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"Brain reserve" and "cognitive reserve" should always be taken into account when studying neurodegeneration – Commentary

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Multiple Sclerosis Journal
2018, Vol. 24(5) 577–578
DOI: 10.1177/1352458517751649

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Cognitive dysfunction is highly prevalent, disabling, and poorly managed in persons with multiple sclerosis (PwMS). In these subjects, the presence and degree of cognitive dysfunction has been consistently associated with gray and white matter changes in the brain detected by magnetic resonance imaging (MRI) and especially with measures of whole brain and regional atrophy, currently interpreted as the best in vivo proxy for neurodegeneration.[1] However, not all PwMS present with cognitive dysfunction, even those having comparable degrees of gray and white matter changes and atrophy; moreover, longitudinal studies have shown great inter-subject variability in the rate of progression of cognitive dysfunction.[2] To explain this "clinico-pathologic paradox," much attention has been drawn to other factors, namely the concept of reserve, that is, protection against clinical manifestations of neurological damage. Following extensive research in the field of degenerative dementia, there is now a growing body of evidence supporting brain reserve and, in particular, cognitive reserve also for mitigating the deleterious effects of MS pathology on cognition in PwMS.[3,4]

In his article, Sumowski highlights how consideration of reserve is of paramount importance to improve research on neurodegeneration, namely to help explain inter-individual differences in the cognitive outcome, inform the development of more accurate prognostic models of risk for cognitive dysfunction and the development of rehabilitative approaches based on reserve-building activities against ongoing neurodegeneration in the brain.

Sastre Garriga observes that information on the measurement and role of brain reserve in MS is still scarce and measures of maximal brain growth are currently not easily estimated for specific regions of interest like the hippocampus or thalamus. Moreover, brain volume measures in use already take into account in different ways the concept of brain reserve. Ultimately, since brain reserve is almost exclusively hereditable, it is outside of one's current control and therefore of little help to inform management strategies. However, PwMS identified as being at higher risk for cognitive dysfunction could still be counseled regarding brain healthy choices (e.g. exercise, diet, smoking), which might prevent or slow the loss of reserve brain volume and also targeted for future treatment trials.

On the other hand, as compared with brain reserve, data on the role of cognitive reserve in MS are more numerous and consistent. Cognitive reserve is a dynamic construct, depending not only on genetics but also on intellectual enrichment in childhood and adolescence[5] but, most probably, also during the entire lifetime of the subject. This shift in the concept of cognitive reserve may have important implications for new treatment approaches based on building and maintaining cognitive reserve over time. Overall, there is increasing correlative evidence coming from neuropsychological and neuroimaging research that the brain of a PwMS is best understood as a dynamic and complex interaction between disease and adaptive/compensatory mechanisms including reserve.[1]

Therefore, the theory of reserve could provide a useful framework for the research and clinical practice. However, much more work is needed to shed some light on these complexities, in order to translate the concept of reserve into a clinically useful tool.

We must be aware of important methodological challenges, highlighted in Sastre Garriga's paper. As for cognitive reserve, the characteristic of being a "moving target" and the variability of proxies currently in use clearly represent important challenges for a uniform and reliable assessment. The complex and largely unknown interplay between cognitive and physical reserve adds further complexity in the field.

Future research should converge on common, well-validated measures of reserve, develop and test algorithms to predict risk of cognitive decline in PwMS, taking proxies of reserve into consideration. Furthermore, since existing evidence on the protective role of intellectual enrichment against cognitive decline in MS comes from observational studies, further, rigorous experimental work is necessary. Finally, the use of MRI or functional MRI (fMRI) to identify neuroanatomical or functional markers of reserve could be helpful in providing measurable proxies for increased reserve as outcomes of early intervention trials.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Maria Pia Amato has received research grants and honoraria as a speaker and member of advisory boards by Byer, Biogen, Teva, Merk, Sanofi Genzyme, Novartis, Roche.

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