Stroke can cause a number of ensuing neuropsychological conditions, as even small focal lesions can significantly disrupt the brain network’s overall connectivity and thus, its functionality (Carrera & Tononi, 2014; Griffis et al., 2019). One syndrome that commonly occurs during the acute stage after predominantly right hemispheric stroke is visuospatial neglect, though it may also be caused by other forms of unilateral brain injury (Karnath & Rorden, 2012; [Li & Malhotra, 2015](#limalhotra15); [Stone et al., 1993](#stone93)). Neglect is often described as a supramodal disorder of spatial attention with a “heterogenous collection of symptoms” (Corbetta et al., 2005; Karnath & Rorden, 2012). The core symptoms include a pathological spatial bias towards the ipsilesional (i.e., typically right) side of space, affecting both gaze direction and exploration. This manifests as sustained and spontaneous deviation of the head- and eye-position towards the ipsilesional side at rest, as well as during goal-directed behaviour, and it persists even in complete darkness (Becker & Karnath, 2010; Karnath, 2012; Karnath & Fetter, 1995). At the same time, patients have difficulties in orienting towards the contralesional side and will typically ignore information located there ([Becker & Karnath, 2010](#beckerkarnath2010); Corbetta & Shulman, 2011; [Karnath, 2015](#karnath2015); [Karnath & Rorden, 2012](#karnathrorden2012)).

Typically, the behavioural core symptoms of neglect, ~~in the form of pathological deviation of the patients’ eyes and heads towards the ipsilesional side with the additional omission of contralesional located information~~, manifest with reference to the patient’s egocentre, i.e., relative to their own body centre (Corbetta & Shulman, 2011; Karnath & Rorden, 2012). However, the behavioural deficits may also occur in an allocentric reference frame: Patients with allocentric neglect ignore the left side of an object (rather than the overall space), irrespective of the object’s location relative to the patient (Li et al., 2014; more). Although some authors argue that ego- and allocentric neglect can dissociate (Hillis et al., 2005), others report significant interactions: For example, the presentation of stimuli in the (egocentric) contralesional space may result in a more severe allocentric bias (Li et al., 2014; Rorden et al., 2012).

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 (Heilman & Valenstein, 1979; Karnath, 2012).

Neglect severely affects the patients’ everyday life, especially in the acute phase (Hammerbeck et al., 2019; Wee & Hopman, 2008). In more harmless cases, patients may fail to respond to people talking to them from their left side or might only eat from the right side of their dish – but in more severe cases, neglect may cause patients to ignore obstacles located on their contralesional side and thus, make them more prone to the risk of falling and injuring themselves (Bartolomeo et al., 2007; Hammerbeck et al., 2019; Urbanksi et al., 2011). Though the symptoms may be alleviated or overcome for a short period of time, this requires top-down (e.g., verbal request) or bottom-up (e.g., visual cues) input, as often times patients are not aware of their deficit (Karnath, 2012; more).

While there is no consensus on the exact prevalence of neglect, estimates of about 30% in the acute phase after stroke seem likely (e.g.: Bowen et al., 1999; Corbetta, 2014; Hammerbeck et al., 2019; but see also Ten Brink et al., 2017 or Stone et al., 1993 for more extreme estimates). Hammerbeck et al. (2019) discovered a sex difference in neglect incidence in their analysis comprising more than 80,000 stroke patients, with women exhibiting a prevalence of 33% versus 27% in men. Recovery rates during the post-acute phase are relatively high at 70-80% (Demeyere & Gillebert, 2019), therefore the prevalence rates of chronic neglect are considerably lower than for acute neglect. Current estimates for chronic neglect prevalence vary from 8-12% (Jehkonen et al., 2000) to up to 17% (Esposito et al., 2021). Still, neglect is commonly considered to be negative predictor for functional outcome in stroke recovery (Jehkonen et al., 2000 & 2007; Wee & Hopman, 2008; Wu et al., 2015).

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 right hemispheric perisylvian network, including the temporo-parietal junction (TPJ), inferior parietal lobule (IPL), superior and middle temporal cortex, insula, and ventrolateral prefrontal cortex (vlPFC), seems to underlie spatial orientation and it has been proposed that its disruption likely contributes to the core neglect deficits (Bartolomeo et al. 2007; Corbetta et al., 2005; Karnath, 2012; [Karnath & Rorden, 2012](#karnathrorden2012)). Other notable cortical regions that have been implicated in neglect are the posterior parietal cortex, inferior frontal cortex, angular gyrus, supramarginal gyrus (Buxbaum et al., 2004; Corbetta & Shulman, 2011; He et al., 2007; Hillis et al., 2005; Verdon et al., 2009). However, there is still an ongoing debate surrounding the exact neurological correlates of neglect with many studies reporting contradictory findings, especially regarding the role of the temporal and parietal cortices in the syndrome (Bartolomeo et al., 2007; Karnath et al., 2001; more).

Further, lesions to certain subcortical regions, such as the thalamus and the basal ganglia (BG), have also been shown to be associated with neglect – however, it is hypothesised that not the lesion to those regions themselves causes neglect, but rather that the disorder emerges from the long-range effects of reduced functionality in the perisylvian network (Karnath, 2012; more).

The idea that the spatial-attentional processes whose disruption underlie neglect might emerge from damage to large networks rather than single brain areas has already been discussed for a long time (Bartolomeo et al., 2007; Corbetta, 2014; Mesulam, 1981; Saxena et al., 2022; Vaessen et al., 2016).

Several studies in animal models have demonstrated that severe experimental neglect could only be induced when disrupting WM connections between the parietal and frontal lobes, whereas the ablation of either of those cortices or a combined ablation resulted in little, if any, neglect symptoms (Burcham et al., 1997; Gaffan & Hornak, 1997; Reep et al., 2004).

Interestingly, this is in line with the results obtained from fibre-tracking studies in neglect patients. It has been established that the WM fibres connecting the perisylvian network, specifically the superior longitudinal fasciculus (SLF), arcuate fasciculus (AF), the inferior fronto-occipital fasciculus (IFOF) and the superior fronto-occipital fasciculus (SFOF) have been shown to be particularly vulnerable to causing neglect after being damaged (Chechlacz et al., 2010; He et al., 2007; Karnath et al., 2009; Urbanski et al., 2011).

DTI studies by Urbanksi et al. (2011) and Thiebaut de Schotten et al. (2014) confirmed that disconnections in the fronto-parietal network contribute to the development of chronic neglect and specifically, damage to the SLF was identified to be the best predictor of neglect. Damage to the IFOF and dorsolateral thalamus was also found to contribute to neglect severity, though not as strongly and consistently as SLF disconnections.

Bartolomeo et al. (2007) and Saxena et al. (2022) found neglect to commonly emerge from intrahemispheric frontoparietal disconnections and to manifest with greater severity than from focal lesions in any of the regions commonly associated with neglect, such as the right perisylvian network. Further, Saxena et al. (2022) detected a strong association of neglect severity with disconnections involving the (middle) temporal cortex, as well as disconnections involving the BG – specifically, the putamen. [–> methodology?]

While the majority of those results were obtained from patients who suffered from an infarct in the territory of the MCA, Bird et al. (2006) described similar associations in patients with PCA-infarction: In those patients, intrahemispheric disconnections of the WM tracts between the parahippocampal gyrus and the angular gyrus was significantly correlated with neglect severity, whereas damage to the individual regions was found to not be sufficient for manifesting neglect. Further, they found that if those patients suffered from additional lesions to the splenium of the corpus callosum, which caused interhemispheric disconnections, neglect severity increased.

Griffis et al. (2019 & 2021) developed a technique to assess brain network dysfunction after stroke based on an indirect measure of structural disconnections – without the need for acquiring DTI images (see Chapter 3: Data Analysis for details). They were able to replicate the findings obtained in seminal studies in the past (see above), in that they also found neglect severity to be primarily linked to disconnections of the SLF, and to a lesser extent of the AF, in the right hemisphere. Moreover, they found that those direction disconnections typically associated with neglect further disrupt connections between the inferior frontal junction and all lobes of the right hemisphere. Those findings are consistent with the ones by He et al. (2007) and support the notion that neglect may arise from long-range interference in the function of the attentional network.

While it still has not been resolved why lesions in the WM increase neglect severity compared to lesions in the GM, Bartolomeo et al. (2007) hypothesise

* + Furthermore, we propose that disconnection might produce more of a deficit than cortical damage/dysfunction alone through several, not mutually exclusive, mechanisms: 1) Damage to the tightly packed fibers of the white matter may result quantitatively more disrupting than damage to equivalent cortical volumes, by impairing the functioning of larger cortical areas (Fig. 3). 2) Brain networks are composed of cortical modules interacting with each other. Disturbed communication between modules might thus produce not only cortical hypofunctioning but also hyper- or inadequate functioning of several cortical areas, resulting in a more severe disintegration of complex functions than the deficit relative to lesion to isolated modules (Catani and ffytche 2005). 3) Cortical lesions may leave the possibility for other cortical areas to functionally compensate for the deficit, through the phenomena of brain plasticity (see, e.g., Duffau 2005); on the other hand, white matter damage, which provokes the dysfunction of a whole network of connected areas, might render compensation more difficult to obtain.
* Chechlacz et al., 2010:
  + Allocentric neglect was associated with damage to posterior cortical regions (posterior superior temporal sulcus, angular, middle temporal and middle occipital gyri).
  + In contrast, egocentric neglect was associated with more anterior cortical damage (middle frontal, postcentral, supramarginal, and superior temporal gyri) and damage within subcortical structures.
  + Damage to intraparietal sulcus (IPS) and the temporo-parietal junction (TPJ) was associated with both forms of neglect.
  + Importantly, we showed that both disorders were associated with white matter lesions suggesting damage within long association and projection pathways such as the superior longitudinal, superior fronto-occipital, inferior longitudinal, and inferior fronto-occipital fascicule, thalamic radiation, and corona radiata. We conclude that distinct cortical regions control attention (a) across space (using an egocentric frame of reference) and (b) within objects (using an allocentric frame of reference), while common cortical regions (TPJ, IPS) and common white matter pathways support interactions across the different cortical regions
* Urbanski et al., 2011:
  + Combining difusion tensor imaging (DTI) tractography (Basser et al. 1994) with direct electrical stimulation of the brain (Duffau et al. 1999), Thiebaut de Schotten et al. (2005) showed that the temporary inactivation of the likely human homologue of the second branch of the superior longitudinal fasciculus (SLF II), a fronto-parietal white matter pathway (Schmahmann and Pandya 2006), can provoke transitory signs of left neglect. This evidence confirmed and specified the findings of Leibovitch et al. (1998) and Doricchi and Tomaiuolo (2003), who reported a maximum lesion overlap on the SLF in stroke patients with neglect. A maximum lesion overlap on white matter was also reported in the relatively rare cases of neglect after lesions in the territory of the right posterior cerebral artery (Mort et al. 2003; Park et al. 2006). The overlap location was compatible with the trajectory of the inferior longitudinal fasciculus (ILF; Bird et al. 2006).
  + The asAF/SLF III resulted to be significantly involved in neglect patients, whereas the participation of the psAF was more variable, leading to statistical indeterminacy (Fig. 2). Concerning the external capsule area, which referred to more ventral networks, the IFOF, but not the ILF, was disconnected in our sample of neglect patients.
  + Disconnection of asAF/SLF III is consistent with accumulating evidence on the importance of SLF damage in neglect. This evidence comes from animal studies (Gaffan and Hornak 1997; Reep et al. 2004), from lesion overlap in stroke patients (Doricchi and Tomaiuolo 2003; Thiebaut de Schotten et al. 2008; Verdon et al. 2010) and from neurosurgical patients, who showed either transitory deficits upon temporary electrical inactivation of the SLF (Thiebaut de Schotten et al. 2005), or the occurrence or worsening of neglect signs after surgical interruption of the SLF (Shinoura et al. 2009).
  + Although damage to the IFOF might not be necessary by itself to produce signs of neglect [for example, the IFOF was intact in both the patients with neglect and SLF damage described by Shinoura et al. (2009)], it might contribute to neglect signs by depriving visual cortex of top-down modulation from more anterior regions, or by decreasing the influence of visual input on the right VLPFC, with consequent deterioration of patients’ level of arousal (Doricchi et al. 2008; Urbanski et al. 2008) or sustained attention (see Singh-Curry and Husain 2009).
* Ciaraffa et al., 2011:
  + We present the anatomo-clinical study of a patient presenting with severe acute left visual neglect due to ischemic infarct limited to the right cerebral hemisphere white matter. Magnetic resonance diffusion tensor imaging tractography was instrumental to accurately localize the injury to the right arcuate fasciculus that is a component of the large-scale networks controlling visuo-spatial attention. These results add to a growing appreciation that neglect may result from disruption of a distributed attentional network
* Bartolomeo et al., 2007:
  + Furthermore, we propose that disconnection might produce more of a deficit than cortical damage/dysfunction alone through several, not mutually exclusive, mechanisms: 1) Damage to the tightly packed fibers of the white matter may result quantitatively more disrupting than damage to equivalent cortical volumes, by impairing the functioning of larger cortical areas (Fig. 3). 2) Brain networks are composed of cortical modules interacting with each other. Disturbed communication between modules might thus produce not only cortical hypofunctioning but also hyper- or inadequate functioning of several cortical areas, resulting in a more severe disintegration of complex functions than the deficit relative to lesion to isolated modules (Catani and ffytche 2005). 3) Cortical lesions may leave the possibility for other cortical areas to functionally compensate for the deficit, through the phenomena of brain plasticity (see, e.g., Duffau 2005); on the other hand, white matter damage, which provokes the dysfunction of a whole network of connected areas, might render compensation more difficult to obtain.
* Corbetta, 2014:
  + The syndrome is worse for large lesions and lesions that go deep into the white matter. Experimental lesions in monkeys disconnecting the frontoparietal white matter cause more severe neglect than lesions that affect the frontal or parietal cortex alone (Gaffan & Hornak, 1997). Because fibertract white matter pathways connect sensory posterior to motor anterior regions of the brain, the whitematter damage is likely responsible for the multimodal sensory and motor impairment in hemispatial neglect (Bartolomeo et al., 2007).
  + In other words, neglect is a syndrome of disrupted integration between multiple regions of the brain. In humans, the region of the white matter more closely associated with severe neglect include the dorsal periventricular white matter that contain fibers of the superior longitudinal fasciculus (SLF, branches I–III) connecting dorsal prefrontal (e.g., frontal eye field) with parietal regions (e.g., intraparietal sulcus [IPS]), ventral prefrontal regions (e.g., inferior frontal gyrus) with ventral (e.g., temporoparietal junction [TPJ]) and dorsal parietal (e.g., IPS) regions. These cortical regions are part of two cortico–cortical networks involved in the control of attention and whose dysfunction plays a critical role in the pathogenesis of neglect (see below) (Corbetta & Shulman, 2011). It is important to underscore that symptoms of hemispatial neglect can be similar for damage to different locations in the brain. Our patient’s symptoms in the right inferior frontal/anterior insula cortex may be indistinguishable from those of patients with lesions in the basal ganglia or temporoparietal region. This suggests two important insights. First, hemispatial neglect is a “network” problem, whereby a similar abnormal behavior emerges when damaging different parts of the brain connected as a network (►Fig. 1). That is why damage to the white matter, by disconnecting multiple nodes of the network, causes more severe neglect than just cortical damage.
* Verdon et al., 2009:
  + Our anatomical voxel-based lesion-symptom mapping analysis pointed to specific neural correlates for each of these components, including the right inferior parietal lobule for the perceptive/visuo-spatial component, the right dorsolateral prefrontal cortex for the exploratory/visuo-motor component, and deep temporal lobe regions for the allocentric/object-centred component. By contrast, standard anatomical overlap analysis indicated that subcortical damage to paraventricular white matter tracts was associated with severe neglect encompassing several tests. Taken together, our results provide new support to the view that the clinical manifestations of hemispatial neglect might reflect a combination of distinct components affecting different domains of spatial cognition, and that intra-hemispheric disconnection due to white matter lesions might produce severe neglect by impacting on more than one functional domain.
* Griffis et al., 2021:
  + In addition, hemi-spatial neglect has been linked primarily to disconnections of the right superior longitudinal fasciculus (SLF) (Shinoura et al., 2009; Thiebaut De Schotten et al., 2014; Toba et al., 2018), while contralesional motor deficits have been linked to disconnections of the ipsilesional cortico-spinal tract (CST) (Feng et al., 2015; Karnath and Rennig, 2017; Lin et al., 2018).
  + The severity of hemi-spatial neglect, as estimated by the attention visual field factor scores, was most strongly correlated with the severity of disconnections sustained by the right SLF. Hemi-spatial neglect severity also correlated with the severity of disconnections sustained by the right AF and right frontal aslant tract (FAT), which have also been previously implicated in post-stroke visuo-spatial neglect (Carter et al., 2017; Thiebaut De Schotten et al., 2014). Left motor deficit severity was most strongly correlated with the severity of disconnections sustained by the right CST. Left motor deficit severity was also strongly correlated with the severity of disconnections sustained by the right fronto-pontine and parieto-pontine pathways, which are part of a poly-synaptic relay linking ipsilesional cortical regions to the contralesional cerebellum (Lu et al., 2011; Middleton and Strick, 2001) that has been implicated in motor deficits after stroke (den Ouden et al., 2019) and that is likely important for motor control (Stoodley et al., 2012).
  + The thresholded maps shown in Fig. 7**C** clearly show that language deficits were most strongly correlated with disconnection severities for voxels located along the trajectories of the left AF and left IFOF, while hemi-spatial neglect was most strongly correlated with disconnection severities for voxels located along the trajectory of the right SLF, and left motor deficits were most strongly correlated with disconnection severities for voxels located along the trajectory of the right CST (Fig. 7**C**, third row).
  + The severity of hemi-spatial neglect was most strongly correlated with the severity of white matter disconnections between parcels in right lateral pre-frontal cortices and parcels in right temporal and parietal cortices, consistent with disconnections of the right SLF and right AF. The severity of left motor deficits was most strongly correlated with the severity of white matter disconnections between parcels in right somatomotor cortex and parcels in the right thalamus, putamen, and the brainstem, consistent with disconnections of the right CST and right cortico-thalamic/cortico-striatal projections.
  + The severity of hemi-spatial neglect was most strongly correlated with indirect disconnections between a parcel located near the right inferior frontal junction (IFJ) (Muhle-Karbe et al., 2016) associated with the ventral attention/salience networks (i.e. per the Schaefer et al., 2018 7-network partition) and parcels distributed throughout the right frontal, right temporal, right parietal, and right occipital lobes (Fig. 7**E**, middle), suggesting that the direct disconnections associated with spatial neglect (Fig. 7**B-D**, middle) tend to disrupt indirect pathways between the right IFJ and parcels distributed throughout the right hemisphere. Interestingly, this finding is consistent with previous work suggesting that this region may integrate information between the ventral and dorsal attention systems and implicating its long-range functional interactions in the pathogenesis of spatial neglect (Asplund et al., 2010; He et al., 2007). Strong correlations were also observed between indirect disconnections among right frontal regions and between right frontal regions and the left parietal lobe.