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Let thy left brain know what thy right brain doeth: Inter-hemispheric compensation of functional deficits after brain damage

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ABSTRACT

Recent evidence revealed the importance of inter-hemispheric communication for the compensation of functional deficits after brain damage. This review summarises the biological consequences observed using histology as well as the longitudinal findings measured with magnetic resonance imaging methods in brain damaged animals and patients. In particular, we discuss the impact of post-stroke brain hyperactivity on functional recovery in relation to time. The reviewed evidence also suggests that the proportion of the preserved functional network both in the lesioned and in the intact hemispheres, rather than the simple lesion location, determines the extent of functional recovery. Hence, future research exploring longitudinal changes in patients with brain damage may unveil potential biomarkers underlying functional recovery.

1. Introduction

Despite its symmetrical appearance, the human brain exhibits anatomical as well as functional hemispheric asymmetries (Concha et al., 2012). Frequently occurring after a lesion in the left rather than the right hemisphere, the observation of language deficits spurred the concept of hemispheric dominance (Broca, 1863). Similarly, the behaviour of right-brain damaged patients suggested a mirror organisation of visuo-spatial functions with the right hemisphere being responsible for spatial deficits (Gainotti et al., 1972). Decades of neuropsychological testing in patients with surgically separated hemispheres corroborated the hypothesis of hemispheric dominance (Sperry, 1974, 1981) and led to the attribution of Roger W. Sperry's Nobel prize in 1981 (Sperry, 1981) (see Fig. 1).

The concept of hemispheric dominance or brain lateralisation became so popular that it currently receives about 90 million hits on Google. However, recent progress in functional neuroimaging (*f*MRI) depicts a different story, in which far from being independent, both hemispheres work together to form a fine network, pooling its resources to elaborate language as well as spatial functions (Hervé et al., 2013). For example, visual processing of words and faces, often considered to depend on specialized areas situated respectively in the left and in the right occipitotemporal cortex, is increasingly being understood as related to graded, not absolute, lateralisation patterns (Behrmann and Plaut, 2015). The (relative) left-lateralisation of reading-related areas seems to result from their preferential connections with the left hemisphere language networks (Bouhali et al., 2014; Thiebaut de Schotten et al., 2014a). Learning to read would "push" face recognition areas towards the right hemisphere (Dehaene et al., 2010). Inter-hemispheric differences would, however, remain relative rather than absolute, with important variability across individuals (Behrmann and Plaut, 2015). Graded degrees of laterality of function can also result from transcortical cell assemblies, i.e., cluster of neurons which function in a coordinated manner across the hemispheres (Pulvermüller and Mohr, 1996). In fact, brain regions related to reading and to face recognition might be less discrete and more intertwisted than previously thought, and might consist of

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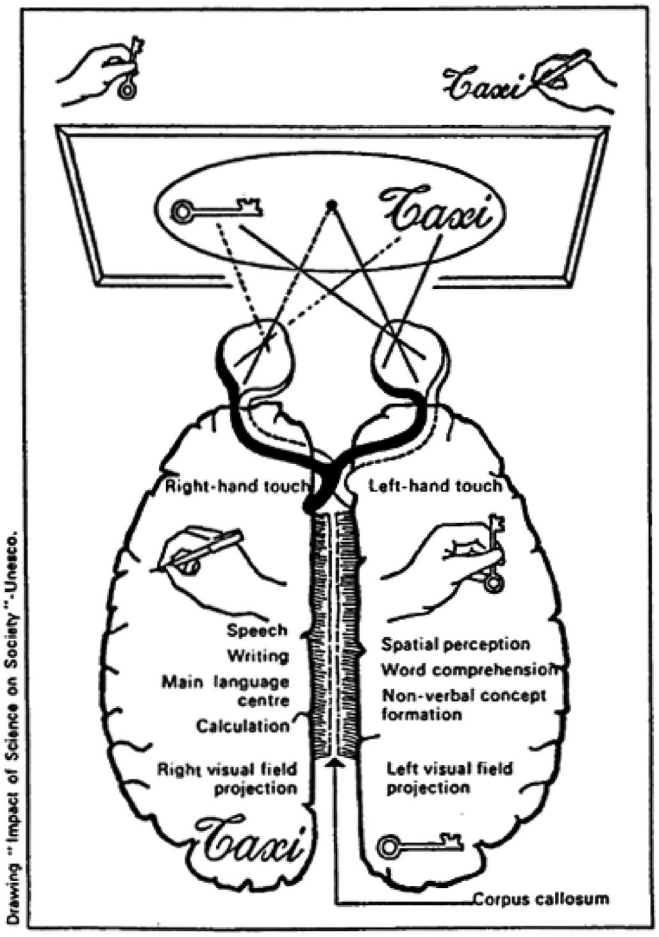

Fig. 1. Roger W. Sperry's illustration of the functional specialisation of both cerebral hemispheres. The left hemisphere is dominant for speech, writing and calculations whereas the right hemisphere is rather dominant for spatial perception, word comprehension, and non-verbal concept formation (Deglin, 1976) (Illustration from the Nobel Committee for Physiology or Medicine, based on "Impact of Science on Society" published by UNESCO. © the Nobel Committee).

anatomically alternated patchy modules along the ventral occipitotemporal cortex (Matsuo et al., 2015).

How would this new understanding of the functioning of the brain account for the lateralisation of functional deficits? To answer this question our review will put forth evidence to show that a brain damage has consequences that spread well beyond the lesion site (Section 2: Consequences of unilateral damage) and within the damaged functional networks (Section 3: The role of the unaffected hemisphere in cognitive recovery after stroke). From this perspective, we will argue that the brain's ability to handle damage relies on the proportion of the preserved functional network in both hemispheres, instead of the strict location of the lesion (Section 4: Inter-hemispheric communication).

2. Consequences of unilateral brain damage

During the acute phase of a vascular stroke, focal brain damage affects cortical activity not only locally, but also in anatomically intact areas that are connected to the lesion site (diaschisis; Carrera and Tononi, 2014; Feeney and Baron, 1986; Monakow, 1914). Diaschisis is classically defined as a remote loss of excitability (Monakow, 1914). Cerebral damage induces reduction of blood flow (Weiller et al., 1993) and disconnection (Metter et al., 1985) of brain areas distant from the lesion that can easily be spotted using perfusion weighted imaging (Beauchamp et al., 1999). Reduction in cerebral blood flow will decrease the metabolism due to selective neuronal loss (Olsen et al., 1986; Weiller et al., 1993) in the lesioned hemisphere (i.e. ipsilateral diaschisis). Disconnections will reduce the metabolism because of neuronal deafferentation (Metter et al., 1985) in the lesioned hemisphere as well as in the unaffected hemisphere (i.e. transcortical diaschisis). These two phenomena are critical for functional recovery, because two subcortical lesion of similar appearance can have drastically different functional outcomes in patients, depending on their impact on distant cortical areas (Hillis et al., 2000, 2002).

Increased excitability can also occur in disconnected areas, both in the lesioned hemisphere and in the unaffected hemisphere (Buchkremer-Ratzmann et al., 1996). Particularly, surface lesions are more likely to present with ipsilateral increased excitability, whereas deeper lesions will tend to involve also the contralateral hemisphere (Buchkremer-Ratzmann and Witte, 1997) through a complex modulation of specific receptors. Immunohistochemical studies in rats with photochemically induced cortical infarcts suggest that ipsilateral increased excitability is in part associated to the down-regulation of gamma-aminobutyric acid (GABA)A receptors alpha1, alpha2, alpha5 and gamma2 within the ipsilateral hemisphere, whereas up-regulation of receptors alpha3 would be linked to contralateral increased excitability. These post-stroke GABA receptor modulations are blocked by N-methyl-D-aspartate–receptor (NMDA) antagonists (Redecker et al., 2002). This suggests that a sequential order of receptor modulation takes place in both hemispheres after a stroke, although the fine details about the pipeline of this chain reaction requires further characterisation at the cellular level (Paik and Yang, 2014).

At the macroscopic level, cortical hyperexcitability is identified using task-based functional MRI (Corbetta et al., 2005). Cortical hyperexcitability tends to appear in both hemispheres during the early weeks after a stroke, and to decrease thereafter. These processes may contribute to spontaneous functional recovery. However, they can also be maladaptive in the case of persistence after the first weeks post-stroke, and thereby correlate with poor behavioural recovery (Cramer, 2008). The significance of post-stroke hyperactivity for functional recovery varies according time. Four partially overlapping temporal epochs can be identified (Fig. 2): (1) an acute phase within hours of the stroke, characterised by local inflammation, oedema and distal diaschisis; (2) a subacute phase during the first weeks after the stroke, when most of the spontaneous recovery occurs and then plateaus, and the distal diaschisis peaks; (3) a chronic phase beginning weeks to months after the stroke, associated with a 'normalisation' of the activity and a stabilisation of the deficits (Cramer, 2008); (4) finally, several months after the injury, preliminary evidence suggests that a rewiring of white matter fibers may also occur, with axonal sprouting near the ischemic injury leading to novel connections to distant cortical targets (Dancause et al., 2005).

These distinct mechanisms may be associated with different forms of functional recovery. For instance, whereas motor deficits usually show a maximum recovery within 30 days, language and other high cognitive functions may improve well beyond this phase, up to a year after stroke (Cramer, 2008). This difference in recovery rate suggests that partly distinct mechanisms may be at work in motor and in cognitive recovery (Grefkes and Ward, 2014). Hence, the late occurrence of cortical rewiring might well have an essential role in the recovery of high level cognitive function. This difference would also suggest that specific recovery mechanisms are in place for functions that developed later along the evolutionary tree.