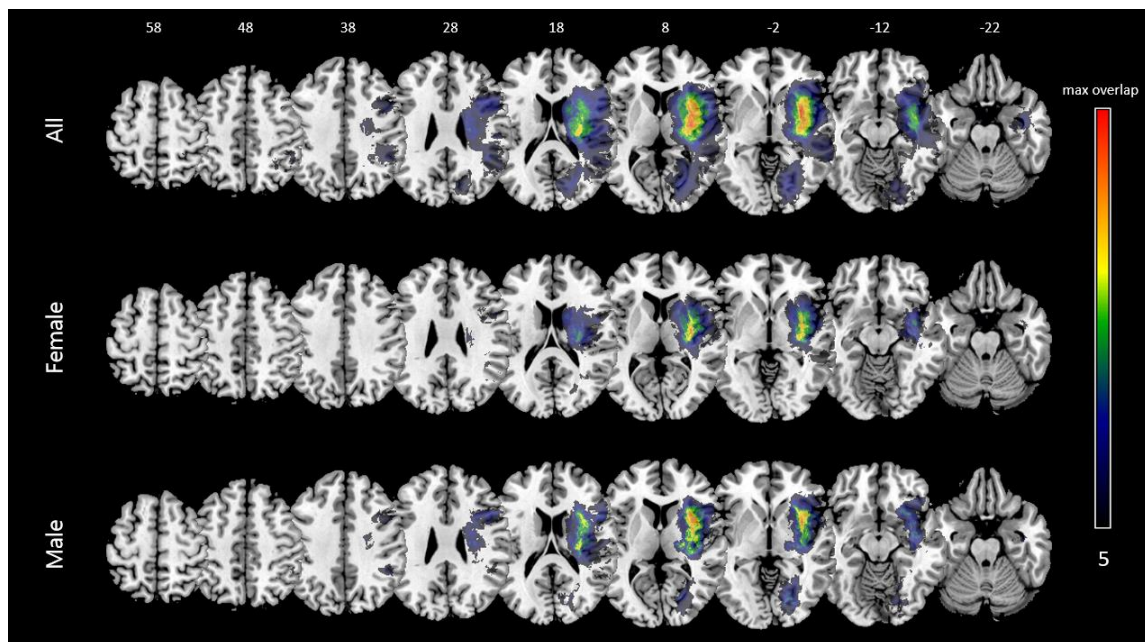


Figure 2: Lesion Overlay Plots

Overlaps of all normalised acute lesions included in the analyses are shown for all patients ($n = 206$), female and male patients ($n = 103$, respectively). Aggregated lesions were overlaid on an axial view of the ch2bet-template in MRIcron (Rorden & Brett, 2000). The voxels' colours indicate the frequency of the lesion overlap and were scaled to the respective sample sizes. Only voxels damaged in at least 5 patients are depicted and were used for subsequent analyses. Colours were scaled from 5 to the maximum overlap value of the respective patient sample (all = 63; female = 37; male = 29). The number given above each slice refers to the z-coordinate in MNI space.

We ran two VLBM analyses using mass-univariate non-parametric Lieberman tests and general linear models in “NiiStat” – firstly, using sex as our behavioural variable and secondly, using the normalised behavioural score as a measure of neglect severity. The first analysis yielded no significant results, meaning that there were no voxels whose damage status was significantly associated with sex.

Figure 3 illustrates the result of the second VLBM analysis, depicting the voxels whose status was significantly correlated with increased neglect severity. Across all patients, 4232 voxels survived the correction and reached significance. The majority of those voxels is located around the IPL, superior temporal gyrus (STG), the posterior superior temporal sulcus (pSTS) and their associated WM fibre tracts. In the female patient subgroup, a total of 323 mostly GM matter voxels clustered around the pSTS and STG reached significance. In the male subsample, damage to a population of 273 voxels that are mainly located in WM tracts surrounding the IPL and between the STG and middle temporal gyrus (MTG) were significantly associated with pathological behaviour.

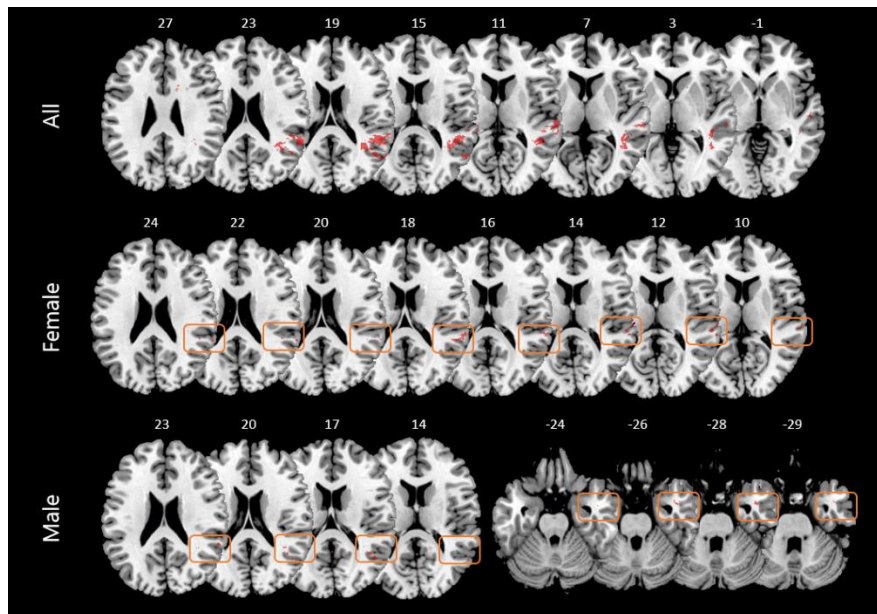


Figure 3: Statistical voxel-wise lesion-behaviour mapping (VLBM) results

Results of the VLBM analyses using mass-univariate GLMs to identify voxels that are significantly correlated with pathological z-scores in the behavioural tasks. Voxels that survived FWE correction based on permutation tests at $p < 0.05$ are overlaid in red on an axial view of the ch2bet-template in MRICron (Rorden & Brett, 2000). The number given above each slice refers to the z-coordinate in MNI space.

3.3. Whole-Brain Disconnectivity Mapping

Figure 4 illustrates the percentage of disconnected fibres for every WM voxel as an overlay plot across the whole patient sample. Disconnections are more pronounced in the right hemisphere, spanning the entire anterior-posterior-axis from the middle frontal gyrus via the orbital gyrus (OrG), BG, and thalamus to the inferior temporal gyrus (ITG) and, finally, the occipital pole. This corresponds to pronounced disconnections affecting the IFOF, SLF and inferior longitudinal fasciculus (ILF).

Further, especially the posterior segments of the corpus callosum are damaged. Disconnections also affected parts of the corticospinal tract (CST), the uncinate fasciculus, as well as the anterior segment of the AF.

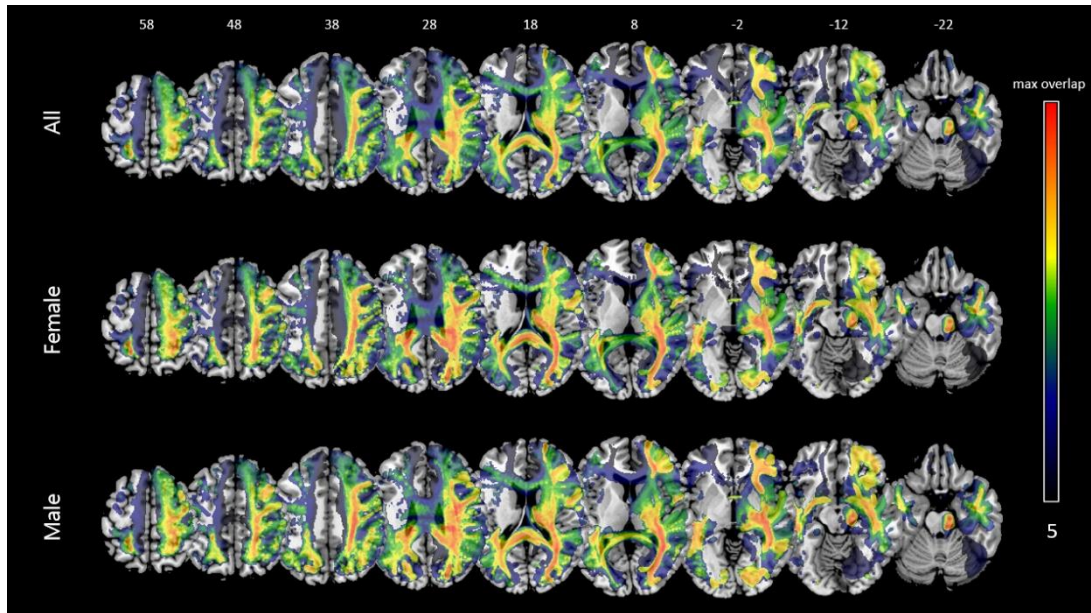


Figure 4: Disconnection Overlay Plots

Overlaps of the whole-brain disconnections included in the analyses are shown for all patients ($n = 206$), female and male patients ($n = 103$, respectively). Aggregated disconnection maps were overlaid on an axial view of the ch2bet-template in MRICron (Rorden & Brett, 2000). The voxels' colours indicate the frequency of the disconnection overlap and were scaled to the respective sample sizes. Only voxels disconnected in at least 5 patients are depicted and were used for subsequent analyses. Colours were scaled from 5 to the maximum overlap value of the respective patient sample (all = 184; female = 86; male = 80). The number given above each slice refers to the z-coordinate in MNI space.

Overall, the disconnection patterns are very similar between the patient (sub-)samples. However, visually comparing the disconnection overlays between the male and female subgroups revealed the following differences: On a purely descriptive level, women exhibited a higher percentage of disconnections in the splenium of the corpus callosum, as well as in the thalamus, compared to men.

The VLBM analyses we applied to identify any voxels whose disconnection proportion is significantly correlated with either sex or neglect severity yielded no significant results, as no voxels survived the threshold.

3.4. Region-to-Region Disconnectivity

Using GLMs to map sex to ROI-to-ROI disconnectivity, we identified 99 significant disconnections at $p = 0.05$ (see Figure 5 & Table 2): 69 of those disconnections were more pronounced in men, the remaining 30 were stronger in women. There was a higher ratio of interhemispheric disconnections that were associated with men (85%), compared to ones with women (60%).

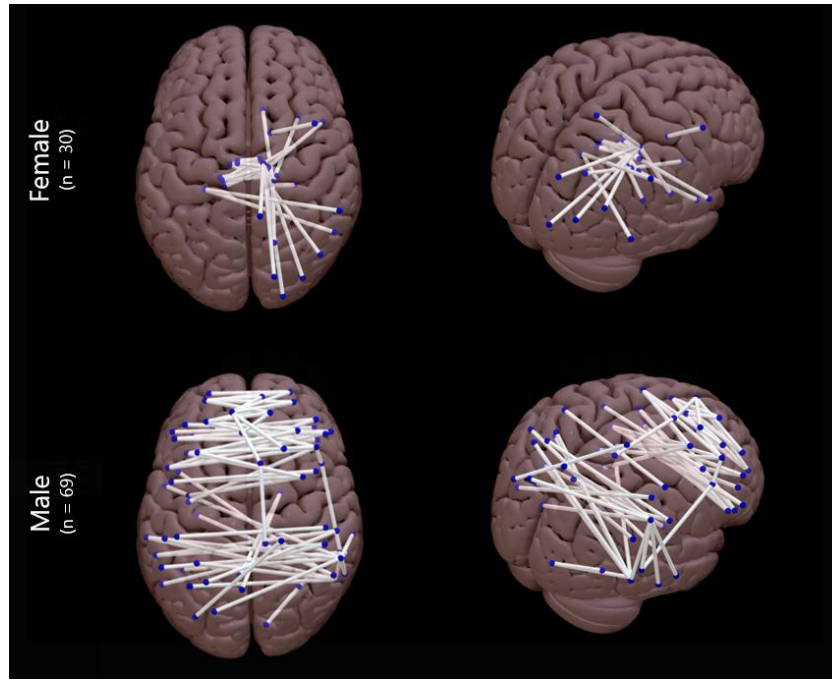


Figure 5: Significant parcel-wise disconnections at $p = 0.05$

Parcel-wise disconnections that were significantly associated with sex, overlaid on a superior view of the MNI152-template in SurfIce (<https://github.com/neurolabusc/surf-ice>). The blue nodes correspond to (sub-)cortical parcels as defined by the BN-246 atlas (Fan et al., 2016) and the white edges to the disconnected fibre streamlines between those parcels as defined by the HCP-842 atlas (Yeh et al., 2018).

The region with the most disconnections was the thalamus (see Table 2 for an overview and Supplementary Table 4 for details), whose disconnections were significantly associated with the female sex, accounting for 71 % of female-specific disconnections. In contrast to this, there were no disconnections involving the Thalamus that were associated with the male sex and the majority of male-specific disconnections were to/from the MFG (see Supplementary Table 4).

Table 2: Overview Significant Parcel-wise Disconnections at $p = 0.05$

	Total (n = 206)	Female (n = 103)	Male (n = 103)
Significant Disconnections (N, Ratio Inter- : Intra-hemispheric, % interhem.)	99, 77 : 22 (77.78%)	30, 18 : 12 (60.0%)	69, 59 : 10 (85.51%)
Node with highest number of disconnections (Anatomical Label, % of (sub-)sample's sign. disconn.)	right caudal area 40 (PFm) of IPL (5.05%)	right lateral pre-frontal Thalamus (11.67%)	right caudal area 40 (PFm) of IPL (6.52%)
ROI with highest number of disconnections (Anatomical Label, % of (sub-)sample's sign. disconn.)	Thalamus (21.72%)	Thalamus (71.67%)	MFG (24.64%)

Selected summary statistics resulting from the parcel-wise disconnection analysis at $p = 0.05$. Results are either given as number of significant disconnections, ratio of interhemispheric disconnections to intrahemispheric disconnections or as anatomical label based on the BN-246 atlas (Fan et al., 2016) (contributing to percentage of disconnections). ROIs are all nodes belonging to a superordinate anatomical region. More details can be found in Supplementary Table 4. Abbreviations: n – Number of patients, *IPL* – inferior parietal lobule, *MFG* – middle frontal gyrus

In women, all 10 of the most significant female-specific disconnections were *inter*-hemispheric disconnections involving the thalamus (see Table 3). The majority of the 10 most significant male-specific disconnections are spread throughout the frontal lobe, with few disconnections to/from the insula, ITG and IPL. Interestingly, there is only one *intra*-hemispheric disconnection, which is between the right ITG and IPL.

Table 3: Most Significant Parcel-wise Disconnections at $p = 0.05$

	Node A	Node B	z-Value
F E M A L E	Left Thalamus (medial pre-frontal thalamus)	Right Thalamus (posterior parietal thalamus)	2.68161634
	Left Thalamus (sensory thalamus)	Right Thalamus (sensory thalamus)	2.68142012
	Left Thalamus (posterior parietal thalamus)	Right Thalamus (sensory thalamus)	2.68142012
	Left Thalamus (lateral pre-frontal thalamus)	Right Thalamus (sensory thalamus)	2.68142012
	Left Thalamus (lateral pre-frontal thalamus)	Right Thalamus (posterior parietal thalamus)	2.68142012
	Left Thalamus (sensory thalamus)	Right Thalamus (lateral pre-frontal thalamus)	2.68127999
	Left Thalamus (occipital thalamus)	Right Thalamus (lateral pre-frontal thalamus)	2.68127999
	Left Thalamus (medial pre-frontal thalamus)	Right Thalamus (medial pre-frontal thalamus)	2.68118658
	Left Thalamus (posterior parietal thalamus)	Right Thalamus (medial pre-frontal thalamus)	2.68118658
	Left Thalamus (medial pre-frontal thalamus)	Right Thalamus (lateral pre-frontal thalamus)	2.68118658
	Left IFG (inferior frontal sulcus)	Right OrG (orbital area 12/47)	2.57348858
	Left PrG (caudal ventrolateral area 6)	Right MFG (inferior frontal junction)	2.50947999
	Left IFG (inferior frontal sulcus)	Right OrG (lateral area 12/47)	2.40203921
	Left IFG (ventral area 44)	Right MFG (ventral area 9/46)	2.28393265
M A L E	Right ITG (caudolateral area 20)	Right IPL (caudal area 40 (PFm))	2.27703233
	Left INS (dorsal dysgranular insula)	Right MFG (ventrolateral area 6)	2.26341103
	Left MFG (area 46)	Right MFG (area 46)	2.26133258
	Left IFG (opercular area 44)	Right MFG (ventrolateral area 6)	2.18345215
	Left OrG (lateral area 11)	Right OrG (lateral area 12/47)	2.17739449
	Left MFG (ventrolateral area 8)	Right MFG (dorsal area 9/46)	2.16445027

Parcel-wise disconnections with the 10 highest z-values following the region-to-region analysis for analysis of the association of disconnection scores with sex. Disconnections are attributed to the sex that exhibited a higher mean disconnection value. Anatomical labels are based on the BN-246 atlas (Fan et al., 2016). Abbreviations can be found in Appendix A. Intrahemispheric disconnections are highlighted in light grey. Z-values were obtained from the Wilcoxon rank-sum analysis, employing maximum statistic permutation at 50,000 permutations.

3.5. Prediction of Patient Status

Table 4 provides an overview of the nu-SVC prediction accuracies that were based on voxel-wise disconnection maps and lesion maps, respectively. Prediction accuracy was highest for the classification of neglect vs non-neglect patients, with the disconnection-based model achieving higher prediction precision than the model based on lesion maps. For the classification of sex-specific patient group, the disconnection-based model outperformed the lesion-based model substantially again, the latter of which performed below chance level. For the prediction of biological sex, however, both models performed below chance level.

Table 4: Prediction accuracy for lesion-based and disconnection-based instance matrices

Predicted Variable	Average Prediction Accuracy	
	Lesion Maps	Disconnection Maps
Female vs Male	48.54 %	46.60%
Neglect vs Non-Neglect	53.40%	66.02%
FNeg vs FNon vs MNeg vs MNon	24.27%	32.52%

nu-SVC model performances as assessed by average prediction accuracy for the models trained on voxel-wise disconnection maps and lesion maps, respectively. Three versions of patient status were predicted: Sex (i.e., Female vs Male), diagnosis (i.e., Neglect vs Non-Neglect) and sex-specific patient group (i.e., female neglect [FNeg], female non-neglect [FNon], male neglect [MNeg], male non-neglect [MNon]). For the two-class classifications (i.e., sex & diagnosis) the chance level lay at 50%, whereas for the four-class classification it lay at 25%.

4. Discussion

The present study investigated sex differences in the neurological underpinnings of acute visuospatial neglect, specifically how (sub-)cortical lesions and the resulting WM disconnections differed between men and women, and if they differently affected neglect severity in the two sexes. To this end, we employed a classical VLBM approach, in addition to permutation-based analyses of indirectly quantified whole-brain and region-to-region disconnectivity measures. Finally, we used binary lesion maps, as well as continuous disconnectivity maps of the whole brain to predict patient status. Regarding our motivating questions, we found no sex differences in either voxel-wise lesion or disconnection localisation. However, we found that men and women exhibit different region-to-region disconnection patterns. Further, we identified sex differences in the lesion patterns associated with neglect severity, but not in disconnection patterns. Finally, we demonstrated that lesion and disconnection data can be used to reliably predict patient status, but not biological sex in predictive modelling.

4.1. Clinical and Demographic Data

The clinical and demographic data of our patient sample are in line with the literature. On average, women are older at stroke onset and develop neglect more often than men do (cf. Gargano et al., 2008; Hammerbeck et al., 2019). There was no significant difference in lesion volume between the sexes (cf. Bonkhoff et al., 2021), and a slight non-significant trend of men suffering from more infarcts and women from more haemorrhages (cf. Appelros et al., 2009). The vast majority of infarcts was localised in regions supplied by the MCA (cf. Bonkhoff et al., 2021; Li & Malhotra, 2015). To the best of our knowledge, there are no known sex differences in the vasculature of the brain that could confound differences in the affected arterial territories. We detected a significant difference in the arterial territories most commonly affected by ischaemic stroke with women being affected significantly more often by infarcts centred in regions supplied by the ACA, compared to men. In general, ACA strokes are uncommon as they make up less than 5% of stroke cases in clinical reports (Matos Casano et al., 2022), but there are reports of women being affected more often by them than men (Medlin et al., 2020). Further, we found a non-significant trend of men being affected more often by strokes in regions supplied by the PCA, compared to women. Interestingly, Bonkhoff et al. (2021) also detected sex differences in PCA-supplied regions: They found that PCA strokes contribute more to stroke severity in women, compared to men – however, they do not report anything about sex differences in the incidence of those strokes.

4.2. Voxel-based Lesion-Behaviour Mapping

The regions identified by the lesion overlays for our whole patient sample are in line with the ones identified by the predominant literature on acute right-hemispheric stroke (cf. Sperber & Karnath, 2016). Visual inspection of the lesion overlay plots suggested that the majority of lesions of the male subsample were spread throughout the BG and the insula, whereas the

female subsample's lesions were more compactly focussed on the BG and spread into the thalamus. Nevertheless, our VLBM analysis detected no statistically significant sex differences in lesion localisation.

Importantly, no voxels were significantly more frequently damaged in women or men. Therefore, we were able to infer that the sex differences we detected in the voxel clusters associated with neglect severity are likely due to a sex-specific effect of neglect itself, rather than just due to general neurological sex differences. We found different clusters contributing to neglect severity for the female and male subsamples, respectively. In women, damage to a cluster of voxels belonging to the caudal STG and caudal pSTS was significantly associated with increased neglect severity. In men, the voxels significantly associated with neglect severity were mainly located in the WM, specifically around the anterior parts of the MTG, as well as near the IPL. All of those regions have been implicated in contributing to neglect severity in previous research (e.g., Corbetta & Shulman, 2011; Karnath & Rorden, 2012). The female-specific cluster was marginally larger than the male-specific one, which could be interpreted to be in line with Bonkhoff et al.'s (2021) conclusion that more regions contribute to stroke severity in women. However, the fact that male-specific clusters are more wide-spread throughout the cortex compared to the rather compact female cluster could be interpreted to stand in contradiction to that.

Generally, the sex-specific effects on the manifestation of neglect severity on a voxel-level we found seem to be small in magnitude, considering the relatively small number of significant voxels. This could be interpreted to be in accordance with the findings of Wu et al. (2015) and Bonkhoff et al. (2021), who both reported that lesions located in the left hemisphere exhibit stronger sex differences in their association with stroke severity than lesions located in the right hemisphere. As we only included right-hemispheric patients in our sample, due to the right hemisphere constituting the typical lesion site of visuospatial neglect, it seems possible that any sex differences in lesion localisations are not as pronounced as they might be for neuropsychological syndromes that occur predominantly after left-hemispheric strokes.

4.3. Whole-Brain Disconnectivity

The whole-brain disconnection overlap revealed that most disconnections in our patient sample were primarily right-hemispheric disconnections of the IFOF, SLF, ILF, and AF. This corresponds to the WM fibre tracts connecting the right-hemispheric perisylvian network, whose damage was identified to be associated with neglect (He et al., 2007; Karnath et al., 2009; Urbanski et al., 2010). This could be interpreted as neglect constituting the most common cognitive disorder after right-hemispheric stroke due to the high likelihood of damage to the right perisylvian network. Further, interhemispheric disconnections via the more posterior segments of the corpus callosum, especially via the splenium, emerged in the disconnection overlap. Previous studies have shown that isolated damage to PCA-supplied regions, such as

the splenium and the thalamus, are neither necessary nor sufficient to cause neglect, but may contribute to neglect severity (Bird et al., 2006; Sperber et al., 2020).

When visually comparing the disconnection overlaps between men and women, we found more disconnections in the splenium of the corpus callosum and in the thalamus in the female subsample. However, there was no statistically significant difference in whole-brain disconnectivity patterns between the sexes as revealed by our VLBM analysis – neither in the pure association with sex, nor in potential sex-specific associations with neglect severity. It seems possible that any potential differences might only emerge in a larger connectomic context and thus, could not be detected in voxel-wise analyses.

4.4. Region-to-Region Disconnectivity

We identified a large number of disconnections that were significantly associated with women and men, respectively. The female-specific disconnections were almost exclusively centred on the thalamus, whereas men exhibited a wide-spread network of disconnections throughout the frontal, parietal and temporal cortices. The majority of those sex-specific disconnections were interhemispheric, regardless of the sex they were associated with – however, females showed a higher percentage of intrahemispheric disconnections, relative to males.

According to the predominant literature on connectivity in healthy individuals, men typically have a higher number of intrahemispheric WM connections, which in addition also exhibit an increased axonal diameter compared to the ones of women (Boespflug et al., 2011; Ingahalikar et al., 2013; Kanaan et al., 2012). In contrast to this, women have larger and more efficient corpora callosa relative to the rest of their WM (Allen et al., 2003; Dubb et al., 2003; Ingahalikar et al., 2013). Interestingly, we found the opposite patterns in sex-specific disconnections of stroke patients: Men suffered from more interhemispheric disconnections, mostly throughout the corpus callosum, whereas women had a higher proportion of intrahemispheric disconnections, as well as more interhemispheric disconnections between the left and right thalami.

Although this may seem counterintuitive at first sight, as one would expect a given sex to suffer more disconnections of the fibre tracts that they possess a larger proportion of in the first place, one could also argue quite the opposite, namely that if a given sex has fewer inter- or intrahemispheric connections and the WM tracts of those connections also are thinner in diameter, that those fibres might be more vulnerable to become (fully) disconnected after a focal stroke, compared to the equivalent tracts in the other sex. This would explain why there are so few intrahemispheric male-specific disconnections. Given that intrahemispheric WM tracts are more abundant and thicker in diameter in men (cf. Ingahalikar et al., 2013; Kanaan et al., 2012), and a WM tract has to be at least 50% damaged to be considered as disconnected (Griffis et al., 2019 & 2021), then either a larger or differently located lesion would be needed to disconnect an intrahemispheric WM tract in men, compared to women. However, since we detected significant differences in neither lesion volume nor lesion localisation between the

sexes, this could be interpreted as men being less vulnerable to intrahemispheric disconnections. Yet, this interpretation should be treated with caution, as we are not able to make inferences about underlying anatomical differences due to us using the same spatial normalisation template and brain atlases for both sexes.

Moreover, we found disconnections involving the thalamus to be strongly associated with the female sex. Though we cannot make inferences about anatomical differences based on our results, there is some a priori evidence for sex differences in thalamic architecture. Even though most studies report no sex difference in thalamic volume after adjusting for total brain volumes (Ritchie et al., 2018; Sullivan et al., 2004; Tan et al., 2016; but see Ruigrok et al., 2014), an interaction of sex and age has been suggested to affect thalamic volumes (Ritchie et al., 2018): Studies have demonstrated that in both sexes the thalamus undergoes a significant reduction in volume and myelination with increasing age (Hughes et al., 2012; Sullivan et al., 2004). Considering the women in our patient sample are on average 3.6 years older than their male counterparts, they likely experienced some more of this natural reduction in thalamic volume, which might increase their vulnerability to thalamic disconnections due to reduced compensation capabilities (cf. Duffau, 2005). However, as this age difference is not particularly pronounced in our patient sample, its contribution to the underlying sex differences may be negligible.

Further, there have been reports of a reliable sex difference in the anatomy of an interhemispheric structure connecting the left and right thalami, known as the interthalamic adhesion (ITA)². The ITA is a fairly small bundle of glia, which contributes to the anterior thalamic radiation (Borghei et al., 2021). It is fully absent in up to 20 – 30% of healthy brains (Allen & Gorski, 1991; Eliot et al., 2021; Nopoulous et al., 2001; Trzesniak et al., 2011). Some studies report that the ITA is present more often in women (Allen & Gorski, 1991; Nopoulous et al., 2001) and that it tends to be larger in women compared to men (Allen & Gorski, 1991; Damle et al., 2017). It seems plausible that women might be more susceptible to thalamic disconnections via the ITA due to their increased likelihood to possess an ITA in the first place compared to men – since fibre tracts, which do not exist to begin with, also cannot become disconnected after a lesion. It is crucial to note however that this interpretation is mere speculation at the time being, as we cannot make any statements about differing thalamic volumes or the (non-)existence of the ITA in our patient sample.

Still, we observed that the thalamus was lesioned more commonly in women compared to men (cf. the lesion overlay plots for the female and male subsamples in Figure 2). Although this difference did not reach statistical significance in our analyses, it follows that men are much less likely to suffer disconnections of or to thalamus, if the thalamus itself has not been directly damaged in any of our male patients.

² The ITA is also sometimes referred to as the massa intermedia or thalamic commissure.

4.5. Prediction of Patient Status

We found that neither lesion maps nor disconnection maps were able to predict biological sex beyond chance level. Importantly though, previous research has demonstrated that is not impossible to reliably predict biological sex from anatomical brain scans of healthy humans: For example, a large-scale study by Anderson et al. (2018) utilised SVMs to predict sex based on GM morphometry data and achieved a prediction accuracy of 93%. Therefore, it seems plausible that not our algorithm was the cause for our low classification accuracy, but it may have been due to the data we based our models on. As we only detected sex differences in the disconnection patterns on the level of region-to-region disconnections, but not on the voxel-level of the lesion maps and whole-brain disconnectivity maps which we used as basis for our classification, it is unsurprising that the model we were not able to predict sex based on data that did not exhibit significant sex differences in the first place.

Neglect diagnosis, however, could be predicted reliably and we found that using disconnection maps as the basis for the classifier achieved higher accuracies, compared to the classification based on lesion maps. In addition to this, we found that this trend of disconnection-based models achieving higher prediction accuracies than lesion-based models was also present when predicting sex-specific patient status. Overall, our results indicated that neglect could be predicted more reliably based on disconnectivity patterns compared to lesion patterns. This can be interpreted to further support the view that neglect might rather be a disconnection syndrome than a syndrome that is caused only by isolated focal cortical lesions (cf. Bartolomeo et al., 2007; Doricchi et al., 2008).

Further, previous research has demonstrated that functional connectivity at least partially depends on structural connectivity (Johnston et al., 2008; O'Reilly et al., 2013; Roland et al., 2017). Since complex cognitive processes, such as visuospatial attention, rely on the structural and functional integrity of WM connections, Griffis et al. (2020) deem it plausible that disconnection measures hold superior predictive power over simple lesion measures, such as volume or voxel-wise damage status.

4.6. Limitations & Outlook

The present study has several limitations, such as the fact that some of our analyses did not yield any significant results. We cannot ascertain if our sample size may have been too small to detect any potentially underlying effects, especially if effect sizes are small. However, we believe that our group sizes of $n = 103$ should have been sufficient to detect effects of interest – therefore, any small magnitude effect that we potentially may have missed likely was of no real significance.

Furthermore, as also numerous other studies investigating sex differences did (e.g., Bonkhoff et al., 2021; Ingalhalikar et al., 2013; Kovalev et al., 2003), we utilised the same sex-unspecific normalisation templates, as well as parcellation and tractography atlases for both our male and

female patients. During spatial normalisation, the structural brain scans of patients are reshaped to match a given template in standard stereotaxic space in order to allow for group-level comparisons and analyses (for an overview see de Haan & Karnath, 2018). It is considered crucial to choose spatial normalisation templates that match both the used imaging modality, as well as the age population of the respective patient as closely as possible. Especially, the usage of different templates for paediatric, young adult and elderly populations is pivotal to account for the changes and atrophy that naturally occur throughout the aging process, such as the widening of sulci and enlargement of ventricles (de Haan & Karnath, 2018; Rorden et al., 2012).

However, as numerous studies have demonstrated, there are certain neuroanatomical aspects in which men and women differ reliably, such as overall brain volume, grey-to-white matter ratio in certain regions, as well as structural brain connectivity (cf. Allen et al., 2003; Ingalhalikar et al., 2013). In addition to those underlying neuroanatomical differences, not all brain structures' volumes decline at the same rate with age in men and women (Coffey et al., 1998). For example, it has been shown that cortical GM volume declines faster in men than in women (Cowell et al., 1994; Sullivan et al., 2004), and that men suffer greater atrophies in the left hemisphere, whereas women exhibit more symmetrical age-related atrophies (Gur et al., 1991). The gold standard normalisation template for older neurological patients by Rorden et al. (2012), which we also used in our study, was created from a mixture of structural scans of female and male patients. By utilising a normalisation template based on the average of those anatomies, it is possible that the resulting normalised brain scans are slightly inaccurate compared to if there had been sex-specific normalisation templates.

Further, the parcellation atlas (i.e., BN-246; Fan et al., 2016), as well as the tractography atlas (i.e., HCP-842; Yeh et al., 2018), which we used for our analyses were also created based on a mixture of male and female brain scans. We are not aware of any sex-specific atlases readily available. As already outlined for the spatial normalisation template, it is possible that the resulting parcellations and the derived (dis)connectome are not entirely accurate for either the female or the male subsample, due to all the underlying neuroanatomical and -pathological sex differences that are not taken into account when using the same template/atlas for both sexes. Therefore, in order to evaluate hereditary difference in connectivity (i.e., the amount of intra- and interhemispheric (dis-)connections) between females and males, one would need sex-specific diffusion templates.

However, it should not be neglected that population-averaged templates and atlases were created to enable group-level comparisons and analyses in the first place. While using sex-specific templates and atlases might have increased the accuracy of representing the neuroanatomy of that given sex, their usage may make drawing meaningful comparisons between men and women statistically challenging. Therefore, we maintain that the approach of using the sex-unspecific templates and atlases, which we used in accordance with the predominant literature (cf. Bonkhoff et al., 2021; Ingalhalikar et al., 2013), is a valid one. However, it might be sensible for future studies to investigate if/how the accuracy of the

presented analyses might be further improved by employing sex-specific normalisation and connectivity templates.

Still, amongst all the discussions surrounding sex differences in the neurosciences, there are also researchers that demand to “dump the dimorphism” due to the fact that human brains have very few significant sex differences and rarely, if ever, be considered to exhibit purely “male” or “female” features (Eliot et al., 2021). A large-scale MRI study by Joel et al. (2015) coined the concept of the human brain mosaic, as they found that “most brains are comprised of unique ‘mosaics’ of features, some more common in females compared with males, some more common in males compared with females, and some common in both females and males” (Joel et al., 2015, p. 15468).

Additionally, there are many other variables related to biological sex, which also affect brain architecture, such as gender, sexual orientation, and different aspects of hormonal status. As those variables are intrinsically entangled with biological sex, it is difficult to decode which differences are purely due to sex and which are due to those related factors. For example, while often times sex and gender align (i.e., in cisgender people), this is not the case for gender-nonconforming people: Studies have demonstrated that the brains of binary transgender individuals (i.e., trans women and trans men) differ significantly from their cisgender counterparts and rather represent a separate, unique brain phenotype (Smith et al., 2015; Mueller et al., 2021). Further, queerness has been shown to also been reflected in brain anatomy, such that there are significant differences in the volume of certain brain structures between homosexual and heterosexual individuals of the same sex (Votinov et al., 2021). Lastly, especially the female hormonal status has been demonstrated to significantly contribute to sex differences in neuroanatomy (for reviews see Catenaccio et al., 2016; Rehbein et al., 2020). Be it on a shorter timescale due to fluctuations of the sex steroids within the menstrual cycle (Dubol et al., 2021; Comasco & Sundström-Poromaa, 2015), or irreversible anatomical changes over the course of life caused by oral contraception intake (Heller et al., 2022; Lisofsky et al., 2016), pregnancy (Hoekzema et al., 2016; Rehbein et al., 2021), or menopause (Kim et al., 2018).

Unfortunately, we had no access to the data that would be necessary to disentangle the underlying causes of the observed sex differences (i.e., neuroanatomical differences, age effects, sex/gender interactions, hormonal effects, or a combination of multiple factors). Still, our study provides a valuable general first look at sex differences of post-stroke syndromes, such as visuospatial neglect.

Overall, it does not seem unlikely that the human brain and cognition are less sexually dimorphic than originally assumed and may rather manifest in some sort of mosaic arising from complex interactions of many factors. Therefore, it would be of interest for future studies to investigate if the discussed potential neurobiological underpinnings of the described sex differences hold up when using sex-specific normalisation templates and atlases. Further, it might be of interest for future neuropsychological studies to consider hormonal status as a factor that significantly affects the pathophysiology of stroke. Especially in the realm of

predictive modelling of patient status, it might be valuable to investigate if the addition of some measure of hormonal status, for example, might further contribute to prediction precision. Overall, further research in this area might be able to inform clinical decisions and thus, contribute to personalised medical care in the future.

5. Conclusion

To the best of our knowledge, the present study is the first investigating sex differences in the anatomical and connectomic correlates of neglect. We demonstrated that women and men exhibit different WM disconnectivity patterns after acute right-hemispheric stroke, despite not differing in their lesion localisations. Our results suggest that women are more susceptible to disconnections involving the thalamus, whereas men are more vulnerable to interhemispheric disconnections between the cortical lobes. We showed that patient status can be predicted based on lesion and disconnection maps and that the usage of disconnection-based models in predictive modelling improved prediction precision, which adds further support to the view of neglect being a disconnection syndrome. Further research is needed to disentangle to which extent the differing disconnection patterns can be attributed to underlying differences in brain architecture between men and women. To this end, we suggest future studies should employ sex-specific templates and atlases to investigate those matters in greater detail.

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Data Usage Statement

To the largest part, custom MATLAB scripts were used for data analysis that were written by Tamara Keßler. In some instances, however, openly available scripts published by other researchers were used:

Röhrig, L. (2022). Dataset for: Right-hemispheric white matter hyperintensities improve the prediction of spatial neglect severity in acute stroke. Mendeley Data, V1, DOI: 10.17632/c8n42jz525.1

Smaczny, S. (2022). Left angular gyrus disconnection impairs multiplication fact retrieval, descriptive data and scripts. Mendeley Data, V2, DOI: 10.17632/yjkr647mzb.2

Sperber, C. (2022). Scripts and tutorials for indirect structural disconnection-symptom mapping by Sperber, Griffis & Kasties. Mendeley Data, V2, DOI: 10.17632/hdzptzz8r5.2

Appendix

Appendix A: List of Abbreviations

ACA	Anterior Cerebral Artery
BG	Basal Ganglia
CoC	Centre of Cancellation
CST	Corticospinal Tract
CT	Computed Tomography
CV	Cross Validation
DTI	Diffusion Tensor Imaging
DWI	Diffusion-weighted Imaging
fMRI	Functional Magnetic Resonance Imaging
FWE	Family-wise Error
GLM	General Linear Model
GM	Grey Matter
IFOF	Inferior Fronto-Occipital Fasciculus
ILF	Inferior Longitudinal Fasciculus
IPL	Inferior Parietal Lobule
ITA	Interthalamic Adhesion
ITG	Inferior Temporal Gyrus
LQT	Lesion Quantification Toolkit
MCA	Medial Cerebral Artery
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MTG	Middle Temporal Gyrus
nu-SVC	nu-Support Vector Classification
OrG	Orbital Gyrus
PCA	Posterior Cerebral Artery
pSTS	Posterior Superior Temporal Sulcus
ROI	Region of Interest
SFOF	Superior Fronto-Occipital Fasciculus
SLF	Superior Longitudinal Fasciculus
SPM	Statistical Parametric Mapping
STG	Superior Temporal Gyrus
SVM	Support Vector Machine
T2FLAIR	T2-weighted Fluid Attenuated Inversion Recovery
VLBM	Voxel-based Lesion-Behaviour Mapping
WM	White Matter

Appendix B: Supplementary Tables and Figures

Supplementary Table 1a: Clinical and Demographic Data of Neglect Patients

	Total (n = 73)	Female (n = 40)	Male (n = 33)	p-value
Age (years)	65.1 (13.9) [29-93]	67.5 (14.3) [34-93]	62.3 (12.8) [29-81]	0.114 ^a
Days between Stroke & Imaging	3.4 (3.5) [0-14]	3.4 (3.6) [0-14]	3.4 (3.4) [0-14]	0.971 ^a
Aetiology (<i>Infarct, Haemorrhage, Both</i>)	55, 15, 3	28, 10, 2	27, 5, 1	0.507 ^b
Lesion volume (cm³)	63.8 (44.8) [0.37-312.6]	58.2 (62.3) [0.09-312.6]	70.0 (51.6) [0.37-194.7]	0.416 ^a
Arterial Territory of Infarct (ACA, MCA, PCA)	5, 47, 5	5, 23, 2	0, 24, 3	0.079 ^b
Days between Stroke & Assessment	4.0 (2.9) [0-14]	4.0 (2.9) [0-14]	3.8 (2.8) [0-13]	0.709 ^a
Letter CoC	0.42 (0.31) [-0.02-0.99]	0.39 (0.31) [-0.02-0.99]	0.44 (0.30) [-0.001-0.96]	0.487 ^a
Bells CoC	0.39 (0.28) [-0.1-0.92]	0.33 (0.28) [-0.1-0.92]	0.46 (0.27) [0-0.91]	0.058 ^a
Copying Errors	2.93 (2.31) [0-7]	2.67 (2.21) [0-7]	3.34 (2.35) [0-7]	0.132 ^a
Mean z-Score	0.97 (1.05) [-0.6-3.04]	0.80 (1.03) [-0.45-3.04]	1.19 (1.03) [-0.6-2.93]	0.116 ^a
Visual field defects (N)	17	9	8	0.940 ^b

Supplementary Table 1b: Clinical and Demographic Data of Non-Neglect Patients

	Total (n = 133)	Female (n = 63)	Male (n = 70)	p-value
Age (years)	61.2 (13.9) [26-88]	62.4 (15.8) [26-88]	60.1 (11.7) [36-83]	0.328 ^a
Days between Stroke & Imaging	2.7 (2.9) [0-11]	2.4 (2.7) [0-11]	2.9 (3.0) [0-11]	0.345 ^a
Aetiology (<i>Infarct, Haemorrhage, Both</i>)	114, 19, 0	51, 12, 0	63, 7, 0	0.507 ^b
Lesion volume (cm³)	20.8 (24.7) [0.09-138.1]	19.6 (19.2) [0.16-70.5]	21.7 (28.7) [0.09-138.1]	0.595 ^a
Arterial Territory of Infarct (ACA, MCA, PCA)	7, 87, 17	6, 38, 5	1, 49, 12	0.041^b
Days between Stroke & Assessment	2.6 (2.6) [0-12]	3.9 (2.3) [1-9]	3.3 (3.0) [0-12]	0.195 ^a
Letter CoC	0.02 (0.07) [-0.06-0.78]	0.02 (0.02) [-0.02-0.08]	0.02 (0.10) [-0.06-0.80]	0.987 ^a
Bells CoC	0.03 (0.09) [-0.11-0.83]	0.03 (0.05) [-0.04-0.26]	0.03 (0.11) [-0.11-0.83]	0.665 ^a
Copying Errors	0.22 (0.58) [0-4]	0.27 (0.65) [0-4]	0.16 (0.51) [0-3]	0.288 ^a
Mean z-Score	-0.5 (0.25) [-0.75-1.99]	-0.5 (0.14) [-0.64-0.09]	-0.51 (0.32) [-0.75-1.99]	0.762 ^a
Visual field defects (N)	15	7	8	0.954 ^b

Results are given as either number of patients or mean (standard deviation) [range]. The lesion volume was computed for the normalised lesion in MNI space. For the calculation of p-values, it was first confirmed that the samples had equal variances and then either an equal variances t-test ('a', for continuous variables) or a Chi² test ('b', for categorical variables) was calculated. p-values < 0.05 are considered significant and highlighted in bold. Abbreviations: *n* – Number of patients, *ACA* – Anterior Cerebral Artery, *MCA* – Medial Cerebral Artery, *PCA* – Posterior Cerebral Artery, *CoC* – Centre of Cancellation (Rorden & Karnath, 2010)

Supplementary Table 2a: Scan Modalities Used for Lesion Delineation

	Total (n = 206)	Female (n = 103)	Male (n = 103)
CT	98	57	41
T2FLAIR	65	28	37
DWI	43	18	25

Supplementary Table 2b: Additional Scans Used for Normalisation

	Total (n = 36)	Female (n = 14)	Male (n = 22)
T2FLAIR + T1	11	4	7
DWI + T1	19	8	11
DWI + T2FLAIR	6	2	4

Results are given as number of patients. MR scans were preferred over CT scans, if both modalities were available. In patients with multiple MR modalities, we preferentially used DWI if the images were acquired less than 48 hours after stroke and T2FLAIR for images that were acquired later. B) The first modality is the one used to delineate the lesion, the second one was used to improve normalisation quality. Abbreviations: See Appendix A.

Supplementary Table 3: Affected Arterial Territories in Ischaemic Stroke Patients

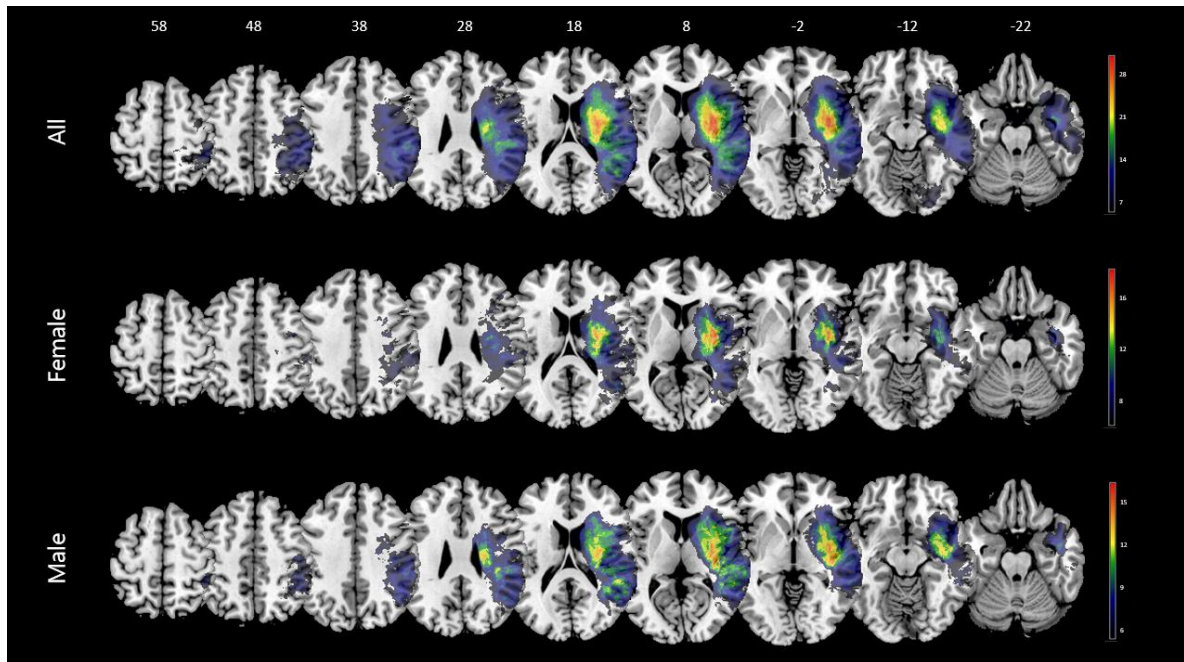
	All (n = 168)	Female (n = 79)	Male (n = 89)	p-value
ACA (incl. BG)	12	11	1	0.001
MCA	134	61	73	0.439
PCA (incl. Tha)	22	7	15	0.125

Results are given as number of patients. For 4 patients (N(F) = 2; N(M) = 2) the arterial territory could not be determined, so they were excluded from this analysis. For the calculation of p-values, we first confirmed that the samples had equal variances and then a Chi² test was calculated. p-values < 0.05 are considered significant and highlighted in bold. Abbreviations: *n* – Number of patients, *ACA* – Anterior Cerebral Artery, *BG* – Basal Ganglia, *MCA* – Medial Cerebral Artery, *PCA* – Posterior Cerebral Artery, *Tha* – Thalamus

Supplementary Table 4: Absolute and Relative Amount of Significant Disconnections per Region at $p = 0.05$

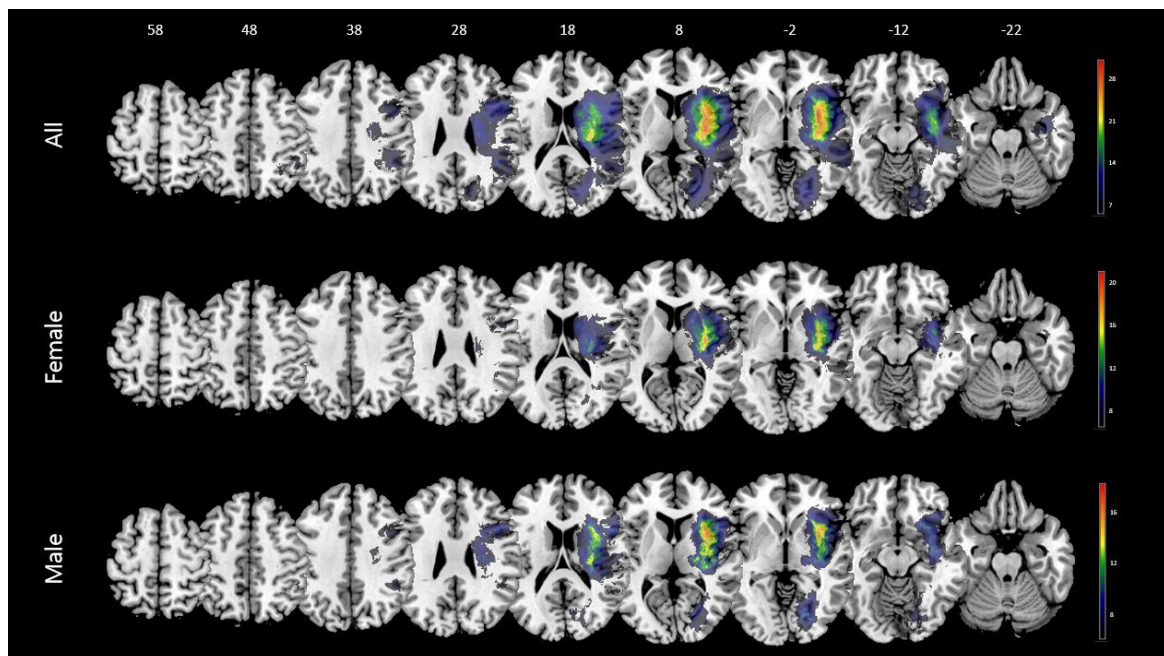
	Total (n = 198)		Female (n = 60)		Male (n = 138)	
Amygdala (Amyg)	3	1.52%	1	1.67%	2	1.45%
Basal Ganglia (BG)	1	0.51%	1	1.67%	0	0%
Fusiform Gyrus (FuG)	4	2.02%	0	0%	4	2.90%
Hippocampus (Hipp)	3	1.52%	3	5%	0	0%
Inferior Frontal Gyrus (IFG)	18	9.09%	0	0%	18	13.04%
Insula (INS)	4	2.02%	0	0%	4	2.90%
Inferior Parietal Lobule (IPL)	20	10.10%	2	3.33%	18	13.04%
Inferior Temporal Gyrus (ITG)	11	5.56%	1	1.67%	10	7.25%
Lateral Occipital Cortex (LOcC)	4	2.02%	3	5%	1	0.72%
Middle Frontal Gyrus (MFG)	35	17.68%	1	1.67%	34	24.64%
Middle Temporal Gyrus (MTG)	6	3.03%	0	0%	6	4.35%
Mediovental Occipital Cortex (MVOcC)	2	1.01%	0	0%	2	1.45%
Orbital Gyrus (OrG)	14	7.07%	1	1.67%	13	9.42%
Paracentral Lobule (PCL)	1	0.51%	0	0%	1	0.72%
Precuneus (Pcun)	4	2.02%	2	3.33%	2	1.45%
Postcentral Gyrus (PoG)	3	1.52%	0	0%	3	2.17%
Precentral Gyrus (PrG)	1	0.51%	0	0%	1	0.72%
Posterior Superior Temporal Sulcus (pSTS)	2	1.01%	0	0%	2	1.45%
Superior Frontal Gyrus (SFG)	14	7.07%	0	0%	14	10.14%
Superior Parietal Lobule (SPL)	2	1.01%	0	0%	2	1.45%
Superior Temporal Gyrus (STG)	3	1.52%	2	3.34%	1	0.72%
Thalamus (Tha)	43	21.72%	43	71.67%	0	0%

Results are given as number of significant disconnections associated with this region (percentage relative to total number of disconnections). Regions are based on the BN-246 (Fan et al., 2016) atlas. It is important to note that the number of disconnections add up to 200% – this is because there are always 2 nodes/regions involved in a disconnection. Thus, there are twice as many disconnected nodes as there are disconnections.



Supplementary Figure 1: Lesion Overlay Plots for Neglect Patients

Overlaps of all normalised acute lesions included in the analyses are shown for all neglect patients ($n = 73$), female ($n = 40$) and male patients ($n = 33$). Aggregated lesions were overlaid on an axial view of the ch2bet-template in MRICron (Rorden & Brett, 2000). The voxels' colours indicate the frequency of the lesion overlap and were scaled to the respective sample sizes. Only voxels damaged in at least 5 patients are depicted and were used for subsequent analyses. Colours were scaled from 5 to the maximum value of the respective patient sample. The number given above each slice refers to the z-coordinate in MNI space.



Supplementary Figure 2: Lesion Overlay Plots for Non-Neglect Patients

Overlaps of all normalised acute lesions included in the analyses are shown for all non-neglect patients ($n = 133$), female ($n = 63$) and male patients ($n = 70$). Aggregated lesions were overlaid on an axial view of the ch2bet-template in MRICron (Rorden & Brett, 2000). The voxels' colours indicate the frequency of the lesion overlap and were scaled to the respective sample sizes. Only voxels damaged in at least 5 patients are depicted and were used for subsequent analyses. Colours were scaled from 5 to the maximum value of the respective patient sample. The number given above each slice refers to the z-coordinate in MNI space.