Stroke can cause a number of ensuing 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 of spatial attention with a “heterogenous collection of symptoms” (Corbetta et al., 2005; more). 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, which 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 on that side ([Becker & Karnath, 2010](#beckerkarnath2010); Corbetta & Shulman, 2011; [Karnath, 2015](#karnath2015); [Karnath & Rorden, 2012](#karnathrorden2012)).

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).

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).

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 part 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).

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 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 incidence in an analysis of data from more than 88,000 stroke patients, with women exhibiting a prevalence of 33% versus 27% in men.

Neglect is often considered to be negative predictor for functional outcome in stroke recovery, even if the patient shows spontaneous recovery from the condition itself during the acute post-stroke phase (Jehkonen et al., 2000 & 2007; Wee & Hopman, 2008; Wu et al., 2015).

* Bartolomeo et al., 2007: Unfortunately, however, despite decades of research there are still important disagreements on the interpretation of the neglect syndrome, even on basic matters such as its lesional basis. […] Most studies devoted to the anatomical correlates of neglect indicate the temporal--parietal junction (TPJ) and the inferior parietal lobule (IPL) (Vallar 2001; Mort et al. 2003), consistent with the known role of posterior parietal cortex in spatial attention (Colby and Goldberg 1999; Gitelman et al. 1999; Corbetta and Shulman 2002). In contrast with this view, another line of findings implicated more rostral portions of the superior temporal gyrus (Karnath et al. 2001, 2004), emphasizing the role of the ventral visual stream in spatial awareness originally hypothesized by Milner and Goodale (1995). In addition, damage to several other brain structures has been reported to determine neglect, including the thalamus, the basal ganglia, and the dorsolateral prefrontal cortex (Vallar 2001; Karnath et al. 2002).

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 (Karnath, 2012; [Karnath & Rorden, 2012](#karnathrorden2012); more sources). 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; He et al., 2007; Hillis et al., 2005; Verdon et al., 2009) - though there is some debate surrounding this topic (see e.g. Karnath et al., 2001; more).

The white matter tracts connecting the perisylvian network, 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). 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 of meta-analyses by Bartolomeo et al. (2007) and Saxena et al. (2022), who investigated (blergh): Both meta-analyses found neglect to commonly emerge from intrahemispheric frontoparietal disconnections and 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.

While those results were mainly 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.

[ Hillis et al. (2002) concluded that neglect can be caused through the disruption of functionality of the frontoparietal network by vascular damage, surgical intervention, or temporary virtual lesions of the WM tracts. ]

* 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.
* Li & Malhotra, 2015:
  + Moreover, neglect results from damage to networks of regions involved in attention (see figure 5), and recent work has shown that it can result from damage to white matter tracts, particularly the superior longitudinal fasciculus, as well as individual cortical and subcortical regions.46 47
* 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.