

**FUNCTIONAL TRAINING IS A SENSELESS STRATEGY IN MS COGNITIVE REHABILITATION.**

**STRATEGY TRAINING IS THE ONLY USEFUL APPROACH.**

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Whilst the prevalence and pattern of cognitive deficits in MS are now relatively well understood,<sup>1</sup> cognitive deficits are amongst the most difficult symptoms in terms of management.<sup>2</sup> 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.<sup>3</sup> MS patients have demonstrated good adherence to computerized cognitive training programs, even when self-administered at home.<sup>4</sup> The safety and acceptability of non-invasive, non-pharmacological, behavioral treatments for cognitive deficits are clear, including the important self-management aspect.<sup>5</sup>

#### *Functional training and cognitive functioning*

Despite the cautious conclusions of systematic reviews,<sup>2</sup> 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 a 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 every day memory function, general contentment and executive functioning, all effects that were sustained for a period of six months.<sup>6</sup> REHACOP, a cognitive rehabilitation program aimed to improve several cognitive domains, has recently demonstrated wide ranging cognitive improvement.<sup>7</sup> We are currently starting to understand how to select the patients who are most likely to benefit from functional training, e.g. 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.<sup>8</sup>

#### *Functional training and changes in the brains' functioning*

Next to 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 have 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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>3</sup> 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.<sup>2</sup>

To sum up, we can see no justification for 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.<sup>2</sup> We have a few well designed RCT’s 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.

## References

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