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Collapsing networks: new avenues for functional connectivity analyses in multiple sclerosis

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Summary

Multiple sclerosis features extensive damage to both the grey and white matter. Over the years, studies have attempted to elaborate the specific mechanisms by which structural damage leads to complex symptoms like cognitive impairment. Recent advances in the field have highlighted the value of functional and structural network changes in multiple sclerosis. In this mini-review, some of these latest findings are discussed in the context of the hypothesis of a "network collapse", though to underlie clinical progression.

Keywords: *multiple sclerosis*, *fMRI*, *cognition*, *progression*, *neurodegeneration*, *disability*, *network*

Multiple sclerosis is a network disorder

Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease of the central nervous system, featuring white and grey matter damage [1]. Clinically, patients commonly present with motor, sensory and cognitive changes that are not easily related to conventional magnetic resonance imaging (MRI) findings, the so-called clinico-radiological paradox [2]. Advanced (research) techniques show that damage extends far beyond lesional areas, indicating a “disconnection syndrome” in MS [3]. Long-range connections seem to be especially affected; these are particularly relevant for maintaining normal brain functioning and hence cognition [4]. Complex network topology calculations can estimate the efficiency of the structural network, which has been shown to be abnormal in MS and strongly related to disability [5]. In fact, this added layer of “network efficiency” was able to explain much more variance than a simpler summary of damage alone, highlighting the added value of such a network approach. As such, MS is now commonly seen as a network disorder, rather than a disease featuring only focal pathology.

Network-based neurodegeneration

New advances have now highlighted that neurodegeneration in MS is non-random and seems to begin in network hub areas such as the thalamus [6], a region connected to almost the entire cortex. Interestingly, thalamic atrophy seems to be driven by its progressive structural disconnection from the cortex [7], although this remains a topic of debate (fig. 1). In more advanced stages of the disease, atrophy is more extensive in the cortex itself, especially in regions belonging to the so-called default-mode network [8]. Cortical atrophy even seems to accelerate in progressive MS [9], which may explain the sudden and relentless clinical deterioration of progressive patients. In fact, neurodegenerative predictors of cognitive decline depend on the disease stage: thalamic in early disease, but cortical in later (progressive) stages of MS [10]. It is therefore tempting to speculate that the spreading of neurodegeneration across the brain is driven by the progressive network disconnection in MS, further highlighting the importance of studying both functional and structural network patterns in MS.

Functional network destabilisation

Looking at patterns of functional (dys)connectivity in MS, network hubs such as the thalamus are also implicated early. Functionally, the thalamus shows extensive changes in connectivity strength in MS [11], which is worst in progressive patients [12]. Overall, thalamic connectivity findings in MS are highly complex, featuring a combination of hyper- and hypo-connectivity, both related to poorer functioning [13]. The cortex also shows functional changes from the very beginning, indicated by a progressive structure-function decoupling [14]. In patients with more severe cognitive deficits, cortical changes again seem to be centred around default-mode areas, which seems to be “stuck” in a highly connected state, having lost normal network dynamics that are essential for normal cognitive functioning [15].

The network collapse

Recent work seems to indicate that functional changes in MS are driven by the severity of white matter damage, heralding a sudden and rapid decline in network complex-

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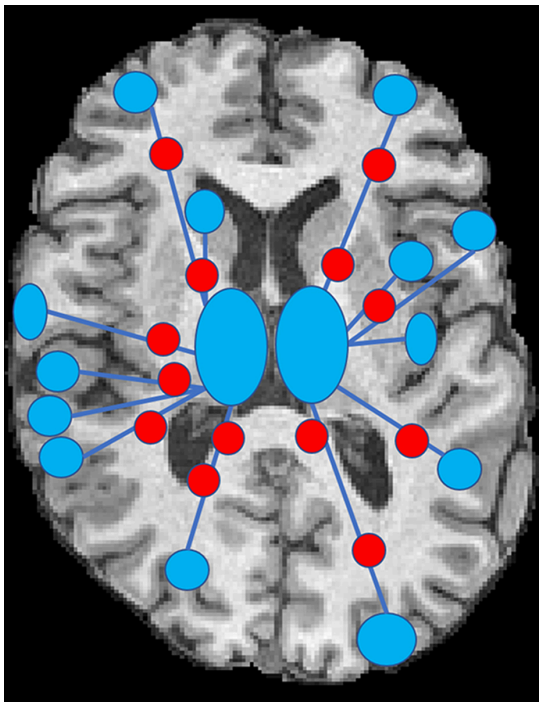
Figure 1: Schematic representation of thalamic disconnection in multiple sclerosis. The thalamus is a network hub in the brain, i.e., it is connected to almost the entire cortex. White matter lesions (red) will commonly damage thalamo-cortical connections (blue lines), resulting in early and progressive thalamic atrophy in multiple sclerosis. Cortical neurodegeneration becomes prominent at later stages, involving hubs such as the default-mode network. It is thought that this neurodegenerative spreading and clinical progression is accelerated after the severity of network disconnection exceeds a certain threshold, the so-called "network collapse".



ity and efficiency [16]. This sudden change has therefore been termed the "network collapse" [17] and hypothesised to underlie clinical progression in MS. The onset of this collapse seems to occur after a specific threshold of damage, perhaps a specific severity of thalamic disconnection and/or atrophy. This hypothesised longitudinal trajectory of functional and structural network changes in MS remains crucially understudied, however, highlighting a new avenue in MS research. By validating these state-of-the-art network techniques for use in clinical practice, we may soon be able to find ways to identify who is most at risk for the collapse, and thus clinical progression, and why.

Key points

- Multiple sclerosis is a network disorder, featuring extensive structural disconnection
- Neurodegeneration and functional network changes seem to spread from the thalamus towards cortical areas as the disease progresses
- A sudden loss of functional network efficiency in MS is termed the "network collapse", and is thought to underlie clinical progression
- This network collapse seems to be driven by the severity of disconnection throughout the network

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