Sex differences in cognitive abilities have been a widely discussed subject of interest already since the 1870s (for a review see [Shields, 1975](#shields1975)). Inspired by F. J. Gall’s phrenology, research mainly utilised measures of head and brain size in an attempt to explain differences in cognitive capacities (cf. [Cornel, 2014](#cornel2014); [Shields, 1975](#shields1975)). Already early on, it was discovered that men had larger crania and brains compared to women. Researchers such as [Romanes (1887)](#romanes1887) proposed that the comparatively smaller brains of women must be directly responsible for their intellectual inferiority and increased emotionality (see also [Fee, 1979](#fee1979); [Shields, 1975](#shields1975)). In her 1975 review, Shields concluded that many researchers at that time lacked the necessary impartiality to investigate the topic of sex differences, as they aimed “to discover the particular physiological determinants of female inadequacy” (p. 740). Over time as new methods to acquire and analyse (neuro-)psychological data were introduced, several researchers pointed out that those presumed cognitive sex differences were inherently grounded in stereotypical gender roles, and that men and women are more alike than previously assumed ([Broverman et al., 1972](#broverman1972); [Sherman, 1967](#sherman1967); [Woolley, 1914](#woolley1914)).

Even so, the view that the brains and cognitive abilities of men and women are fundamentally different (also referred to as the “gender differences hypothesis”) remained relatively common throughout both the minds of the general population, as well as the scientific community (Hyde, 2005).

With the advent of neuroimaging, new possibilities emerged for more objective research of sex differences in the cognitive neurosciences. Nevertheless, there still is no consensus on the exact neural mechanisms underlying those cognitive sex differences.

Several structural magnetic resonance imaging (MRI) studies and meta-analyses thereof found that the volume of the crania and brain lobes are generally larger in men than in women (Allen et al., 2003; Eliot et al., 2021; Goldstein et al., 2001), with some studies reporting a difference in total brain volume of up to 8-11% (Filipek et al., 1994; Goldstein et al., 2001; Swaab & Hofman, 1984). A study by Allen et al. (2002) found that while the gross volumes of brain lobes differs between the sexes, the proportional sizes of those regions to the total brain volume are nearly identical. Further, it has been reported that certain brain structures differ in (relative) size between the sexes. Some examples include larger volumes in the amygdala, putamen and globus pallidus in males, and larger volumes in the hippocampus and caudate in females (Cosgrove et al., 2007; Giedd et al., 1996a & 1996b). However, such findings are not uncontroversial, as sex differences in the volume of brain structures may disappear when correcting for total brain volume and/or intracranial volume (Choleris et al., 2018; Eliot et al., 2021; Tan et al., 2016).

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

Some researchers consider sexual dimorphism to be stronger in the WM than in the grey matter (Allen et al., 2003; more). Even though men have a higher proportion of cortical WM, women have larger corpora callosa in proportion to their total WM volume (Allen et al., 2003; Gur et al., 1999; Dubb et al., 2003; Ingalhalikar et al., 2013).

Further, multiple studies have found that the corpora callosa of men and women differ in shape: Splenia are larger and more bulbous in women, whereas men have more tubular-shaped splenia, as well as larger genua (Allen et al., 1991; Dubb et al., 2003). Allen et al. (2003) proposed that WM tracts might be less sexually dimorphic than other WM components, such as glial cells and blood vessels.

Studies employing diffusion tensor imaging (DTI) investigated the architecture of WM and its fibre tracts found that over all age ranges, men tend to have increased measures of fractional anisotropy and decreased mean diffusivity than women. Higher measures of fractional anisotropy are thought to reflect increased axonal diameter, fibre bundle density and myelination, while the inverse relation holds for mean diffusivity ([Boespflug et al., 2011](#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.

DTI may not only be used to study isolated fibre tracts, but also to study the structural connectome of brain networks. Studies have found that women have a greater local brain network efficiency (Yan et al., 2011), as well as increased cortical connectivity (Gong et al., 2009) – independent of total brain volume. A large-scale DTI study investigating sex-differences in the structural connectome by Ingalhalikar et al. (2013) found a higher proportion of intrahemispheric WM tracts in men and a higher ratio of interhemispheric connections, especially via the corpus callosum, in women. Based on these differences in the ratio of inter- and intrahemispheric connections, they argue that men exhibit a greater hemispheric asymmetry than women and further, that these support the hypothesis that differences in hemispheric asymmetry give rise to sex differences in cognitive abilities (Grabowska, 2016; Ingalhalikar et al., 2013; Kovalev et al., 2003; see Hirnstein et al., 2019 for a review).

Generally, hemispheric asymmetry in the functional connectome (also referred to as functional cerebral asymmetry (FCA)) is regarded as a fundamental principle of brain organisation. Well-known examples for this are the left lateralisation of language and the right lateralisation of visuospatial processing (for reviews see Hausmann et al., 2017; Hirnstein et al., 2019), which are present in most, albeit not all, individuals (Kim et al., 1990; Hausmann et al., 1998). A number of studies have compared FCA between the sexes for different modalities and tasks and found small, but robust, effects of women exhibiting lower levels of FCA compared to men tasks (Hiscock et al., 1995, 1999 & 2001; Liu et al., 2009; Voyer, 1996).

There is also some evidence that anatomical hemispheric asymmetries and FCAs are related.

* + 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).
* Also Hirnstein et al., 2013
* Gotts et al, 2013

[cognitive differences]

* According to this theory, male brains possess greater hemispheric asymmetry with more pronounced intrahemispheric connections, whereas female brains have stronger interhemispheric connectivity and thus, are organised more bilaterally. [where the left hemisphere would be clearly specialized for verbal processing and the right hemisphere for spatial processing. In females, the brain would be more “bilateral”, that is, both the left and the right hemisphere would be carrying out verbal processing]
* [Ingalhalikar et al. (2013)](#ingalhalikar2013) interpreted those findings as male brains being structured in a way that facilitates spatial processing and coordinated motor action, while female brains promoting attention, memory and verbal abilities.
* Contrary to popular conceptions of sex differences, meta-analyses and meta-syntheses demonstrated that if any gender differences were detectable in cognitive tests, they often 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. [(details) Voyer et al.’s (2016)](#voyer2016) meta-analysis identified a significant, albeit small male advantage in visuospatial working memory tasks. Thus, the “gender similarities hypothesis” was coined, stating that men and women are similar in most, but not all, psychological domains and that most existing differences tend to be small in magnitude ([Hyde, 2005](#hyde2005)).

[sex hormones may be the reason for differences in hemispheric asymmetry]

Many researchers argue that those differences in brain organisation and cognition may be caused, or at least influenced, by sex hormones (e.g., Cosgrove et al., 2007; Grabowska, 2016; Kimura & Hampson, 1994; Varnava et al., 2007; Hirnstein et al., 2017)

**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 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. Women suffered more often from strokes (6.44 million incident cases, 56.4 million prevalent cases) compared to men (5.79 million incident strokes, 45.0 million prevalent cases) (Feigin et al., 2021). Most likely, this can at least be partially attributed to the higher life expectancy of women (Giroud et al., 2017; Bonkhoff et al., 2021). Nevertheless, there were no significant sex differences in the number of stroke-related deaths across the different age groups ([Feigin et al., 2021](#GBDstroke2021)).

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; 2009; Silva et al., 2010). Multiple studies have found that in the chronic post-stroke phase women are more likely to have significantly decreased quality of life, including impaired locomotor function and mental abilities, compared to men (Gibson, 2013; Reeves et al., 2008, Sturm et al., 2004) – the effects of which can even persist up to 5 years after initial stroke onset (Fukuda et al., 2009). Importantly, the increased stroke severity in women remains significant even after adjusting for age differences at stroke onset and does not arise from differences in lesion size (Bonkhoff et al., 2021; Dehlendorff et al., 2015, Silva et al., 2010).

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

Further, Bonkhoff et al. (2021) detected no differences in lesion volume between men and women, but found that more regions contributed to stroke severity in women and thus, that similar lesion patterns elicit more severe strokes in women, compared to men. The most robust sex differences were strictly left lateralised, meaning that women are more vulnerable to the effects of a left hemispheric stroke, especially to regions supplied by the PCA, such as the hippocampus, thalamus, or precuneus. Interestingly, those sex-specific effects were not present when comparing men and women below the age of 52, which is the median age of menopause onset (McKinley et al., 1992), suggesting that sex hormones play an important role in the neuropathology of stroke.

Many researchers believe that (neuro)biological sex differences, such as sex chromosomes or sex steroid hormones that contribute to different responses to cerebral ischemia ([Bonkhoff et al., 2021](#bonkhoff2021); [Bushnell et al., 2018](#bushnell2018); [Gibson, 2013](#gibson2013)). 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](#gibson2013); [Liu et al., 2010](#liu2010); [Wise et al., 2001](#wise2001)). 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., 2015; Suzuki et al., 2009).

There is some experimental evidence in animal models that showed that acute administration of oestradiol reduces infarct size and tissue damage, as well as improves post-infarct blood flow ([Gibson et al., 2009](#gibson2009); [Liu & Yang, 2013](#liuyang2013); McCullough et al., 2001; [Suzuki et al, 2009](#suzuki2009)). Interestingly, oestradiol administration also reduces injury in male animals, suggesting that its neuroprotective effects are independent of (gonadal) sex (Bushnell et al., 2018; Manwani et al., 2015). However, clinical trials in humans have not been successful so far (CHECK) ([Gibson et al., 2013](#gibson2013); [Henderson & Lobo, 2012](#hendersonlobo2012)).

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, 2013; Manwani & McCullough, 2012; Sohrabji et al., 2017). [🡪 this sentence is too long/complicated/simply bad, please help]

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 ([Li et al., 2005](#li2005); [Liu et al., 2008](#liu2008); Koellhoffer & McCullough, 2013). The same effects have also been demonstrated in aged mice: At low sex steroid levels, animals with XX chromosomes had larger infarcts, higher inflammatory responses and more severe neurological deficits. However, the detrimental effect of a second X chromosome only emerged after reproductive maturation. Therefore, it seems likely that ischemic strokes are affected by a complex interaction of aging, sex-specific neuro-steroids, and sex chromosomes (Bushnell et al., 2018; McCullough et al., 2013; Manwani et al., 2015).

**Neglect**

Stroke is a neurological condition that can cause a number of subsequent neuropsychological conditions, as even small focal lesions can significantly disrupt the brain network’s 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](#limalhotra15); [Stone, Halligan & Greenwood, 1993](#stone93)). Neglect is often described as a supramodal disorder with a “heterogenous collection of symptoms”. The core symptoms include pathological spatial biases towards the ipsilesional (i.e., typically right) side of space, affecting gaze direction and exploration at rest, as well as during goal-directed behaviour. At the same time, patients have difficulties in orienting towards the contralesional side and will typically ignore stimuli located on that side. ([Becker & Karnath, 2010](#beckerkarnath2010); Corbetta & Shulman, 2011; [Karnath, 2015](#karnath2015); [Karnath & Rorden, 2012](#karnathrorden2012)).

These core symptoms become 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 Section 2.2. Behavioural Data for more detail; see also Rorden & Karnath, 2010 for an overview).

Those characteristic spatial biases 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). Even though neglect is considered to be a basal disorder, meaning that the symptoms do not merely emerge in higher-order cognitive tasks, the biases are not due to underlying paralysis or sensory deficits (Karnath, 2012; Kleinman et al., 2008)

* differentiate between egocentric & allocentric; either the contralesional side of space or object is neglected
* can be alleviated/overcome for a short period of time through top-down (e.g., verbal request) or bottom-up (e.g., visual cues) input

While there is no consensus on the exact prevalence of neglect, estimates of a prevalence of about 30% in the acute phase after stroke seem likely (e.g.: Bowen et al., 1999; Corbetta, 2014; Hammerbeck et al., 2019; but see also Ten Brink et al., 2017 or Stone et al., 1993 for more extreme estimates). Hammerbeck et al. (2019) established a sex difference in neglect prevalence in an analysis of data from more than 88,000 stroke patients, with women exhibiting a prevalence of 33% versus 27% in men.

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).

* RH perisylvian network seems to underlie spatial orientation, its disruption leads to neglect;
* Speech (LH) & spatial orientation (RH) organised in homologous networks/areas
* Subcortical lesion (e.g. to thalamus (esp. pulvinar) & BG (esp. putamen & sometimes caudate nucleus)) can also induce neglect
  + Theory: not the lesion to those neurons/regions themselves causes neglect, but rather the long-range effects; reduction of metabolism/blood perfusion 🡪 reduced function in perisylvian network

Karnath, H.-O. (2012). Neglect. In H.-O. Karnath & P. Thier (Eds.), Kognitive Neurowissenschaften (3rd Ed., pp. 279-292). Springer.