



Commentary: Localized vs. Systematic Neurodegeneration: A Paradigm Shift in Understanding Neurodegenerative Diseases

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A commentary on

Localized vs. Systematic Neurodegeneration: A Paradigm Shift in Understanding Neurodegenerative Diseases

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Neurodegenerative disorders are one of the most important causes of disability in humans (Batista and Pereira, 2016), causing a limitation in the professional, social, and personal activities of its sufferers and also impacting their families, as well as a severe socioeconomic burden to the social security (Uryu et al., 2010; Kivimaki et al., 2015). For instance, only in United States of America (USA) the annual cost of medical care related to head injury reaches around U\$200 million every year (see Humphreys et al., 2013 for a review), which varies depending on the severity of lesion, population evaluated and time period (Dismuke et al., 2015).

Neurodegeneration can be induced by acute injury or chronic diseases. The first condition is elicited by the brain and spinal cord trauma and involves two main events: (1) Primary neuronal degeneration, which induces an abrupt process of tissue degradation and cell death by a mechanical disturbance of the nervous tissue, causing breakdown of the blood-brain barrier (BBB), intense inflammatory response and tissue swelling, with an irremediable tissue damage (Maas et al., 2008); and (2) Secondary neuronal degeneration, a condition correlated to the intensity of the primary insult, which occurs gradually and involves impairment of nervous tissue initially spared by the primary lesion. Inflammation and excitotoxicity are factors involved with the spreading of the primary lesion, ultimately affecting the healthy tissue (Choi, 1992; Morganti-Kossmann et al., 2002; Guimaraes et al., 2009; Freire, 2012). Inflammatory response, a physiological event that aims to safeguarding the tissue against harmful agents, promoting healing, and tissue repair, can have detrimental effects when becomes exacerbated, generating imbalanced production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-1 beta (IL-1 β) that further contribute to tissue impairment in both central and peripheral tissues (Allan and Rothwell, 2001; Araujo et al., 2014; Friese et al., 2014). Excitotoxicity, in turn, possesses a pivotal role in the impairment of the nervous system, increasing tissue lesion by an overactivation of glutamatergic receptors, with a consequent influx of ion calcium and production of free radicals, leading to apoptotic cell death (Manev et al., 1989; Dong et al., 2009).

One of the significant features of acute brain injury is the phenomenon called diffuse axonal injury, characterized by a widespread pattern of lesion that causes a disturbance in the axonal physiology, especially in the white matter (Johnson et al., 2013), normally presenting a

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fast progression, with well-evident motor and/or cognitive disorders (Lin and Wen, 2013). In addition, traumatic brain injury is pointed as an important risk factor for the development of neurodegenerative diseases (Gupta and Sen, 2016).

In chronic neurodegenerative diseases, such as Parkinson's disease and Amyotrophic Lateral Sclerosis, conversely, it is possible to determine accurately the initial site where neuronal death begins. In Parkinson's disease, for instance, dopaminergic neurons of the midbrain are primarily affected (Sulzer and Surmeier, 2013). Following the progression of the pathology, other neuronal groups also collapse (Sulzer and Surmeier, 2013). Likewise acute brain lesions, impairment of normal tissue physiology in chronic brain pathologies is also related to inflammatory response and excitotoxicity (Akiyama et al., 2000; Gao and Hong, 2008; Ambrosi et al., 2014; Amor et al., 2014; Santos et al., 2014).

As abovementioned, acute and chronic degenerations present particularities regarding both location and kinetics of tissue impairment. In this context, a recent opinion article published by Bayati and Berman (2017) in *Frontiers in System Neuroscience* raises an important point: mechanistic progression and the characteristic patterns of degeneration of neurological diseases are critical points to be approached in order to establish an effective diagnostic and/or proper treatment of their symptoms (Bayati and Berman, 2017). As pointed by authors, a comprehensive characterization of specific types of degenerative pathologies regarding their location and progression of cell loss would be valuable to researchers and medical professionals in

order to provide an early diagnosis, aiming at least to slow down the progression of the diseases. For instance, Alzheimer's disease, the most prevalent chronic neurodegenerative disease, presents a pattern of global brain impairment, and because of this characteristic, is not possible to establish a treatment focused in a specific brain region, as made for Parkinson's disease. Thus, the localization of function, as stated by Bayati and Berman, is advantageous to an early characterization of cell loss and tissue impairment in specific regions of the brain in some neurodegenerative pathologies.

In conclusion, Bayati and Berman's paper offers a new and interesting perspective about how neurodegenerative diseases can be approached, in light of their systematic or localized characteristics. So, a proper understanding concerning both acute and chronic pathological conditions is a key factor for the development of effective progress in therapeutics.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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