Pathophysiological interrelated deactivation/activation processes in the exhausted brain after whiplash injury

Abstract
In this paper pathophysiological interrelated deactivation/activation phenomena are set out in the example of whiplash injury. These phenomena could have been underestimated in previous positron emission tomography studies as their focus was on hypoperfusion rather than hyperperfusion. In addition, statistical parametric mapping analysis of cerebral studies is normally not fine-tuned to special interesting areas rather than to obvious clusters of difference.

Introduction

Interrelated activation/deactivation phenomena in the brain are not new. Already in 1980, Baron et al. described the so-called “crossed cerebellar diaschisis”, in which reduced cerebral blood flow has been demonstrated in the cerebellar hemisphere contralateral to ischemic lesions of the cerebral hemispheres, the thalamus, or the internal capsule [1]. In the recently reported Baloyannis-Grammaticos syndrome, fatigue, atherosclerosis and toxic substances (such as chronic alcohol abuse) induce a decrease of perfusion in the cerebral cortex, the hippocampus and the anterior thalamus, whereas most of the subcortical regions remain normally supplied, a misbalance with the potential to trigger uncontrolled behavior [2]. Even more, we think that in many conditions of the affected or exhausted brain, for example traumatic brain injury, whiplash injury or even insomnia [3, 4], there is a cascade of repair mechanisms or at least the coexistence of different pathophysiological deactivation/activation processes—much more than we already know from the processes in ischemic stroke, such as the concept of ischemic penumbra [5].

The aim of this paper was to revisit functional neuroimaging data of a recent $^{15}$O-H$_2$O-labeled positron emission tomography (PET) study in whiplash injury patients, a condition in which the brain shows many signs of fatigue comprising visual and vestibular problems, cognitive limitations or emotional disturbances, and the perfusion studies exhibit a colorful rendezvous of results confusing the physician as well as the expert as recently reported in the HJNM [6, 7].

Retrospective view on $^{15}$O-H$_2$O-PET data in whiplash injury

The selected study
One of the latest functional neuroimaging studies in whiplash injury is the case-control study by Vállez García et al. (2016) [8], who studied regional changes in blood flow through $^{15}$O-H$_2$O-PET in 12 female patients with late whiplash syndrome compared to 8 healthy age matched female subjects under four different conditions (resting state and different levels of non-painful cervical electrical stimulation). In the patient group, statistical parametric mapping (SPM12) revealed increased perfusion in the posterior cingulus and precuneus and decreased in the upper temporal, parahippocampal and inferior gyri, thalamus, and insular cortex (Figure 1). In this illustration no adjacent activation/deactivation areas are visible.
Pathophysiological interrelated deactivation/activation processes

Upon restricting the analysis to the parietal, occipital, and temporal lobes, small clusters of hypoperfusion were seen in the posterior parietal occipital region including some areas of hyperperfusion in this region (Figure 2), which may show that the brain in whiplash patients attempts to compensate for hypoperfused (deactivated) brain states by hyperperfusion (activation) in the vicinity of the affected areas (Figure 3).

Note that only upon restricting the SPM data the adjacent activation/deactivation areas are visible.

Figure 1. Voxel-based analysis of $^{18}$O-H_{2}O PET scans in the study from Vállez García et al. 2016, showing the significant regions of increased or decreased regional cerebral blood flow (rCBF) in patients with late whiplash syndrome compared to healthy volunteers; height threshold $P=0.005$ uncorrected, extent threshold $k=100$ voxels, voxel size=2x2x2mm. (Copyright 2016 by Vállez García D, Doorduin J, Willemsen ATM, Dierckx RAJO, Otte A. DOI: https://doi.org/10.1016/j.ebiom.2016.07.008. Published by Elsevier B.V. under the open-access license CC BY NC ND [http://creativecommons.org/licenses/by-nc-nd/4.0/])

Figure 2. Statistical parametric map projections showing decreased (a) and increased (b) regional cerebral blood flow in chronic whiplash associated disorders patients compared to healthy volunteers, restricted to the parietal, occipital, and temporal lobes (Sandwich Estimator toolbox, height threshold $P=0.005$ uncorrected, extent threshold $k=0$ voxels, voxel size=2x2x2mm) (Copyright 2016 by Vállez García D, Doorduin J, Willemsen ATM, Dierckx RAJO, Otte A. DOI: https://doi.org/10.1016/j.ebiom.2016.07.008. Published by Elsevier B.V. under the open-access license CC BY NC ND [http://creativecommons.org/licenses/by-nc-nd/4.0/])
Discussion

The progress achieved by PET and single photon emission tomography (SPET) in the diagnosis of the many facets of diseases disposed in the neurosciences (neurology, psychiatry, neurobiological systems) has been astounding. Nevertheless, in line with the Socratic paradox "I know that I know nothing", it seems that we are still at the beginning of understanding the brain. Deafferentation processes, neural fiber connections, and cerebrovascular regulation mechanisms triggered by vasopeptides and other substances [2] are some of the essential challenges in the neurosciences that are not well understood and, as we think, need to be revisited.

What are the principal differences between the cardiovascular system and the neurovascular system? And what are the principle differences of the peripheral arterial system (with its ability of building collaterals upon stenosis) as opposed to the (limited) coronary and cerebral arterial system?

This paper is analyzing only one example study of one special indication: late whiplash syndrome after whiplash injury. It shows, however, that there are certain interrelated hypoperfusion/hyperperfusion processes, which most likely can be explained by compensation mechanisms between the de-activated regions of the brain that undergo stress and the surrounding brain regions that are not or are less affected. In whiplash syndrome, one theory for the production of hypoperfusion in the posterior parietal occipital region has been the nociceptive-vascular hypothesis [9]. This is based on a previous study by Moskowitz and Buzzi, already from 1991, in which widespread effects on local vasoactive peptides and the cranial vascular system were seen upon experimental stimulation of pain-sensitive afferents in the trigeminal system [10]. As the hypoperfusion of the posterior parietal occipital region is localized to the posterior watershed zone between the territories of the large cerebral arteries (A. cerebri media and A. cerebri posterior), this region seems to be the most vulnerable zone and, as we think, reacts, by vasoconstriction, on increased vasopeptide production triggered by nociceptive afferents from the upper cervical spine which is under chronic pain (stress) (Figure 4).

If this hypothesis applies, it may be speculated that the hyperperfused (or activated) areas of the "whiplash brain" could be explained in the context of either less vasopeptide production or a better perfusion situation in the vicinity of the hypoperfused areas.

Furthermore, based on the reported cognitive deficits in late whiplash syndrome (oscillopsia, memory and attention deficits), previous PET and SPET studies focused on areas of significant hypoperfusion [11-15]. Hyperperfusion was not systematically investigated. This approach can also be observed in PET and SPET studies of other neurological indications, such as traumatic brain injury, neuropsychiatric systemic lupus erythematosus, migraine, or stroke. On the other hand, newer studies introduced the SPM technique superseding the qualitative and later the conventional (manually placed) region-of-interest technique. With all advantages of SPM over these observer-dependent approaches, the presented case-controlled study shows that even with SPM it is important to define where to look at. With a height threshold of \( P=0.005 \) uncorrected, an extent threshold of \( k=100 \) voxels, and a voxel size of \( 2\times2\times2 \) mm, the "gold standard approach for SPM studies", smaller areas of difference cannot be seen (Figure 1). In our example these could only be shown when the extent threshold was set to 0 and restricting the SPM analysis to special areas (parietal, occipital, and temporal lobes) (Figure 2). However, this is normally not routinely done, which may lead to an underestimation of the situation.

Figure 3. Statistical parametric map projections simultaneously showing increased (grey) and decreased (red) regional cerebral blood flow in chronic whiplash associated disorders patients compared to healthy volunteers, illustration derived from Figure 2.
Therefore, re-analyzing older perfusion PET or SPET studies may be an interesting aspect open for discussion. Hereby, even more, artificial intelligence algorithms utilizing deep learning for recognizing special patterns of perfusion changes could be a future scenario worth looking for to augment nuclear medicine research [16].

In conclusion, the phenomenon of interrelated deactivation/activation processes could have been underestimated in previous studies on whiplash injury. Besides, SPM analysis of cerebral studies is normally not fine-tuned to special interesting areas rather than to obvious clusters of difference.

Bibliography