Is cognitive impairment in multiple sclerosis reversible?

**A R T I C L E   I N F O**

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Sickness behaviour (SB) is an evolutionary conserved behavioural response mediated by pro-inflammatory cytokines, predominantly interleukin-1 and tumour necrosis factor alpha, which modulates changes in the neurophysiology of the CNS (Hanken et al., 2014). Cytokine-mediated changes in inflammation or stress and tumour necrosis factor alpha, which modulates changes in the neuro-endocrine system, are thought to mediate SB and include anorexia, fatigue, hypersomnolence, mood, anhedonia, poor concentration and attention span, and reduced physical activity (Dantzer, 2004). From an evolutionary perspective, SB probably developed to maximise an animal's chance of recovering from infection. In Multiple Sclerosis (MS) and other autoimmune diseases SB is maladaptive and indicates ongoing inflammation.

MS has a high socioeconomic impact relatively early in the course of the disease; approximately 50% of people with MS (pwMS) are unemployed at EDSS 3.0-3.5 a level that is not overtly associated with physical disability (Kobelt and Gisela, 2004). What is driving early unemployment rates in MS is cognitive impairment, which typically manifests with fatigue, depression and anxiety. Early-effective treatment of MS is now being promoted as a treatment strategy to prevent irreversible damage from accruing that is linked to poor outcomes and long-term disability (Giovannoni, 2016).

In this issue Fenu and colleagues demonstrate in a brief longitudinal study over approximately 2 months that an improvement of cognitive function, due to practice effects, using the Symbol Digit Modality Test (SDMT) was lower in patients with Gd-enhancing lesions at baseline compared to patients without Gd-enhancing lesions (Fenu et al., 2018). Their findings imply that patients with active MS, as measured using Gd-enhanced MRI, have either reduced ability to learn or diminished cognitive reserve. It is not clear whether this represents sickness behaviour due to MS-related CNS inflammation or structural damage. If reduced learning is due to SB then cognitive function should improve with suppression of inflammatory activity, i.e. reversal of the so-called ‘inflammatory MS encephalopathy’, which is hypothesised to be due to ‘sickness behaviour’. In support of these findings and the SB hypothesis is an observational study of patients with MS treated with natalizumab, which documented cognitive improvement over 5 years of treatment (Mattioli et al., 2015). Similarly, in a prospective one-year study, patients treated with natalizumab scored better in several cognitive domains and in global cognitive measures. The improvement was similar to control patients that were stable on interferon beta treatment (Sundgren et al., 2016). These studies suggest that cognitive impairment in MS is not necessarily permanent and potentially reversible with disease modifying therapies.

In summary, MS is associated with early cognitive impairment that reduces quality of life, daily functioning (Glanz et al., 2010) and employability (Iao et al., 1991). New insights from studying patients on disease-modifying therapies, in particular high-efficacy therapies, infer that at least a component of the early cognitive impairment may be reversible. We suspect this is due to suppression of inflammation that allows some patients to recover from maladaptive sickness behavior and augments neuronal mechanisms such as axonal, synaptic and cortical plasticity. The demonstration of early cognitive impairment may not necessarily be bad news.

**References**


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