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 (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) (GBD 2019 Stroke Collaborators, 2021). This can likely be at least 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 ([GBD 2019 Stroke Collaborators, 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 comorbidities, 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 frontooccipital fasciculus, superior longitudinal fasciculus, corticospinal tract, and anterior thalamic radiation, also correlated with higher stroke severity. They 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 – the median age of menopause onset – which suggests 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)).

It has been well established in 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)). These hormones 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 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 apoptotic/cell death mechanisms, stimulating angiogenesis/the formation of new blood vessels, decreasing cerebral vascular resistance, and thus, improving cerebral blood flow (Krause et al., 2006; Manwani et al., 2014; Suzuki et al., 2009). 🡪 [too much jargon?]

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., 2014). However, clinical trials in humans have not been successful so far (CHECK) ([Gibson et al., 2013](#gibson2013); [Henderson & Lobo, 2012](#hendersonlobo2012))

* Manwani et al. (2014):
  + Ischemic stroke is recognized as a sexually dimorphic disease with women enjoying a lower stroke incidence relative to men until an advanced age.1 Preclinical studies in animal models confirm and replicate this clinical epidemiology. 2,3 This sexual dichotomy has largely been attributed to the activational effects of gonadal hormones—predominantly androgens and estrogens. 4 The male gonadal hormone, testosterone has been shown to contribute to the male ‘ischemic sensitivity’ phenotype both clinically5 and in animal models. 6,7 However, the role of testosterone in ischemic stroke remains controversial, as other studies have seen an age and dose-dependent protection with testosterone supplementation. 8 In contrast, estrogens have been consistently shown to be neuroprotective in the majority of preclinical studies. 9 Ovariectomized females have increased histologic injury compared with ovary intact females, and this is reversed with estradiol supplementation. Exogenous estradiol administration also reduces injury in males, suggesting that estrogen exercises its beneficial effects independently of the gonadal sex
* 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
  + These hormones clearly contribute to, but do not fully account for, sex-specific responses to cerebral ischemia. (McCullough et al., 2003)
  + The underpinning mechanisms responsible for this shift from an ‘‘ischemia-protected’’ to an ‘‘ischemia-sensitive’’ phenotype in aging females are not clearly defined but involve loss of estrogen, increased systemic inflammation, and age-related changes in gene expression (Sohrabji et al., 2017)

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 is important to note that the strongest observed sex differences were strictly lateralized to the left hemisphere. Previous research suggests that male or female sex and respective sex hormones contribute to induce functional cerebral asymmetries27. Men appear to have a stronger hemispheric asymmetry; however, while robustly replicated, determined effect sizes have been small28. Such an enhanced asymmetry in men was also found in some early lesion studies on intelligence29. However, further early lesion studies suggested that lateralization differences between the sexes might be even more complex, i.e., female brains may be asymmetric to a comparable degree, yet in different ways30,31. In particular, it was found that lefthemispheric lesions in women led to both verbal and performance scale IQ deterioration, while only one quality—either verbal or performance—was affected in all other lesion and sex constellations30,32.
* Nonetheless, we also find that particularly women are vulnerable to left-hemispheric lesions. Indeed, we can relate the most robust excess vulnerability of female vs. male patients to anatomically precise lesion locations in the left-hemispheric PCA territory, specifically featuring hippocampal, thalamic, and precuneal regions. Based on existing knowledge on these regions’ physiological functions, it may be suggested that lesions in these regions more likely underlie (higher) cognitive, than, for example, basic motor functions
* We furthermore observed signs of an interaction effect of sex with age, when stratifying the entire sample based on the median age at menopause26. None of the female-specific lesion pattern effects could be detected, when comparing men and women below the age of 52 years.
* Wu et al., 2015:
  + Our findings suggest that if one does not take into consideration age, sex, or lesion volume, locations of the lesion are associated with degree of stroke severity and long-term disability—and more so with lesions in the left hemisphere. Interestingly, including age and sex into our model for mRS increased the number of voxels in the right hemisphere. This suggests that for a given age and sex, the risk that a patient will have greater admission stroke severity and long-term disability is increased by where the stroke is located. Patients with strokes in certain regions of the right hemisphere—in particular, the insula, operculum, or putamen—are more likely to have more severe long-term disability.
  + Once volume is included in the models, lesion location in the right hemisphere is no longer significant for either NIHSS or mRS. That is, for a given acute DWI lesion volume for a patient with specific age and sex, if the lesion is located in certain regions (in particular, left-hemispheric white matter and subcortical gray matter), the likelihood of greater severity on admission and long-term disability is increased. We speculate that the reason individual voxels in the right hemisphere are no longer significant once volume is taken into consideration is that the size of the lesion in right hemispheric strokes determines the degree of admission stroke severity and outcome, independent of where the large lesion is located in the right hemisphere. A major determinant of poor outcome in right hemispheric stroke is unilateral neglect,19 which is typically associated with large strokes.