Thesis

submitted in partial fulfilment of the requirements for the degree

**Master of Science**

“Sex Differences in Acute Visuospatial Neglect – An Exploratory Study Investigating Differences in Lesion Patterns and Disconnectome”

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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]

Cognition and brain health are influenced by many variables, one of them being biological sex.

## Introduction: Sex Differences in Neuropsychology

### Sex Differences in the Healthy Brain and General Cognition

Sex differences in cognitive abilities have already been a widely discussed subject of interest since the 1870s already (for a review see [Shields, 1975](#shields1975)). In those early years after the conception of formal psychology, researchers mainly relied measures of head and brain size in an attempt to explain differences in cognitive capacities. Researchers reported that women had smaller overall brain volumes, which they proposed to be directly responsible for their lower intelligence scores and increased perceptual abilities and emotionality. Shields (1975) describes that many researchers at that time lacked the necessary impartiality to investigate the topic, as they aimed “to discover the particular physiological determinants of female inadequacy”. [something something less obvious misogyny in science] While some reviews at the time found no noteworthy differences in mental abilities between men and women ([Hollingworth, 1918](#hollingworth1918); [Woolley, 1914](#woolley1914)), various studies report superior performance in spatial and analytical tests for men, while women score higher in verbal tasks (for a review see [Sherman, 1967](#sherman1967)). Theories of higher intellectual abilities in men, as measured by IQ, being linked to genetics were prominent, even though not uncontroversial ([Wittig, 1976](#wittig1976)). However, even back then, researchers have already pointed out that these described differences are inherently linked to stereotypical ([Broverman et al., 1972](#broverman1972); [Sherman, 1967](#sherman1967); [Woolley, 1914](#woolley1914)).

[With the advent of neuroimaging, new possibilities emerged for more detailed and objective research of sex differences in the cognitive neurosciences.]

The view that men and women are fundamentally different in certain cognitive domains/tasks remained relatively common throughout both the minds of the vast population, as well as the scientific community. [Nosek et al. (2009)](#nosek2009) found that about 70% of people from different nationalities hold implicit stereotypes of associating mathematics and science more strongly with men than with women.

However, meta-analyses and meta-syntheses showed that if any gender differences in cognitive tests were detectable, they typically were negligibly small ([Hirnstein et al., 2019](#hirnstein2019); [Hyde, 2005](#hyde2005); [Zell et al., 2015](#zell2015)). [Hyde (2005](#hyde2005) & [2014)](#hyde2014) found that in most cognitive tasks, women and men achieved equal performances. The strongest and most robust difference in cognitive tasks that [Zell et al.’s (2015)](#zell2015) meta-synthesis identified was mental rotation.

Several structural magnetic resonance imaging (MRI) studies found that the volume of the crania and brain lobes are generally larger for men than for women – with those differences being more pronounced in white matter (WM) than for grey matter ([Allen et al., 2003](#allen2003); [Goldstein et al., 2001](#goldstein2001)). These findings were interpreted as women having less WM than their male counterparts, rather than women having more grey matter. [However, the reported grey/white matter ratios vary across lobes and hemispheres.] (DETAILS) Interestingly, the corpus callosum was found to be less sexually dimorphic than white matter overall, which could be an indicator that white matter tracts are less sexually dimorphic than other white matter components, such as glial cells and blood vessels ([Allen et al., 2003](#allen2003)).

Studies employing diffusion tensor imaging (DTI) to investigate the architecture of WM and its fibre tracts found that over all age ranges, men tend to have increased measures of fractional anisotropy (FA) and decreased mean diffusivity (MD) than women. Higher measures of FA are thought to reflect increased axonal diameter, fibre bundle density and myelination, while the inverse relation holds for MD ([Boespflug et al., 2011](#boespflug2011); [Zasler & Kaplan, 2017](#zaslerkaplan2017)). However, in a similar vein to [Allen et al.’s (2003)](#allen2003) findings of women having larger corpora callosa in proportion to the rest of their WM, [Kanaan et al. (2012)](#kanaan2012) were able to show that the corpus callosum in women has higher FA than in men. This could be interpreted as women’s corpora callosa exhibiting greater efficiency.

* Goldstein et al., 2001:
  + A permutation test showed that, compared to other brain areas assessed in this study, there was greater sexual dimorphism among brain areas that are homologous with those identified in animal studies showing greater levels of sex steroid receptors during critical periods of brain development.
* Choleris et al. (2018):
  + Sex differences in various aspects of cognition have been seen across a number of species and in humans, with women on average exhibiting greater verbal ability, and perceptual speed while men on average exhibiting better spatial ability than women. However, it is important to be aware that these sex differences often have small effect sizes and there are no indications that there are large sex differences in IQ (Hyde, 2016). (reviewed in Hyde, 2016).
  + Nevertheless, the largest sex difference, with males outperforming females, is seen in spatial ability, and meta-analyses indicate that spatial superiority in males exist in both rodents and primates (Jonasson, 2005; Voyer et al., 2016).
  + Although a meta-analysis suggests that men have larger hippocampal volumes than women, this advantage disappears when hippocampal volume is adjusted for total brain or intracranial volume (Tan et al., 2016).
  + In past research using seasonal breeders, such as deer mice and meadow voles, work by Liisa Galea and colleagues has consistently found a slight, but statistically significant, sex difference, with males outperforming females, in acquisition of the Morris water maze even when the animals were pre-trained (Galea et al., 1994; Galea et al., 1995; Chow et al., 2013). Interestingly, this sex difference was observed only when comparing females to males during periods when females were exposed to higher levels of estradiol (i.e., during the breeding season). Thus, high endogenous levels of estradiol in females were negatively associated with performance, whereas low endogenous levels of estradiol were associated with no sex difference (Galea et al., 1994; Galea et al., 1995). Indeed, many studies using exogenous manipulations of estradiol in females or androgens in males find a greater influence of estradiol in female performance and strategy use than of androgens in male performance, indicating a greater activational role of estrogens in female spatial performance than in male spatial performance.
* Hausmann (2017)
  + Functional cerebral asymmetries (FCAs) refer to the relative differences between the left and the right hemispheres in some neural functions and cognitive processes and represent a relatively simple model for investigatingfunctional connectivity in the brain. Although FCAs are a fundamental principle of brain organization (e.g., the vast majority of human individuals are left lateralized for language), about half of the variation in FCAs is attributable to individual differences (Kim et al., 1990). This variation was simply treated as random error, and was usually ignored in the past (Hellige, 1993).
  + In healthy adults, sex differences in FCAs have been reported for many cognitive domains, including language, spatial orientation, spatial attention, and face recognition. Although contrary findings, most studies reporting sex differences have revealed reduced FCAs in females compared with males. Moreover, there is some evidence that women exhibit a greater degree of interindividual variability in FCAs, whereas FCAs in males are rather robust.
  + Merrill Hiscock and colleagues found stronger hemispheric asymmetry in males across a range of auditory (Hiscock et al., 1994), visual (Hiscock et al., 1995), tactile (Hiscock et al., 1999), and dual task interference (Hiscock et al., 2001) laterality tasks and concluded that, on the population level, sex differences in FCAs (i.e., larger FCAs in men than in women) are small but reliable (Hiscock et al., 2001). Daniel Voyer (1996, 2011) came to the same conclusion in his meta analyses. Small effect sizes imply that only studies using a large sample will reliably find sex differences in FCAs.
  + Hirnstein et al. (2013) compiled behavioral data from 1,782 participants (885 females) and found that sex differences in the degree of language lateralization, as measured with a well-established verbal dichotic listening task (Hugdahl, 1995), were dependent on age, with the largest effect (Cohen’s d= 0.31) in adolescents. […] The sex difference in this task observed by Hirnstein et al. (2013) is in line with a recent study by Bless et al. (2015) that assessed language lateralization in over 4,000 participants with a smartphone application (iDichotic). This study also revealed greater language lateralization in men than in women, with a small effect of Cohen’s d = 0.18. Although effect sizes in sex differences of language lateralization are small, they are consistent with, for example, recent anatomical findings showing greater leftward asymmetry of the planum temporale (which overlaps with Wernicke’s area) in men than in women (e.g., Guadelupe et al., 2015), which is established very early in ontogenesis (Li et al., 2014).
* Varnava, Halligan & Peter (2007):
  + Hellige (2001) suggested that differences occur because the hemispheric asymmetry is not the same for males and females. This is plausible in view of the evidence that sex hormones influence cognition and brain function both at critical stages of ontogenetic development (Geschwind & Galaburda, 1987) and in adulthood as various hormonal levels fluctuate over time (Kimura & Hampson, 1994).
* Ingalhalikar et al. (2014):
  + With the advent of neuroimaging, multiple studies have found sex differences in the brain (4) that could underlie the behavioral differences. Males have larger crania, proportionate to their larger body size, and a higher percentage of white matter (WM), which contains myelinated axonal fibers, and cerebrospinal fluid (5), whereas women demonstrate a higher percentage of gray matter after correcting for intracranial volume effect (6). Sex differences in the relative size and shape of specific brain structures have also been reported (7), including the hippocampus, amygdala (8, 9), and corpus callosum (CC) (10). Furthermore, developmental differences in tissue growth suggest that there is an anatomical sex difference during maturation (11, 12), although links to observed behavioral differences have not been established.
  + Advances in fiber tractography with diffusion imaging can be used to understand complex interactions among brain regions and to compute a structural connectome (SC) (31). Similar functional connectomes (FCs) can be computed using modalities like functional MRI, magnetoencephalography, and EEG. Differences in FCs have revealed sex differences and sex-by-hemispheric interactions (32), with higher local functional connectivity in females than in males (33). Although SCs of genders have displayed small-world architecture with broad-scale characteristics (34, 35), sex differences in network efficiency have been reported (36), with women having greater overall cortical connectivity (37).
  + The myelinated axons of WM facilitate distant signal conduction. Previous data from structural imaging showed a higher proportion of cortical WM in the males, except in the CC (40, 41). A higher proportion of myelinated fibers within hemispheres in males compared with an equal or larger volume of WM in the callosum suggests that male brains are optimized for communicating within the hemispheres, whereas female brains are optimized for interhemispheric communication.

### 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](#bonkhoff2021); [Feigin et al., 2014](#feigin2014); [Katan & Luft, 2018](#katanluft2018)). The Lancet’s Global Burden of Disease (GBD) review for the year 2019 reported 12.2 million global incident cases of stroke: 62.4% of those strokes were of an ischaemic nature, while the remaining 37.6% were haemorrhages. They further identified stroke to be the second-leading cause of death, accounting for a total of 6.55 million global deaths, and one of the top leading causes of long-term disabilities as measured by disease-adjusted life years (DALYs). Women suffered more often from strokes (6.44 million incident cases, 56.4 million prevalent cases) than men (5.79 million incident strokes, 45.0 million prevalent cases). However, there were no significant sex differences in the number of stroke-related deaths ([GBD 2019 Stroke Collaborators, 2021](#GBDstroke2021)).

Researchers believe that women’s higher burden of stroke may be in part due to their higher life expectancy, but also due to (neuro)biological sex differences, such as sex chromosomes or sex steroid hormones that contribute to different responses to cerebral ischemia ([Bonkhoff et al., 2021](#bonkhoff2021); [Bushnell et al., 2018](#bushnell2018); [Gibson, 2013](#gibson2013)). Studies have shown that in both hippocampal and astrocytic cells derived from neonatal populations, male-derived (XY) cells are more vulnerable than female-derived (XX) cells to ischaemic injuries – even in low hormonal concentrations ([Li et al., 2005](#li2005); [Liu et al., 2008](#liu2008); MORE). [Manwani et al. (2014)](#manwani2014) also demonstrated the same effects in mice. However, by dissociating the effects of gonadal sex hormones from sex chromosomes via the removal of gonads, they were able to show that this female-specific ischaemic protection stemmed from circulating oestrogen and oestradiol (see also Bushnell et al., 2018 for a review). [übergang]

It has been well established by rodent studies that female brains sustain less injuries after experimental ischaemic stroke compared to male brains, which is likely due to neuroprotective properties of sex steroid hormones, such as oestradiol, oestrogen and progesterone ([Gibson et al., 2013](#gibson2013); [Liu et al., 2010](#liu2010); [Wise et al., 2001](#wise2001)). There is also some experimental evidence in animal models that showed that acute administration of such hormones reduces infarct size ([Gibson et al., 2009](#gibson2009); [Liu & Yang, 2013](#liuyang2013); [Suzuki et al, 2009](#suzuki2009)), however clinical trials have not been successful so far (CHECK) ([Gibson et al., 2013](#gibson2013); [Henderson & Lobo, 2012](#hendersonlobo2012))

* Gibson (2013)
  + Such gender differences have largely been attributed to the longer life expectancy of women, consistent with the fact that age is the strongest independent risk factor for stroke1 and also a negative predictor for clinical outcome.
  + In terms of stroke onset, women tend to be, on average, approximately 4 years older than men at the age of ischemic stroke onset. A recent meta-analysis on data from 2,566 patients revealed that the mean age of onset of first ischemic stroke was 66.6 years in men compared with 70.0 years in women.8
  + For example, The Framingham study reported that the incidence of ischemic stroke is lower in women than men within the 45- to 54-year-old age cohort, composed mainly of premenopausal and preimenopausal women, but is equalized in the 55- to 64-year-old cohort.10
  + Gender may also influence both the mechanisms of injury and outcome after ischemic stroke and thus, gender should be considered in both experimental and clinical stroke studies
  + However, a systematic review and meta-analysis revealed that women with stroke are more likely than men to have a parental history of stroke, which is accounted for by an excess maternal history of stroke.24 Such a finding could be explained by sex-specific genetic, epigenetic, or non-genetic mechanisms.
  + However, the general consensus seems to be that women have poorer functional outcomes, than men, after ischemic stroke.5,33,34 Such a gender difference appears to be sustained even after making adjustments for age and other sex differences in medical history and presentation. In fact, one study34 found that at 6 months poststroke, female sex is still an independent predictor of poor prognosis even when adjusting for other predictors of functional outcome. Others have reported that at 3 months poststroke, women are more likely to have a poorer functional outcome4 and, in addition, women show significantly worse locomotor function than men at both 1- and 5-year-follow-up after ischemic stroke.14 After ischemic stroke, women are less likely to be discharged home35 and more likely to have impairments and activity limitations on followup.5 It is reported that poststroke women experience more mental impairment,35 depression,36 fatigue,37 and have a lower overall quality of life38–40 than men. It may be though that if women are more likely to delay in seeking care for stroke symptoms,30 this could result in treatment delays, which would contribute to worse outcomes.
  + In female animals, the absence of aromatase, which converts androgens to estrogens, results in increased infarction area after ischemic stroke.108 In vitro, femalederived astrocytes are protected from oxygen and glucose deprivation compared with male-derived astrocytes, which is abolished by pharmacological inhibition of aromatase56 suggesting that gender differences in estradiol production, by aromatase, may also contribute to the sex differences in sensitivity to cell death after ischemic insult.
  + Cerebral ischemia triggers a cascade of pathologic events including excitotoxicity, cell necrosis, apoptosis, inflammation, blood–brain barrier breakdown etc., which ultimately culminate in cellular dysfunction and death. […] Ischemic cell death is triggered by an influx of calcium, with subsequent oxidative damage and mitochondrial dysfunction activating several distinct cell death pathways.78 […] Over the past decade, both caspase-dependent and caspase-independent cell-death pathways have been recognized, adding considerable complexity to studies of ischemic cell death.79 Although cell death and apoptosis occur after ischemic injury, it is relevant to consider that the mechanism of injury between the genders could differ. Previous studies have shown that ischemic cell death pathways are different in the male and female brains, females often showing caspase-mediated cell death of individual neurons, whereas males are more sensitive to caspase-independent cell death.77
  + Although the aging process itself is associated with a greater risk of mortality and poorer long-term functional outcomes,52,112,113 these detrimental effects, in terms of mortality and longer-term functional ability, seem to be direct consequences of the aging process per se. If the infarct volume is reduced in aged females, by hormone supplementation, to a similar size to that seen in young females, greater functional disability and increased mortality remain in aged females.52 Possible explanations for worse outcome in aged females include the fact that female rodents demonstrate an age-related impairment in astrocyte function, which is not present in males.114 This could directly contribute to the infarct severity by inefficient glutamate clearance and enhanced cytokine production. Thus, normal aging and female gender may both be associated with an increased inflammatory response.11
* Bushnell et al. (2018):
  + The incidence of human stroke is sexually dimorphic until late in life, well beyond the years of reproductive senescence and menopause. From early through midadulthood years, stroke incidence is lower in women compared to men. However, with advancing age, the incidence of stroke and stroke-related mortality becomes higher in women.1 This overarching observation has led to much work and the notion that biologic mechanisms of cell death in the ischemic brain are influenced in part, by biologic sex and in part, by the availability of female and male sex steroids before or after injury. These hormones clearly contribute to, but do not fully account for, sex-specific responses to cerebral ischemia.106
  + Biologic sex influences many variables that are important to brain health in general, and to stroke or cerebral ischemia in particular, such as general health status, cerebrovascular anatomy and function, unique risk factors such as pregnancy and preeclampsia, symptomatology, and therapeutic response.
* Bonkhoff et al. (2021):
  + women are often reported to experience higher acute stroke severity than men.
* Katan & Luft (2018):
  + The most prominent causes of death are vascular in nature, and stroke is currently the second leading cause of death worldwide.2 Ischemic heart disease and stroke together accounted for 15.2 million deaths (15–15.6 million) in 2015.2 While ischemic strokes comprise the highest number of stroke, much of the global burden of stroke measured in proportion to mortality and by mortality and disability-adjusted life-years (DALYs) is allocated to hemorrhagic stroke.3
  + Stroke is one of the leading causes of long-term disability in the United States, especially in the elderly population in which stroke incidence is highest.
  + Moreover, an increase in stroke incidence and DALYs in adults aged 20 to 64 years has been observed.
* Haast, Gustafson & Kiliaan (2012):
  + While premenopausal women experience fewer strokes than men of comparable age, stroke rates increase among postmenopausal women compared with age matched men. This postmenopausal phenomenon, in combination with living longer, are reasons for women being older at stroke onset and suffering more severe strokes.
  + Ischemic stroke accounts for 87% of all strokes, while 10% are intracerebral hemorrhage and 3% are subarachnoid hemorrhage strokes. (see also 2011 AHA Stroke Update)
  + Nevertheless, prevalent stroke increases exponentially in both sexes with age. (see also Truelsen et al., 2006)
  + Excess stroke in women at high age may arise from longer life expectancy and reaching ages of highest stroke risk compared with men. (see also Truelsen et al., 2006)
  + Sex hormones, such as estrogen, progesterone, and testosterone, influence physiologic (e.g., vascular reactivity, CBF, and blood– brain barrier) and pathophysiologic (e.g., atherosclerosis) aspects of cerebral circulation. (Krause, Duckles & Pelligrino, 2006) One of the most extensively studied sex steroid hormones in relation to the physiology and pathophysiology of the circulatory system is the female hormone, estrogen. There is a large amount of evidence that estrogen, particularly 17b-estradiol (E2), is protective against cellular death in premenopausal stroke. (Liu et al., 2010)
  + Epidemiologic studies have revealed a clear age-by-sex interaction leading to several mechanistic hypotheses of stroke risk and onset. Premenopausal women appear less vulnerable to stroke than similarly aged men. However, after menopause the m/f ratios for prevalence and incidence decrease, indicating an increase in stroke among postmenopausal women (or decrease in men). This shift is reflected in mortality and case fatality rates, which are higher for women at older ages. When evaluating these data it should be taken into account that women have longer life expectancy, are older at stroke onset, and suffer more severe strokes. […] Premenopausal women are most likely protected against stroke because of sex steroid hormone-dependent mechanisms. This is a natural conclusion, since there are dramatic changes in the female sex hormone milieu before, during, and after menopause. Estrogen, testosterone, and progesterone affect different physiologic and pathophysiologic functions of the cerebral circulation. Estrogen promotes blood flow by decreasing vascular reactivity while testosterone has opposite effects.

### Visuospatial Neglect

Visuospatial neglect is a neurological syndrome that commonly occurs in the acute stage after predominantly right hemispheric stroke, though it may also be caused by other forms of unilateral brain injury ([Karnath & Rorden, 2012](#karnathrorden2012); [Li & Malhotra, 2015](#limalhotra2015); [Stone](#stone1993) et al., 1993). While there’s no consensus on the exact prevalence of neglect, more conservative estimates report a prevalence of ~16% in the acute phase after stroke (e.g.: [Ten Brink et al., 2016](#tenbrink2016)), while others report a prevalence of about 30-45% (e.g.: [Bowen](#bowen1999) et al., 1999; [Buxbaum et al., 2004](#buxbaum2004); [Corbetta, 2014](#corbetta)), with a few studies reporting prevalence to be as high as 82% (e.g.: [Stone](#stone1993) et al., 1993).

Visuospatial neglect is often described as a “heterogenous collection of symptoms”. After right hemispheric lesions, neglect patients exhibit pathological spatial biases towards the ipsilesional (right) side of space. This manifests as a deviation of their eye and head position, as well as an attentional bias both at rest and during goal-directed behaviour towards the ipsilesional side. At the same time, patients have difficulties in orienting towards the contralesional side and will typically ignore stimuli and people located on that side ([Becker & Karnath, 2010](#beckerkarnath2010); [Karnath, 2015](#karnath2015); [Karnath & Rorden, 2012](#karnathrorden2012)). [MORE] [REAL LIFE EXAMPLE]

[Attentional system? Model?]

This biased behaviour becomes especially obvious when patients are asked to engage with a scene or set of stimuli, for example during visual search or while copying an image, as patients will typically omit the left half of the scene. Therefore, many clinical tests that are used for diagnosing and/or quantifying the severity of neglect employ cancellation tasks to assess the spatial extent of a patient’s visual search (see 2.2. Behavioural Data for more detail; see also Rorden, Karnath, 2010).

Often times, visuospatial neglect may affect multiple modalities and, in some cases, may even affect mental representations and perceptual memories ([Bisiach & Luzzatti, 1978](#bisiachluzzatti1978); [Beschin et al., 1997](#beschin1997)). [is this even relevant?]

On a neurological level, stroke-induced neglect most often occurs after right unilateral brain damage in the territory of the middle cerebral artery (MCA) ([Li & Malhotra, 2015](#limalhotra2015)). The perisylvian network, including the temporo-parietal junction (TPJ), inferior parietal lobule (IPL), superior and middle temporal cortex, insula and ventrolateral prefrontal cortex (vlPFC), have been implicated in contributing to the core deficits ([Karnath & Rorden, 2012](#karnathrorden2012); more sources); The white matter connections in between those areas, specifically the superior longitudinal fasciculus (SLF), the inferior occipitofrontal fasciculus (IOF) and the superior occipitofrontal fascicle (SOF) have been shown to be particularly vulnerable to causing neglect after being damaged (He et al., 2007; Karnath, Rorden & Ticini, 2009;

* 1. Motivation
* Choleris et al. (2018)
  + Thus, one reason it is important to study sex differences in cognition is to understand the involvement of sex as a factor in the severity of cognitive disturbances with disease, as this can lead to clues about how the manifestation and/or treatment of the disease may need differ between the sexes.
* H

## Material & Methods

### Patient Sample

This study reanalysed a subset of 206 patients from the Division of Neuropsychology’s RHLM (Right-Hemispheric Lesion ?) databank, which comprises a total of 551 right-hemispheric stroke patients. All data were acquired at the Centre of Neurology at the University Clinic of Tübingen between January 2000 and February 2021. The patient data had been used for previous studies conducted at the Division for Neuropsychology at the University Clinic of Tübingen. 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.

The inclusion criteria for the study were as follows:

* Imaging data must have been acquired during the acute phase after the patient’s stroke, i.e., within 14 days
* The imaging data revealed a demarcated 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
  + If only two of the three tests were completed, their results must be sufficient for a clear diagnosis, i.e., the patient must exhibit clear symptoms/a lack of symptoms indicative of neglect in both tests

Following these criteria, a total of 345 patients had to be excluded. 140 patients were excluded due to missing data, 57 for medical counterindications, 55 for exceeding the 14-day threshold of the acute stroke phase, and two patients were excluded as no clear diagnosis was possible based on their diagnostic test scores. Additionally, 40 patients had to be excluded due to the poor quality of their (normalised) brain scans. In order to achieve equal group sizes to ensure comparable power between the groups, data of 66 male patients had to be excluded as well.

Thus, the study included a total of 206 right-hemispheric stroke patients, comprised of 103 female and 103 male patients (see table 1.1). The mean age at stroke was 62.6 years (SD = 13.8 years) overall, while for women it was 64.4 years (SD = 15.4 years) and 60.8 years (SD = 12.1 years) for men. 169 of the 203 patients experienced an infarct/ischaemic stroke (F = 79; M = 90), while 34 patients suffered from a haemorrhagic stroke (F = 22; M = 12) and 3 patients experienced a combination of ischaemic and haemorrhagic strokes (F = 2; M = 1).

Patients were assessed for primary visual field tests (hemi- or quadrantanopia) via standard neurological confrontation testing. 32 of the included patients exhibited primary visual field defects. 25 patients (F = 14; M = 12) were diagnosed with hemianopia and 6 with quadrantanopia (F = 2; M = 4).

A total of 73 were diagnosed with visuospatial neglect, meaning that they exceeded the threshold in at least 2 out of the 3 diagnostic tests (see [2.2. Behavioural Data](#_Behavioural_Data) for details). 40 neglect patients were women, while the remaining 33 were men (see [appendix B](#appendixB), [table S1a](#tableS01a) & [S1b](#tableS01b) for more detail on their clinical and demographic data).

**Table 2.1:** 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, Control)* | 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 |
| Days between Stroke & Assessment | 3.7 (2.6) [0-14] | 4.0 (2.5) [0-14] | 3.5 (2.7) [0-13] | 0.195b |
| 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  *(z-scored)* | 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, 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 would have been considered significant.  
Abbreviations: *CoC* – Centre of Cancellation ([Rorden & Karnath, 2010](#rordenkarnath2010)), *N* – Number of patients

### Behavioural Data

The behavioural data were collected by members of our group. Three commonly used diagnostic tests were used for the visuospatial neglect examination: the Letter Cancellation Task ([Weintraub & Mesulam, 1985](#weintraubmesulam1985)), the Bells Cancellation Test ([Gauthier, Dehaut & Joanette, 1989](#gauthier1989)) and a copying task ([Karnath & Niemeier, 2002](#karnathniemeier2002); see [Rorden & Karnath, 2010](#rordenkarnath2010) 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 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](#rordenkarnath2010)) 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. A 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 7 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. We calculated the z-scores based on the entire patient sample to ensure comparability between groups, since those groups 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 Tübingen. Since those scans were acquired for diagnostic and medical purposes, we did not have any influence on their modality or when the images were acquired. Thus, we included structural imaging 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.

If images of multiple modalities were available for a patient, MR scans were preferred. In patients with available MR scans, we preferentially used diffusion-weighted imaging (DWI) for scans acquired within the first two days after stroke onset (n = 11) and T2-weighted fluid attenuated inversion recovery (T2FLAIR) images for images acquired at a later point (n = 54). For the remaining patients (n = 43), we used a combination of two modalities (e.g., DWI and T1; see [appendix B](#appendixB), [table S2](#tableS02) for a full list).

The neuroimaging data were pre-processed using MATLAB R2016b and R2020a 64bit ([MathWorks](https://se.mathworks.com/products/matlab.html)) and SPM12 toolbox ([Wellcome Department of Cognitive Neurology, London](https://www.fil.ion.ucl.ac.uk/spm/software/spm12/)). Generally, we followed the guidelines to lesion-behaviour mapping as described in [de Haan and Karnath, 2018](#dehaankarnath2018) and [Karnath et al., 2019](#karnath2019).

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. If only a single image was available, this step was skipped.

Then, we used the Clusterize toolbox ([Clas et al., 2012](#clas2012); [de Haan et al., 2015](#dehaan2015)) 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 according to a previously selected intensity threshold. Following [Clas et al. (2012)](#clas2012), we used a default minimum cluster size of 100 voxels. The algorithm flags areas as potential lesions, which are then manually reviewed, selected, and modified, resulting in a binary voxel-based 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 (typically hyperintense for the haemorrhage hypointense for the stroke), 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 correctness by overlaying it on top of the anatomical scan using the MRIcron software ([Rorden & Brett, 2000](#rordenbrett2000); [NITRC, 2008](https://www.nitrc.org/projects/mricron/)).

Thereafter, the Clinical toolbox ([Rorden et al., 2012](#rorden2012); [NITRC, 2014](https://www.nitrc.org/projects/clinicaltbx)) was used to normalise every patient’s anatomical scan, as well as the previously created lesion map, to MNI space (Montreal Neurological Institute; [Evans et al., 1993](#evans1993MNI)) 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. We used enantiomorphic correction to control for the lesions during the normalisation process (cf. [Karnath et al., 2019](#karnath2019)). Afterwards, we masked the extracerebral space, as well as the lateral ventricles and cerebellum to optimise the normalisation 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

### Lesion Analysis

We first used MRIcron ([Rorden & Brett, 2000](#rordenbrett2000); [NITRC, 2008](https://www.nitrc.org/projects/mricron/)) to create descriptive overlap and subtraction lesion plots for all relevant groups. Overlap plots are topographies of all patients’ normalised lesion maps. Only voxels that are damaged in at least 5 patients are depicted and used for further analyses. Subtraction plots are maps that showcase which areas of the brain exhibit lesions more frequently in one patient group (typically with the cognitive deficit of interest) compared to another one (without the deficit of interest).

Subsequently, we analysed the voxel-based lesion maps using mass-univariate general linear models (GLMs) with the NiiStat toolbox ([NITRC, 2014](https://www.nitrc.org/projects/niistat/)) to identify voxels, for which damage is associated with a more severe behavioural deficit. We performed one-sided tests at p<0.05 and corrected for family-wise errors by employing 5000 permutations with maximum statistic permutation ([Nichols & Holmes, 2001](#nicholsholmes2001)).

At first, we analysed it for the entire patient sample to identify damage to which voxels is generally associated with more severe symptoms. This also served as a sanity check to confirm that our results are in line with the literature. Then, we repeated the analysis separately for the female and male patient sample, to investigate if different clusters of voxels are associated with neglect severity in women and men.

### Whole-brain disconnectivity mapping

To identify which WM tracts were damaged by the focal stroke-induced lesions, we used the Lesion Quantification Toolkit (LQT; [Griffis et al., 2021](#griffis2021LQT)). 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](#yeh2018)).

More specifically, the LQT embeds the binary lesion map as a region-of-interest (ROI) into the tractography atlas and filters to 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 the NiiStat toolbox ([NITRC, 2014](https://www.nitrc.org/projects/niistat/)) to investigate if damage to a specific WM tract was significantly associated with more severe behavioural deficits. As already described in 3.1. for the voxel-based lesion-symptom mapping, we repeated this analysis three time: 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 damage as estimated in 3.2., we once again employed the LQT ([Griffis et al., 2021](#griffis2021LQT)) to create parcel-wise disconnectivity matrices for every patient. This was done by combining the HCP-842 connectome atlas ([Yeh et al., 2018](#yeh2018)) with a brain parcellation atlas. We chose the Brainnetome atlas (BN-246; [Fan et al., 2016](#fan2016)) 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)](#griffis2021LQT) recommendations, we defined structural connections between a parcel pair as the number of fibres that bilaterally end within the two parcels. Further, we set our binarisation threshold for the calculation of the structural shortest path lengths (SSPLs) to 50% and set the Gaussian smoothing kernel to 2. This resulted in symmetric 246-by-246 disconnectivity matrices for every patient.

In order to assess which direct disconnections between two grey matter regions are significantly associated with increased (i.e., pathological) scores in the behavioural tasks, we used custom MATLAB scripts employing mass-univariate GLMs. For this, we loaded the symmetric 246-by-246 disconnectivity matrices into MATLAB and removed the diagonal and 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 (All = 40; F= 20; M = 20) (SOURCE). After removing those data, we computed a GLM for the remaining ROI-to-ROI connections, using the disconnectivity score as the independent variable and the behavioural score as the dependent variable. To correct for multiple tests, we calculated 50.000 permutations and computed the maximum statistic permutation (????). This yielded a one-sided corrected threshold at different statistical significance levels.

### Shortest Structural Path Lengths (SSPLs)

### Prediction of Patient Group

[exploratory]

To investigate if it would be possible to predict either a patient’s sex or their patient group (e.g. “female neglect patient” or “male control patient”) from their lesion-derived data, we used a supervised machine learning approach in the form of a nu-support vector machine (nu-SVM; [Schölkopf et al., 2000](#schölkopf2000) & [2001](#schölkopf2001)). The nu-SVM was implemented using custom scripts employing the libsvm package’s MATLAB version ([Chang & Lin, 2011](#changlin2011)).

To create the instance matrix, we concatenated the voxel-wise maps of all patients, such that matrix rows comprised patients, while columns contained the associated binary status (‘damaged’/1 vs ‘healthy’/0) of all their voxels. We then used principal component analysis (PCA) for dimensionality reduction: 52 components were cumulatively needed to explain 95% of the data’s variance. Thus, our instance matrix had a dimension of 206x52.

For labels, we used a numerical representation of either sex (‘1’ = female, ‘2’ = male), patient group (‘1’ = neglect, ‘2’ = control) or sex-specific patient group (‘1’ = female neglect, ‘2’ = male neglect, ‘3’ = female control, ‘4’ = male control).

Once again using the LQT (Griffis et al., 2021), we analysed the lesion-induced disconnectivity on a parcellation-level to identify which direct disconnections between two grey matter regions are significantly associated with increased (i.e., pathological) scores in the behavioural tasks. ~~We combined this with the HCP-842 tractography atlas provided by the LQT to generate structural disconnectivity matrices for every patient.~~

Using custom MATLAB scripts, we analysed associations between parcel-wise disconnections and behavioural scores by employing mass-univariate general linear models (GLM). For this, we firstly loaded the symmetric 246-by-246 disconnectivity matrices into MATLAB and removed the diagonal and 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) = 45; n(female) = 20; n(male) = 25) (SOURCE). After removing those data, we computed a GLM for the remaining ROI-to-ROI connections, using the disconnectivity score as the independent variable and the behavioural score as the dependent variable. We calculated 50.000 permutations and computed the maximum statistic permutation (????). This yielded a one-sided corrected threshold at different statistical significance levels.

## Results

### Clinical and Demographic Data

The mean age at stroke was higher for women than for men. This finding was consistent across all groups: For the entire patient samp

For both the all patients and the neglect patients groups, the mean normalised lesion volume was lower for women than for men. Only in case of the control group did women exhibit marginally larger lesions. [calculate significance]

[description]

[create mean age/sex across groups bar graph]

### Voxel-based Lesion-Behaviour Mapping / Lesion Analysis

* Overlay plots

We used MRIcron ([Rorden & Brett, 2000](#rordenbrett2000); [NITRC, 2008](https://www.nitrc.org/projects/mricron/)) to create topographies of the normalised acute lesion overlaps for all relevant groups (see figure 1). Only voxels lesioned in at least 5 patients were included in the subsequent analyses.

* Subtraction Plots
* NiiStat

### Whole-brain disconnectivity mapping

* 1. Region-to-Region disconnectivity

## Discussion

* **Limitations**
  + Would require sex-specific atlases (maybe even normalization templates?) that don’t exist yet

## Conclusion

## References

[delete this later]

**MRIcron** -> Rorden & Brett, 2000

**Clusterize** -> de Haan et al., 2015

**Clinical** -> Rorden et al., 2012

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## Appendix

### Appendix A: List of Abbreviations

|  |  |
| --- | --- |
| CoC | Centre of Cancellation |
| CT | Computed Tomography |
| DTI | Diffusion Tensor Imaging |
| DWI | Diffusion-weighted Imaging |
| FA | Functional Anisotropy |
| GLM | Generalised Linear Model |
| HCP | Human Connectome Project |
| IOF | Inferior Occipitofrontal Fasciculus |
| IPL | Inferior Parietal Lobule |
| LQT | Lesion Quantification Toolkit |
| MCA | Middle Cerebral Artery |
| MD | Mean Diffusivity |
| MNI | Montreal Neurological Institute |
| MRI | Magnetic Resonance Imaging |
| ROI | Region Of Interest |
| SLF | Superior Longitudinal Fasciculus |
| SOF | Superior Occipitofrontal Fascicle |
| T2FLAIR | T2-weighted Fluid Attenuated Inversion Recovery |
| TPJ | Temporo-Parietal Junction |
| vlPFC | Ventrolateral Prefrontal Cortex |
| WM | White Matter |
| (nu-)SVM | nu-Support Vector Machine |
| SSPL | Shortest Structural Path Length |
| PCA | Principal Component Analysis |

### Appendix B: Supplementary Tables and Figure

**Table S1a:** 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 |
| 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 |

**Table S1b:** Clinical and Demographic Data of Control 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] |  |
| Days between Stroke & Imaging | 2.7 (2.9) [0-11] | 2.4 (2.7) [0-11] | 2.9 (3.0) [0-11] |  |
| Aetiology *(Infarct, Haemorrhage, Both)* | 114, 19, 0 | 51, 12, 0 | 63, 7, 0 |  |
| 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] |  |
| Days between Stroke & Assessment | 2.6 (2.6) [0-12] | 3.9 (2.3) [1-9] | 3.3 (3.0) [0-12] |  |
| 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] |  |
| 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] |  |
| Copying Errors | 0.22 (0.58) [0-4] | 0.27 (0.65) [0-4] | 0.16 (0.51) [0-3] |  |
| 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] |  |
| Visual field defects *(N)* | 15 | 7 | 8 |  |

**Table S2:** Used Scan Modalities for all patients

|  |  |  |  |
| --- | --- | --- | --- |
|  | Total  (N = 206) | Female  (N = 103) | Male  (N = 103) |
| CT | 98 | 57 | 41 |
| T2FLAIR | 54 | 24 | 30 |
| T2FLAIR + T1 | 11 | 4 | 7 |
| DWI | 18 | 8 | 10 |
| DWI + T1 | 19 | 8 | 11 |
| DWI + T2FLAIR | 6 | 2 | 4 |

**Table S3:** Arterial territory for all patients who suffered from an infarct

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total  (N = 172) | Female  (N = 81) | Male  (N = 91) | p-value |
| Anterior | 3 | 3 | 0 |  |
| Anterior/Medial  (incl. Basal Ganglia) | 9 | 8 | 1 |  |
| Medial | 134 | 61 | 73 |  |
| Posterior  (incl. Thalamus) | 22 | 7 | 15 |  |
| (no info) | 4 | 2 | 2 | / |