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G. Pardo has served on advisory boards and/or speakers bureaus for Biogen, Bristol Myers Squibb-Celgene, EMD Serono, F. Hoffmann-La Roche Ltd, Genentech, Inc., Horizon Therapeutics, Novartis, Sanofi Genzyme, TG Therapeutics, Greenwich Biosciences and Teva.

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The late onset of emotional distress in people with progressive multiple sclerosis during the COVID-19 pandemic: longitudinal findings from the CogEx study

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Background: An earlier follow-up study from the CogEx rehabilitation trial showed little change in symptoms of depression, anxiety and psychological distress during the first COVID-19 lockdown compared to pre-pandemic measurements.
Objective: Here we provide a second follow-up set of behavioral data on the CogEx sample.
Method: Data were obtained from the CogEx study, a randomized controlled trial of exercise and cognitive rehabilitation in people with progressive MS involving 11 centres in North America and Europe. Participants completed the same COVID Impact Survey and self-report measures of depression, anxiety and MS symptoms that had been obtained during the first pandemic lockdown period.
Results: The average time between measurements was 11.4 (SD=5.56) months. Sample size declined from 131 to 72 largely because pandemic restrictions prevented data collection from sites in Denmark and England. There were no significant differences in age, sex, EDSS, disease course and duration between those who participated in the current follow-up study (n=74) and the group that could not (n=57). One participant caught Covid in the time between assessments. Participants now took a more negative view of their mental/psychological wellbeing (p=.0001), physical wellbeing (p=.0009) and disease course (p=.005) compared to their last assessment. Depression scores increased on the HADS-depression scale ($p = .01$) and now exceeded the clinically significant threshold of $\geqslant 8.0$ for the first time. Anxiety scores on the HADS remained unchanged. Poorer mental wellbeing was predicted by HADS depression scores (p=.012) and a secondary-progressive disease course (p=.0004).
Conclusions and Relevance: A longer follow-up period revealed the later onset of clinically significant depressive symptoms on the HADS and a decline in self-perceptions of mental and physical wellbeing associated with the COVID-19 pandemic.

Disclosure

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Nancy D. Chiaravalloti is on an Advisory Board for Akili Interactive and is a member of the Editorial Boards of Multiple Sclerosis Journal and Frontiers in NeuroTrauma.

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Amber Salter is a statistical editor for Circulation: Cardiovascular Imaging.

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Neuregulin-1 treatment facilitates neurogenesis and cognitive recovery in chronic cuprizone mouse model of multiple sclerosis

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Cognitive impairments such as memory loss, learning, depression and anxiety are common symptoms in progressive multiple sclerosis (MS). Degree of cognitive dysfunction in MS correlates with the extent of neurodegeneration and hippocampal atrophy. Continuous adult neurogenesis by neural precursor cells (NPCs) supports learning and memory, and its decline in progressive neurodegeneration underlies MS associated cognitive deficits. Thus, development of targeted treatments aimed at enhancing neuroprotection and NPC neurogenesis is a critical step towards promoting cognitive recovery in progressive MS. We previously demonstrated that Neuregulin-1 (Nrg-1), an important factor for development, maintenance and physiology of NPCs, neurons and oligodendrocytes, diminishes in demyelinating lesions of MS brain and MS mouse models. Restoration of Nrg-1 bioavailability by peptide treatment was able to promote oligodendrogenesis and remyelination in acute demyelinating lesions in mice. To date the impact of Nrg-1 on brain neurogenesis and cognitive behavior in chronic demyelinating conditions is unexplored. Here, we have performed *in vivo* and *in vitro* studies using a cuprizone-induced demyelination mouse model of progressive MS and relevant *in vitro* platforms to evaluate whether Nrg-1 treatment can attenuate neurodegeneration and promote hippocampal neurogenesis and cognitive recovery. We induced demyelination in Nestin-Cre reporter mouse that allows tracking NPCs and their progenies. In chronically demyelinated cuprizone mice, we found evidence of hippocampal atrophy that was associated with a significant increase in the expression of neurodegenerative markers and a concomitant decline in spatial and long-term memory assessed by Y-mase and novel object recognition tests. *In vitro* neurosphere assay on NPCs isolated from hippocampus of chronic cuprizone mice confirmed smaller number of NPCs and their reduced neurogenic capacity. We delivered Nrg-1 subcutaneously to the mice that received 10 weeks of cuprizone diet. Our tissue analysis after 4 weeks of daily Nrg-1 treatment showed a significant increase in proliferation and neurogenesis of hippocampal NPCs and attenuation of neurodegeneration. These findings identify, for the first time, the potential of Nrg-1 treatment in enhancing neurogenesis in progressive demyelinating conditions and its promise as a therapeutic strategy to promote cognitive recovery associated with progressive MS.

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Analysis of long-term disability trajectories in patients with primary progressive multiple sclerosis

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