



Functional training is a senseless strategy in MS cognitive rehabilitation: Strategy training is the only useful approach – NO

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While the prevalence and pattern of cognitive deficits in multiple sclerosis (MS) are now relatively well understood,¹ cognitive deficits are among the most difficult symptoms in terms of management.² Cognitive impairment can severely diminish the quality of life of our patients with MS and is one of the main reasons for unemployment. This means that we are in great need for evidence that cognitive rehabilitation is an effective way to reduce the cognitive deficits people with MS experience.

Some might argue that patients will be best served by strategy training and use of external aids (i.e. teaching patients compensatory strategies such as using a calendar and set phone reminders). However, we think *there is more to offer*. Rather than just teaching “tips and tricks,” we should use the brain’s plasticity to retrain specific cognitive functions and ideally influence the brain in such a way that prolonged training effects will appear in daily life functioning. We expect that for a large majority of the people with MS, functional training will become the first-choice treatment in the near future.

Functional training can be thought of as feasible computer interventions (possibly commercial programs) or manualized interventions aimed to improve specific cognitive functions in people with MS.³ MS patients have demonstrated good adherence to computerized cognitive training programs, even when self-administered at home.⁴ The safety and acceptability of non-invasive, non-pharmacological, behavioral treatments for cognitive deficits are clear, including the important self-management aspect.⁵

Functional training and cognitive functioning

Despite the cautious conclusions of systematic reviews,² the majority of MS cognitive rehabilitation studies (including functional training) report an improvement on several neuropsychological test scores after a training period, compared to scores at baseline. Most randomized controlled trials (RCT) show cognitive function improvement over several months’ follow-up. In an RCT accepted as Class 1

evidence, Chiaravalloti and colleagues demonstrated improved verbal learning in patients who attended five weekly groups of specific memory training (modified Story Memory Technique), compared to patients who were in the placebo group. Positive effects were additionally observed for objective measures of everyday memory function, general contentment, and executive functioning, all effects that were sustained for a period of 6 months.⁶ REHACOP, a cognitive rehabilitation program aimed to improve several cognitive domains, has recently demonstrated wide ranging cognitive improvement.⁷ We are currently starting to understand how to select the patients who are most likely to benefit from functional training, for example, previous studies demonstrated improved learning and memory performance as a result of a memory-training program, which was uniquely found in moderately cognitively impaired patients.⁸

Functional training and changes in the brain’s functioning

Next, for improvement on neuropsychological test scores and activities of daily living (ecological validity), positive outcomes and “proof” of the effectiveness of functional training can also be measured using magnetic resonance imaging (MRI). Knowledge of the neural substrates of cognitive dysfunction has shed light on the most important brain changes associated with cognitive deficits. White matter lesions are, at most, mildly associated with cognitive impairment; damage to the cortical and subcortical gray matter (both atrophy and lesions) correlates moderately with cognitive deficits, with atrophy consistently achieving the strongest correlations with cognitive performance.⁹ However, it seems that rather than being closely coupled with structural tissue damage, cognitive functioning is largely dependent on the (micro)structural and functional integrity of the brain’s networks.¹⁰ This means that a successful functional training not only improves cognitive functioning but also lead to improved network efficiency. Good news! There is mounting evidence that neural plasticity underlies improvements in cognitive performance after functional training.

The first results of the studies investigating changes in brain activation and brain connectivity in response to cognitive retraining in patients with MS are promising. After a 12-week computerized-rehabilitation program aimed to improve attention, information processing speed, and executive functioning, increased brain activation was observed during the Stroop task (attention). The posterior cingulate cortex, precuneus, and dorsolateral prefrontal cortex showed increased activation which corresponded with improved behavioral functioning.¹¹ More recently, improved cognitive functioning (attention and executive functioning) was observed together with increased functional connectivity of the cingulate cortex, precuneus, and bilateral parietal cortices, while a decreased functional connectivity was observed in the cingulate and left prefrontal cortex.³ These findings resulted from analyses comparing an active treatment to a control or placebo group, indicating that they reflect a real change in response to the intervention and cannot easily be attributed to fluctuations over time in our functional MRI measures. Therefore, we speculate that the changes in brain activation and connectivity after functional training reflect improved network efficiency.²

To sum up, we can see no justification regarding functional training as “senseless.” Additionally, strategy training might be the “last resort” when patients do not respond well to functional training. For example, in patients with extensive tissue loss, neural plasticity might be hampered and no or little effect will result from functional training. In that particular patient group, strategy training might help patients to work around the problems that are present.

However, for many patients, we would expect that functional training will lead to improved cognitive functioning on neuropsychological tests, improved functioning in everyday life, and ultimately will lead to an improvement in network efficiency.² We have a few well-designed RCTs that give clear, positive, sustained results for functional training.

However, there are still a few things on our to-do list. We need multi-center trials demonstrating that these functional training interventions can be delivered effectively in many clinics, how they can be optimized regarding patient characteristics, and that they are cost-effective in terms of benefits to the individual and society. The final challenge will be to operationalize functional training protocols for international roll-out and to negotiate the resource implications. We owe it to our patients, because cognition is a precious asset.

Declaration of Conflicting Interests

The author(s) declared the following conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. H.E. Hulst declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Prof. D.W. Langdon received consultancy fees from Novartis, Bayer, TEVA, Biogen, and Merck. She was involved as speaker via the speaker bureau for Almirall, TEVA, Biogen, Novartis, Bayer, Exceme and received research grants from Novartis, Biogen, Bayer. All are paid into DL's university.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Cognitive impairment (CI) associated with multiple sclerosis (MS) (CIAMS) is a disabling manifestation that is frequently observed from the early stages of the disease with significant impact in terms of quality of life, vocational status and compliance to therapy. Until recently, research focusing on cognitive rehabilitation for CIAMS was limited, with a few studies showing disappointing results.¹ The methodological limitations of these studies (few controlled trials, limited sample sizes, short follow-up periods and inappropriate outcomes) explain these results. More recently, several controlled studies have been published on the effect of cognitive rehabilitation on not only neuropsychological outcomes but also functional and morphological magnetic resonance imaging (MRI). The question raised in this controversy concerns the value of two different approaches, functional training and strategy training. The first one aims to improve cognitive functioning by restoring or improving network efficiency in the brain. The second aims to educate patients to use adaptive strategies, such as external aids and reminders.

One important argument developed by Leavitt is that timing is key. Indeed, functional training could be limited when brain damage is extensive and limits neuroplasticity. In these advanced cases, strategy training should be preferred. Leavitt gave some evidence of the usefulness of these strategies. However, it could be difficult to determine in a given patient, if neuroplasticity could still occur. MRI, diffusion tensor imaging or measures of functional connectivity are good candidates for selecting patients for functional training strategies. However, the interpretation of functional reorganization in MS is difficult, since reorganization could be adaptive or maladaptive.² The second important argument developed by Leavitt is

that there is no clear evidence that functional training results in transfer of the benefits of a trained task transfer to another, untrained, task. However, this transfer has not been properly studied.

Hulst and Langdon reviewed the recent randomized clinical trials (RCT) of cognitive rehabilitation in MS. Several RCT showed significant improvement in some tests of episodic memory,³ information processing speed, working memory and executive functioning.^{4–6} These studies clearly demonstrated a therapeutic effect of functional training. The clinical meaningfulness of these improvements has, however, not been systematically studied. An effect on subjective report of overall functioning was reported in one study,³ but a clear demonstration of the effect of cognitive rehabilitation of daily cognitive functioning is still lacking. However, several studies showed change in brain activation on task-based functional magnetic resonance imaging (fMRI), change in functional connectivity and, for one study, microstructural changes by diffusion tensor imaging after rehabilitation.^{7–9} These results suggested that functional training could modify brain functioning and improve network efficiency in some way. The characteristics of change in brain activation and connectivity observed after cognitive rehabilitation (homologous region adaptation, local activation expansion and extra-region recruitment) and the observed association with neuropsychological improvement suggest that adaptive neuroplasticity may occur after functional training.⁷

In conclusion, functional training is a promising way for improving cognitive functioning in MS but more research is needed, in particular in patients at the early stages of the disease for demonstrating a clinically meaningful effect. These strategies need to be improved