Thesis

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**Master of Science**

“Sex Differences in the Lesion Patterns and Disconnectome 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.

Date / Signature: \_

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Abstract

[200 words]

1. Introduction: Sex Differences in Neuropsychology
   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 women 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 gender 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 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 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 within between 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 processing (Hausmann, 2016; Hirnstein et al., 2019; 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 are largely 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; Rupprecht, 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. Further, there is evidence that high levels of progesterone and oestradiol during the midluteal phase may down-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. Sex Differences in Stroke

Vascular diseases, such as stroke and ischemic heart diseases, currently constitute the second leading cause of death worldwide and are one of the leading causes of disability, especially in the elderly population (Bonkhoff et al., 2021; Feigin et al., 2014; Katan & Luft, 2018). The Lancet’s Global Burden of Disease review for the year 2019 reported 12.2 million global incident cases of stroke: 62.4% of those strokes were ischaemias/infarcts, while the remaining 37.6% were haemorrhages. They further identified stroke to be the second-leading cause of death, accounting for a total of 6.55 million global deaths. Women suffered more often from strokes (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 (Giroud et al., 2017; Bonkhoff et al., 2021).

A meta-analysis by Gargano et al. (2009) concluded that women are on average 4 years older than men are when suffering their first ischemic strokes. Since increased age is positively correlated with stroke risk and negatively correlated with functional outcomes, elderly women suffer the largest burden of stroke-induced disability and death (Appelros et al., 2009; Gibson, 2013; Reeves et al., 2008; Silva et al., 2010). Multiple studies have found that in the chronic post-stroke phase women are more likely to have significantly decreased quality of life, including impaired locomotor function and mental abilities, compared to men (Gibson, 2013; Reeves et al., 2008, Sturm et al., 2004). 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 in 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). Rodent models have well established that female brains sustain less injuries after experimental ischaemic stroke compared to male brains, which is attributed to the neuroprotective properties of sex steroid hormones, such as oestradiol and progesterone (Gibson et al., 2013; Liu et al., 2010; Wise et al., 2001). These hormones, taken together with testosterone, are also referred to as “neuroactive steroids” or “neuro-steroids”, as they can be synthesised within the brain and are able to alter neuronal excitability (Rupprecht, 2003).

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

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

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

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

* 1. 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; 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) established that neglect is associated with higher age at stroke onset of 3 years on average, with more severe strokes, greater disability, and mortality. Further, they discovered a sex difference in acute neglect incidence, with women exhibiting a prevalence of 33% versus 27% in men. Recovery rates for the core symptoms during the post-acute phase are relatively high at 70-80% (Demeyere & Gillebert, 2019), making the prevalence rates of chronic neglect considerably lower than for acute neglect. Current estimates for chronic neglect prevalence vary from 8-12% (Jehkonen et al., 2000) to up to 17% (Esposito et al., 2021). Still, neglect is commonly considered to be a negative predictor for functional outcome in stroke recovery (Jehkonen et al., 2000 & 2007; Wee & Hopman, 2008; Wu et al., 2015).

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

The heterogeneity of clinical symptoms is also reflected in the neuroanatomy of neglect: Most often, the syndrome manifests after right unilateral brain damage in the territory of the MCA (Li & Malhotra, 2015). The right hemispheric perisylvian network – including the temporo-parietal junction (TPJ), inferior parietal lobule (IPL), superior and middle temporal cortex, insula, and ventrolateral prefrontal cortex (vlPFC) – seems to underlie spatial orientation and it has been proposed that its disruption likely contributes to the core neglect deficits (Bartolomeo et al. 2007; Corbetta et al., 2005; Karnath, 2012; Karnath & Rorden, 2012). Other notable cortical regions that have been implicated in neglect are the posterior parietal cortex, inferior frontal cortex, angular gyrus, 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 (BG), have also been shown to be associated with neglect. However, it is hypothesised that not the lesion to those regions themselves causes neglect, but rather that the disorder emerges from the long-range effects of reduced functionality in the perisylvian network (He et al., 2007; Karnath, 2012; Karnath & Niemeier, 2002).

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

Interestingly, this is in line with the results obtained from fibre-tracking studies in neglect patients. It has been established that the WM fibres connecting the perisylvian network, specifically the superior longitudinal fasciculus (SLF), arcuate fasciculus (AF), the inferior fronto-occipital fasciculus (IFOF) and the superior fronto-occipital fasciculus (SFOF) have been shown to be particularly vulnerable to causing neglect after being damaged (Chechlacz et al., 2010; He et al., 2007; Karnath et al., 2009; Urbanski et al., 2010). It also has been shown that neglect severity is greater when lesions reach deep into the WM, compared to cortical lesions of a similar size (Corbetta, 2014).

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

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

While the majority of those results were obtained from patients who suffered from an infarct in the territory of the MCA, Bird et al. (2006) described similar associations in patients with PCA-infarction: In those patients, intrahemispheric disconnections of the WM tracts between the parahippocampal gyrus and the angular gyrus 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 technique to assess brain network dysfunction after stroke based on an indirect measure of structural disconnections – without the need for acquiring DTI images (see Chapter 3: Data Analysis for details). They were able to replicate the findings obtained in seminal studies in the past, 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 likely is 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. 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 disconnections affect neurological post-stroke syndromes, such as visuospatial neglect.

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

Even though visuospatial neglect is a syndrome that commonly affects survivors of right-hemispheric stroke, research has not paid much attention to sex as a factor that might affect the manifestation of this syndrome significantly. While a difference in neglect incidence between the sexes have 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 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).

Therefore, we aimed to evaluate if there are any sex differences in lesion localisation and/or disconnections of right-hemispheric stroke patients, and if any of those differences are associated with the severity of visuospatial neglect. 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 in neglect severity. Thirdly, we used a recently introduced method of indirect lesion-connectome mapping (Griffis et al., 2019) to assess different disconnectivity measures based on lesion data. We examined if there are any sex differences or sex-specific differences in neglect severity in the whole-brain disconnectivity or region-to-region disconnectivity. 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, diagnosis, or a combination of both) based on lesion data, as well as whole-brain disconnectivity data.

## Material & Methods

### Patient Sample

This study reanalysed data from 206 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., exceeding/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](#table01clinicaldata_all) 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](#_Behavioural_Data) for details, and [Supplementary Tables 1a](#s_table01Aclinicaldata_neglect) and [1b](#s_table01Bclinicaldata_non) 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 *(years)* | 62.6 (14.0) [26-93] | 64.4 (15.4) [26-93] | 60.8 (12.1) [29-83] | 0.064a |
| Patient Group *(Neglect, Non-Neglect)* | 73, 133 | 40, 63 | 33, 70 | 0.308b |
| Days between Stroke & Imaging | 2.9 (3.1) [0-14] | 2.8 (3.1) [0-14] | 3.1 (3.1) [0-14] | 0.580a |
| Aetiology *(Infarct, Haemorrhage, Both)* | 169, 34, 3 | 79, 22, 2 | 90, 12, 1 | 0.137b |
| Lesion volume *(cm3)* | 36.0 (44.8) [0.09-312.6] | 34.8 (44.8) [0.16-312.6] | 37.3 (43.8) [0.09-194.7] | 0.688a |
| Arterial Territory of Infarct *(ACA, MCA, PCA)* | 12, 134, 22 | 11, 61, 7 | 1, 73, 15 | **0.003b** |
| Days between Stroke & Assessment | 3.7 (2.6) [0-14] | 4.0 (2.5) [0-14] | 3.5 (2.7) [0-13] | 0.195a |
| 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] | 0.851a |
| 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] | 0.385a |
| Copying Errors | 1.16 (1.93) [0-7] | 1.13 (1.81) [0-7] | 1.19 (2.04) [0-7] | 0.794a |
| 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] | 0.833a |
| Visual field defects *(N)* | 32 | 16 | 16 | 0.849b |

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)

### 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.

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.

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.

### 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](#table01clinicaldata_all)).

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](#s_table02Ascans_lesion) and [2b](#s_table02Bscans_normalisation) 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 1mm3. 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.

## Data Analysis

### 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.](#_Region-to-Region_Disconnectivity)).

Subsequently, we conducted a voxel-based lesion-behaviour mapping analysis using   
mass-univariate general linear models (GLMs) 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 ran the analysis using binary voxel status (i.e., 0 = undamaged, 1 = damaged) as independent variable and sex as dependent variable, before repeating the analysis using the normalised behavioural score as dependent variable. This was done to dissociate which effects are fully attributable to sex, and which effects were due to sex differences that are associated with neglect. To identify voxels whose damage is associated with more severe symptoms, we first applied the VLBM analyses to the entire patient sample. Then, we repeated the 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 5000 permutations with maximum statistic permutation (Nichols & Holmes, 2002).

### 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-neglect severity. As already described in [Section 3.1.](#_Voxel-based_Lesion-Behaviour_Mappin) for the VLBM analysis, we ran this analysis once using sex as dependent variable, and once using the behavioural scores as dependent variable in order to dissociate the effects of sex and neglect severity. We then repeated the neglect severity analysis three times: for the whole patient sample, for the female patients and for the male patients, separately.

### Region-to-Region Disconnectivity

To identify which grey matter regions were disconnected from each other due to the stroke-induced WM tract damage as estimated in [Section 3.2.](#_Whole-Brain_Disconnectivity), 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 can be ascribed to a purely sex-specific effect, we used custom MATLAB scripts employing mass-univariate 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(All) = 40; N(F)= 20; N(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 repeated the rank-sum test 50,000 times. We saved the maximum of the absolute z-statistic for every permutation, which describes how different the two group means are from each other. Then, we compared the z-statistics derived from the original disconnection data 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).

### 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 improve 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, …, 215 and nu = 0.01, 0.06, …, 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.

## Results

### 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](#table01clinicaldata_all)). 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](#s_table01Aclinicaldata_neglect) & [1b](#s_table01Bclinicaldata_non) 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](#table01clinicaldata_all)). Further, there was no significant difference between the sexes in performance in any of the three diagnostic tests (see [Table 1](#table01clinicaldata_all) & [Figure 1](#figure01behaviour)).



**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 (µ = 34.8 ± 44.8 cm3) than men (37.3 ± 43.8 cm3). However, this difference was non-significant (see [Table 1](#figure01behaviour)). This trend was also present in the neglect and non-neglect groups (see [Supplementary Tables 1a](#s_table01Aclinicaldata_neglect) & [1b](#s_table01Bclinicaldata_non) 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 medial cerebral artery (MCA; see [Supplementary Table 3](#s_table03arteries)). 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 posterior cerebral artery (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.

### Voxel-based Lesion-Behaviour Mapping

The topography of overlay plots of the patients’ acute lesions can be seen in [Figure 2](#figure02lesionoverlay_all), while the overlay plots for the neglect and non-neglect groups can be found in [Supplementary Figures 1](#s_figure01lesionoverlay_neglect) and [2](#s_figure02lesionoverlay_non). 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 value of the respective patient sample. The number given above each slice refers to the z-coordinate in MNI space.

We ran two VLBM analyses using mass-univariate 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 correlated with sex.

[Figure 3](#figure03niistatlesion) 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, STG, the posterior superior temporal sulcus (pSTS) and their associated WM fibre tracts. In the female patient subgroup, a total of 323 mostly grey 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.

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Automatisch generierte Beschreibung

**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.

### Whole-Brain Disconnectivity Mapping

[Figure 4](#figure04DCoverlay_all) 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 OrG, BG, and thalamus to the inferior temporal gyrus (ITG) and, finally, the occipital pole. This corresponds to pronounced disconnections affecting the IFOF 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.



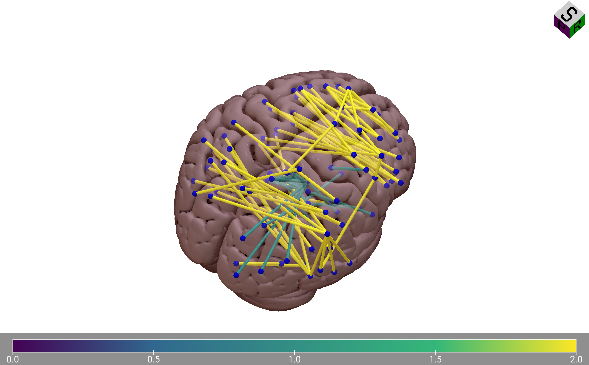
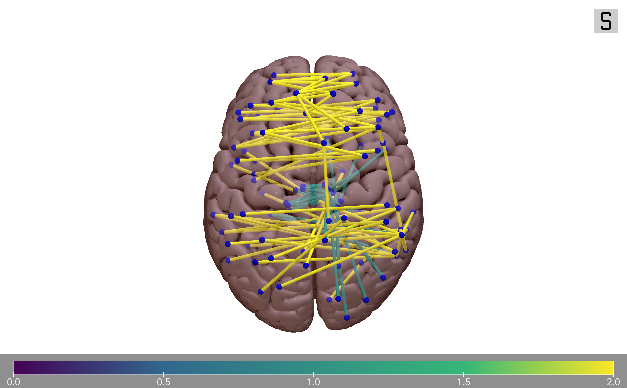
**Figure 4:** Disconnection Overlay Plots   
Overlaps of the whole-brain disconnections included in the analyses are shown for all patients (N = 206), female and male patients (N = 103, respectively). Aggregated disconnection maps were overlaid on an axial view of the ch2bet-template in MRIcron (Rorden & 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 value of the respective patient sample. 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 status is significantly correlated with either sex or neglect severity yielded no significant results, as no voxels survived the threshold.

### 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 interhemispheric disconnections associated with women (60%).



**Figure 5:** Significant parcel-wise disconnections at p = 0.05   
Significant parcel-wise disconnections, 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 coloured edges to the disconnected fibre streamlines between those parcels as defined by the HCP-842 atlas (Yeh et al., 2018). Yellow edges (n = 69) had a higher disconnection score in the male subsample, green edges (n = 30) were more severely disconnected in the female subsample.

~~Generally, disconnections involving the IPL were the most common (see~~ [~~Table 2~~](#table02roiDCs_summary) ~~for an overview, and~~ [~~Supplementary Table 4~~](#s_table04sigDCs_regions) ~~for details): 34.8% of all disconnections across the whole patient sample had one of their endpoints in the IPL. IPL-related disconnections were also the most common disconnection in the male subsample, attributing for 30.9% of their disconnections. In the female subsample, however, the majority of disconnections (48.3%) was associated with the ITG. Here, IPL-related disconnections were the third most common (27.8%), after disconnections involving the pSTS (36.1%).~~

**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 sign. disconnections (Anatomical Label, % of all disconnections)~~ | ~~right A39rv (PGa) of IPL (5.38%)~~ | ~~right cpSTS  (18.54%)~~ | ~~right A39rv (PGa) of IPL (6.87%)~~ |
| ~~ROI with highest number of sign. disconnections (Anatomical Label, % of all disconnections)~~ | ~~IPL (34.8%)~~ | ~~ITG (48.3%)~~ | ~~IPL (30.9%)~~ |

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). ~~More details can be found in~~ [~~Supplementary Table 4~~](#s_table04sigDCs_regions)~~.~~

~~In women, the five disconnections that were most significantly associated with pathological behavioural scores were all right~~ *~~intra-~~*~~hemispheric disconnections involving the thalamus, specifically the occipital and caudal temporal segments of the thalamus. In contrast to this, the five most significant disconnections in men were all~~ *~~inter-~~*~~hemispheric disconnections involving the right caudoventral ITG.~~

~~Further, the disconnection that most significantly was associated with pathological behavioural scores in women was between the ventrolateral ITG and the occipital thalamus of the right hemisphere. In men, however, the interhemispheric disconnection between the left extreme lateroventral ITG and the right caudoventral ITG was associated most significantly with neglect severity.~~

**Table 3:** Most Significant Parcel-wise Disconnections

|  |  |  |  |
| --- | --- | --- | --- |
|  | Node A | Node B | T-value |
| T O T A L | left MTG  (rostral area 21) | right ITG (caudoventral area 20) | 7.5929 |
| left MTG (anterior STS) | right ITG (ventrolateral area 37) | 7.3804 |
| left STG (lateral area 38) | right ITG (caudoventral area 20) | 7.3375 |
| left IPL (rostroventral area / PFop) | right ITG (extreme lateroventral area 20) | 7.3282 |
| left IPL (caudal area 40/PFm) | right ITG (caudoventral area 20) | 7.3147 |
| F E M A L E | right ITG  (ventrolateral area 37) | right Thalamus (occipital thalamus) | 5.2566 |
| right SPL (postcentral area 7) | right Thalamus (occipital thalamus) | 5.0743 |
| right SPL (rostral area 7) | right Thalamus (caudal temporal thalamus) | 5.0445 |
| right IPL (rostrodorsal area 39 / Hip3) | right Thalamus (caudal temporal thalamus) | 4.8381 |
| right IPL (rostrodorsal area 40 / PFt) | right Thalamus (occipital thalamus) | 4.8380 |
| M A L E | left ITG (extreme lateroventral area 37) | right ITG (caudoventral area 20) | 6.6931 |
| left MTG  (rostral area 21) | right ITG (caudoventral area 20) | 6.6168 |
| left IPL (rostroventral area 39 / PGa) | right ITG (caudoventral area 20) | 6.3379 |
| left IPL (caudal area 40 / PFm) | right ITG (caudoventral area 20) | 6.3214 |
| left pSTS (caudoposterior STS) | right ITG (caudoventral area 20) | 6.3154 |

Parcel-wise disconnections with the highest T-values following the region-to-region analysis for the patient (sub-) samples. 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. T-values were obtained from the GLM analysis, employing maximum statistic permutation at 50,000 permutations.

### Prediction of Patient Status

[Table 4](#table04predictionacc) 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. Prediction accuracy of the model trained on lesion maps was below chance level for the classification of sex (<50%), as well as for sex-specific patient groups (<25%). The disconnection-based model achieved a prediction accuracy of 32.5% for the classification of sex-specific patient group, which is above chance-level for a four-class classification.

**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]).

## Discussion



## Conclusion



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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

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## Appendix

### Appendix A: List of Abbreviations

|  |  |
| --- | --- |
| ACA | Anterior Cerebral Artery |
| CoC | Centre of Cancellation |
| CT | Computed Tomography |
| CV | Cross Validation |
| DTI | Diffusion Tensor Imaging |
| DWI | Diffusion-weighted Imaging |
| fMRI | Functional Magnetic Resonance Imaging |
| GLM | General Linear Model |
| IFOF | Inferior Fronto-Occipital Fasciculus |
| IPL | Inferior Parietal Lobule |
| ITG | Inferior Temporal Gyrus |
| LQT | Lesion Quantification Toolkit |
| MCA | Medial Cerebral Artery |
| MNI | Montreal Neurological Institute |
| MRI | Magnetic Resonance Imaging |
| MTG | Middle Temporal Gyrus |
| nu-SVC | nu-Support Vector Classification |
| PCA | Posterior Cerebral Artery |
| pSTS | Posterior Superior Temporal Sulcus |
| ROI | Region of Interest |
| SLF | Superior Longitudinal Fasciculus |
| SFOF | Superior Fronto-Occipital Fasciculus |
| SPL | Superior Parietal Lobule |
| SSPL | Shortest Structural Path Length |
| STG | Superior Temporal Gyrus |
| STS | Superior Temporal Sulcus |
| T2FLAIR | T2-weighted Fluid Attenuated Inversion Recovery |
| TPJ | Temporo-Parietal Junction |
| VLBM | Voxel-based Lesion-Behaviour Mapping |
| vlPFC | Ventrolateral Prefrontal Cortex |
| 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] | 0.114a |
| Days between Stroke & Imaging | 3.4 (3.5) [0-14] | 3.4 (3.6) [0-14] | 3.4 (3.4) [0-14] | 0.971a |
| Aetiology *(Infarct, Haemorrhage, Both)* | 55, 15, 3 | 28, 10, 2 | 27, 5, 1 | 0.507b |
| 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] | 0.416a |
| Arterial Territory of Infarct *(ACA, MCA, PCA)* | 5, 47, 5 | 5, 23, 2 | 0, 24, 3 | 0.079b |
| Days between Stroke & Assessment | 4.0 (2.9) [0-14] | 4.0 (2.9) [0-14] | 3.8 (2.8) [0-13] | 0.709a |
| 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] | 0.487a |
| 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] | 0.058a |
| Copying Errors | 2.93 (2.31) [0-7] | 2.67 (2.21) [0-7] | 3.34 (2.35) [0-7] | 0.132a |
| 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] | 0.116a |
| Visual field defects *(N)* | 17 | 9 | 8 | 0.940b |

**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] | 0.328a |
| Days between Stroke & Imaging | 2.7 (2.9) [0-11] | 2.4 (2.7) [0-11] | 2.9 (3.0) [0-11] | 0.345a |
| Aetiology *(Infarct, Haemorrhage, Both)* | 114, 19, 0 | 51, 12, 0 | 63, 7, 0 | 0.507b |
| 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] | 0.595a |
| Arterial Territory of Infarct *(ACA, MCA, PCA)* | 7, 87, 17 | 6, 38, 5 | 1, 49, 12 | **0.041b** |
| Days between Stroke & Assessment | 2.6 (2.6) [0-12] | 3.9 (2.3) [1-9] | 3.3 (3.0) [0-12] | 0.195a |
| 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] | 0.987a |
| 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] | 0.665a |
| Copying Errors | 0.22 (0.58) [0-4] | 0.27 (0.65) [0-4] | 0.16 (0.51) [0-3] | 0.288a |
| 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] | 0.762a |
| Visual field defects *(N)* | 15 | 7 | 8 | 0.954b |

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](#_Appendix_A:_List).  
  
**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**: Number of significant disconnections per Region at p = 0.05

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total  (N = 893) | | Female  (N = 205) | | | | Male (N = 611) | | | |
| Amygdala (Amyg) | 12 | (1.34%) | 0 | (0.00%) | | 7 | | (1.14%) | |
| Basal Ganglia (BG) | 60 | (6.72%) | 2 | (0.96%) | | 37 | | (6.06%) | |
| Fusiform Gyrus (FuG) | 24 | (2.69%) | 1 | (0.49%) | | 18 | | (2.94%) | |
| Hippocampus (Hipp) | 27 | (3.02%) | 3 | (1.46%) | | 13 | | (2.13%) | |
| Inferior Frontal Gyrus (IFG) | 12 | (1.34%) | 0 | (0.00%) | | 4 | | (0.65%) | |
| Insula (Ins) | 8 | (0.89%) | 0 | (0.00%) | | 9 | | (1.47%) | |
| Inferior Parietal Lobule (IPL) | 311 | (34.83%) | 57 | (27.80%) | | 189 | | (30.93%) | |
| Inferior Temporal Gyrus (ITG) | 286 | (32.03%) | 99 | (48.29%) | | 261 | | (42.72%) | |
| Lateral Occipital Cortex (LOcC) | 93 | (10.41%) | 9 | (4.39%) | | 80 | | (13.09%) | |
| Middle Frontal Gyrus (MFG) | 31 | (3.47%) | 3 | (1.46%) | | 23 | | (3.76%) | |
| Middle Temporal Gyrus (MTG) | 174 | (19.48%) | 45 | (21.95%) | | 160 | | (26.19%) | |
| Medioventral Occipital Cortex (MVOcC) | 15 | (1.68%) | 0 | (0.00%) | | 12 | | (1.96%) | |
| Orbital Gyrus (Org) | 15 | (1.68%) | 2 | (0.96%) | | 19 | | (3.11%) | |
| Paracentral Lobule (PCL) | 4 | (0.45%) | 0 | (0.00%) | | 0 | | (0.00%) | |
| Precuneus (Pcun) | 33 | (3.70%) | 6 | (2.93%) | | 19 | | (3.11%) | |
| Parahippocampal Gyrus (PhG) | 3 | (0.34%) | 0 | | (0.00%) | | 5 | | (0.82%) | |
| Postcentral Gyrus (PoG) | 59 | (6.61%) | 3 | | (1.46%) | | 25 | | (4.89%) | |
| Precentral Gyrus (PrG) | 33 | (3.70%) | 2 | | (0.96%) | | 24 | | (3.93%) | |
| Posterior Superior Parietal Sulcus (pSTS) | 107 | (11.98%) | 74 | | (36.10%) | | 33 | | (5.40%) | |
| Superior Frontal Gyrus (SFG) | 17 | (1.90%) | 0 | | (0.00%) | | 14 | | (2.29%) | |
| Superior Parietal Lobule (SPL) | 151 | (16.91%) | 35 | | (17.07%) | | 91 | | (14.89%) | |
| Superior Temporal Gyrus (STG) | 156 | (17.47%) | 18 | | (8.78%) | | 118 | | (19.31%) | |
| Thalamus (Tha) | 155 | (17.36%) | 51 | | (24.88%) | | 61 | | (9.98%) | |

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 these percentages 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.

Ein Bild, das Text enthält.

Automatisch generierte Beschreibung

**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.