Combining cognitive interventions in multiple sclerosis

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See **Articles** page 912

Cognitive impairment can be one of the most disabling aspects of multiple sclerosis, substantially affecting everyday functioning, community participation, and self-care.[1] People with progressive multiple sclerosis are more likely to have cognitive impairment, and impairment can be more severe across cognitive domains, than in the relapsing-remitting stage.[2] Worsening of cognitive impairment is related to greater neural damage, older age, and increased fatigue and depression, as well as background factors such as lifestyle and cognitive reserve.[1]

Computerised cognitive training is a common cognitive rehabilitation approach with strong evidence for improving cognitive function in people with multiple sclerosis[3] or other neurological disorders such as Parkinson's disease.[4] Computerised cognitive training seems to be safe, scalable, and can be adapted to individual needs. However, the evidence base in multiple sclerosis is skewed towards people with relapsing-remitting disease, pooled effect sizes are rather small (approximately 0·3 SD), and the potential to attenuate cognitive decline in the long term remains unclear.[3]

In *The Lancet Neurology*, Anthony Feinstein and colleagues[5] examined whether combining computerised cognitive training with aerobic exercise would lead to synergetic effects on cognitive performance in people with progressive multiple sclerosis. Using a two-by-two factorial design the CogEx trial assessed efficacy of the combined intervention (computerised cognitive training plus aerobic exercise) compared with each intervention plus a sham version of the other intervention (ie, sham computerised cognitive training plus aerobic exercise, and computerised cognitive training plus sham aerobic exercise) as well as a double sham condition. Changes in cognitive, fitness, and subjective clinical endpoints were measured at the end of the 12-week intervention period and 6 months post-training. The trial was powered to detect a 4-point mean difference in the Symbol Digit Modality Test (SDMT) between the computerised cognitive training plus aerobic exercise group and the double sham condition. This difference (roughly equivalent to 0·5 SD) was proposed as a threshold for clinical meaningful effect definition by the Multiple Sclerosis Outcomes Assessments Consortium.[6]

The results of this impressive international trial suggest that these interventions are feasible even at scale, as evident by adherence and compliance rarely seen in large trials, as well as by the modest improvement in aerobic performance within the exercise groups. Approximately 60% of participants across all arms improved their SDMT scores above the 4-point threshold, but neither the combined intervention nor its components led to a greater improvement in SDMT scores compared with the double sham group (range of mean difference −0·71 to −2·78). None of the secondary cognitive and clinical outcomes suggested a benefit. Paradoxically, perceived disease burden (as assessed with the 29-item Multiple Sclerosis Impact Scale) increased in the computerised cognitive training plus aerobic exercise group compared with the other groups that received an active intervention. Therefore, apart from the non-specific benefits of trial participation, none of the interventions was efficacious for cognitive performance and combining them was associated with no additional benefit, potentially due to excessive cognitive and physical demands.

Previous evidence offers no clear indication that people with progressive multiple sclerosis will be less responsive to computerised cognitive training compared with people who have relapsing-remitting multiple sclerosis,[3] and in fact suggests that effect sizes might increase with greater cognitive impairment.[4,7] Given the weak efficacy signal from the CogEx trial, other methods could be considered to augment the effects of cognitive training in this population. First, a network meta-analysis in adults aged 60 years or older has suggested that physical exercise can augment cognitive training only when these interventions are provided simultaneously,[8] not in separate sessions as done in the CogEx trial. Second, the efficacy of computerised cognitive training might increase when supplemented by other cognitive rehabilitation approaches, including compensatory strategies, psychoeducation, motivational support, and personalisation.[9] Such techniques might be even more important in people with progressive multiple sclerosis, in whom other symptoms (eg, depression and fatigue) and lower cognitive reserve might impede compliance and the efficacy of cognitive training.[1]

Third, variations in the cognitive training programme dose, content, and delivery might affect outcomes. Although the approach selected for the CogEx trial was efficacious in smaller trials,[3] it is not necessarily optimal for large and heterogeneous cohorts. As cognitive training technology improves, it will be important to compare different approaches, to consider the emerging evidence for facilitating factors (eg, gamification, social support, and cognitive enhancing medications), and to adapt training to individual needs.

Finally, the CogEx trial highlights the importance of early prevention strategies. Long-term engagement in structured cognitive training remains the intervention with the strongest evidence for efficacy with a clear potential to reduce the rate and effect of cognitive decline in people with multiple sclerosis and other neurodegenerative conditions.[3,4,7] Further thinking, creativity, and experimentation will be needed to realise its clinical potential.

AL reports grants from the Australian Medical Research Future Fund. CF reports grants from Deutsche Forschungsgemeinschaft (the German Research Foundation) and the German Ministry of Education and Research.

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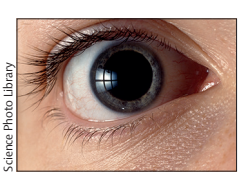
The prognostic potential of pupillometry in patients with acute brain injury



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Published **Online** August 28, 2023 https://doi.org/10.1016/S1474-4422(23)00314-9

See **Articles** page 925

Pupillary assessment is highly regarded by clinicians who are responsible for diagnosing neurological impairment. Abnormal or absent pupil reactivity can herald a neurological emergency due to either life-threatening compression or intrinsic injury to pupillary pathways in the brainstem.[1] Conversely, normal pupil reactivity signifies brainstem integrity, which is an important marker of recovery. However, the diagnostic and prognostic potential of longitudinal pupillometry has been limited by the subjectivity and lack of reliability of pupil assessments.[2,3]

Quantitative pupillometry, in which an automated device records and stores information on pupil size, speed of constriction and dilation, and latency, has been used increasingly in intensive care units over the past decade. The technique is an improvement on previous manual assessment standards that often characterise pupils broadly as brisk, sluggish, and unreactive. Automated, quantitative pupillometry permits standardisation of the assessment of abnormalities and the tracking of subtle changes over time that could provide an early warning of catastrophic evolving injury—previously unfeasible without a quantitative tool. In a recent study, quantitative pupillometry was used in the assessment of patients with hypoxic-ischaemic brain injury after cardiac arrest.[4] The findings suggested that the Neurological Pupil index (NPi)—a proprietary composite measure of reactivity reported by the NeurOptics pupillometer (NeurOptics; Irvine, CA, USA), with scores ranging from 0 to 5 (values <3 are deemed abnormal)—might be sensitive and specific for identifying patients with poor recovery potential.

However, many questions remain regarding the clinical significance of quantitative pupillometry and the NPi. Is an abnormal NPi score also prognostic in patients with other acute brain injuries? Moreover, is it more