**Sex Differences in Brain Connectivity**

Sex differences in cognitive abilities have been a widely discussed subject already since the 1870s (for a review see Shields, 1975). The so-called “gender differences hypothesis”, which maintained that the brains and cognitive abilities of men and women are fundamentally different, remained relatively common throughout both the minds of the general population, as well as the scientific community (Hyde, 2005; Hirnstein et al., 2019). However, contrary to popular conceptions of psychological sex differences, numerous meta-analyses and meta-syntheses demonstrated that if any gender differences are detectable in cognitive tests, they often are negligibly small (Hirnstein et al., 2019; Hyde, 2005; Zell et al., 2015). Hyde (2005 & 2014) found that in most cognitive tasks, women and men achieved equal performances. The strongest and most robust difference in cognitive tasks that a meta-synthesis by Zell et al. (2015) meta-synthesis identified was better performance of men in mental rotation tasks. Voyer et al.’s (2016) meta-analysis identified a significant, albeit small male advantage in visuospatial working memory tasks. A few studies found a small female advantage in certain language tasks, such as verbal fluency, but this effect was not consistently found across other tests in the language domain (Hyde, 2014 & 2016; Sommer et al., 2004). Since most existing differences tended to be small in magnitude, this led researchers to coin the “gender similarities hypothesis”, stating that men and women are similar in most, but not all, psychological domains (Hyde, 2005; Zell et al., 2015).

Still, even differences that are small in magnitude may be highly relevant. [why?: establish necessary baselines for patient-centred / personalised medicine] There still is no consensus regarding the exact neurobiological mechanisms underlying cognitive sex differences, but a complex interaction of nature and nurture has been proposed (Hirnstein et al., 2019; Miller & Halpern, 2014). A particularly influential theory proposes that cognitive sex differences may arise from differences in brain connectivity and hemispheric asymmetry (Ingalhalikar et al., 2013; Pletzer, 2014; see Hirnstein et al., 2019 for a review).

A large-scale diffusion tensor imaging (DTI) study by Ingalhalikar et al. (2013) investigating sex-differences in the structural connectome found a higher proportion of intrahemispheric WM tracts in men, and a higher ratio of interhemispheric connections, especially via the corpus callosum, in women. In other words, men exhibit a stronger hemispheric asymmetry. These differences in the ratio of inter- and intrahemispheric connections grew more pronounced throughout development from childhood and adolescence to (young) adulthood. Further, they found men to have significantly stronger intrahemispheric connections between the four lobes (e.g., between the right frontal and right temporal lobes) and increased intralobar connectivity, compared to women. Moreover, they concluded that male brains possess enhanced modularity, meaning that their brains can clearly be delineated into sub-networks that emphasise local short-range connectivity within the lobes.

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

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

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

A number of studies have compared functional lateralisation between the sexes for different modalities and tasks and found lower levels of lateralisation in women compared to men (Hiscock et al., 1995, 1999 & 2001; Liu et al., 2009; Voyer, 1996). This means that cognitive representations and brain activation patterns tend to be more bilateral and symmetrical in women, while they are largely restricted to one hemisphere in men – or in other words: in female brains there is a less strict separation of functions between the hemispheres. Ingalhalikar et al. (2013) argue that those differences in functional lateralisation are related to the different ratios of inter- and intrahemispheric connections between the sexes: Male brains possess increased levels of lateralisation with more pronounced intrahemispheric connections, whereas female brains have stronger interhemispheric connectivity and thus, process information more symmetrically.

While so far there is not enough research to determine if anatomical WM asymmetries and functional lateralisation are really related in such a way (for reviews see Corballis & Häberling, 2017; Ocklenburg & Güntürkün, 2012), many researchers argue that differences both in brain connectivity may be caused, or at least influenced, by sex hormones (e.g., Cosgrove et al., 2007; Grabowska, 2017; Hirnstein et al., 2019; Kimura & Hampson, 1994).

Sex hormones, such as oestradiol, progesterone, and testosterone, have been shown to be able to alter neuronal excitability (Hausmann, 2016; Rupprecht, 2003) and there is great evidence that functional lateralisation fluctuates throughout the menstrual cycle due to the varying levels of those hormones (e.g., Bibawi et al., 1995; Hausmann, 2005; Hausmann et al., 2002; Wisniewski, 1998). Studies have established that lateralisation is stable over time in men, as well as in post-menopausal women. Further, there is evidence that high levels of progesterone and oestradiol during the midluteal phase may down-regulate interhemispheric interactions and thus, further decrease lateralisation, whereas increased levels of functional lateralisation were found during the menses when levels of oestradiol and progesterone are the lowest (Bibawi et al., 1995; Hausmann et al., 2002; Hausmann & Güntürkün, 2000; Mead & Hampson, 1997).