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A multifaceted approach to understand cognitive impairment in MS: exploring the nonlinearity of cognition

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**The importance of network
changes for cognition**



3.1

Coupling structure and function in early MS: How a less diverse repertoire of brain function could lead to clinical progression

M. van Dam, H.E. Hulst & M.M. Schoonheim.

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MS is characterized by extensive tissue damage in the CNS, which affects both the structural and functional brain network and its individual connections. Recent evidence has shown that network abnormalities in MS play an important role in complex symptoms such as cognitive impairment,¹ although interpreting these findings has been difficult. For instance, increased functional connectivity has been described as beneficial, maladaptive or both at the same time.¹ To address this problem, the field has since moved towards more advanced network techniques, indicating that clinical progression is related to a sudden loss of network efficiency, the so-called network collapse.² However, these studies have mostly been performed in relatively late MS stages, leaving behind a crucial lack of knowledge on early MS. Taken together, we are currently unable to predict which patient is most at risk for the network collapse and why. Interestingly, in the very few datasets on early MS, functional connectivity changes seem already extensive when compared to the healthy situation, despite limited structural damage.³ But what does this mean?

This paradoxical finding (i.e. little structural but extensive functional network changes) could indicate that some patients with early MS might be more prone to early network changes than others. To quantify this vulnerability a joint analysis of brain structure and function is therefore needed. Conceptually, such a measure of “coupling” would be high when structure and function overlap to a great extent (i.e. are more similar), and low when there is little overlap between structure and function. This coupling seems to be low in the healthy human brain, as the brain displays a seemingly limitless functional repertoire, despite a static structural network.⁴ This combination could therefore enable the functional network to reorganize itself when needed, which seems to be disturbed in later stages of MS.⁵ Studies in neurology outside MS have additionally shown that structure-function coupling can detect more subtle network alterations that are clinically relevant, compared to unimodal approaches.⁶ Unfortunately, such analyses in MS remain rare.

In this issue of Multiple Sclerosis Journal, Koubiyr et al.⁷ address this research gap by investigating how the changing structure-function coupling explains clinical progression in 32 clinically isolated syndrome (CIS) patients and 10 matched healthy controls. Subjects were followed over a period of five years, and were measured at baseline, year one and year five. Structural connectivity was derived using probabilistic tractography on diffusion tensor imaging and functional connectivity using resting-state functional MRI. Coupling between the two modalities was calculated for each individual by correlating structural and functional connectivity matrices, signifying the amount of similarity and hence coupling. Short-term effects of the cohort had been investigated previously,³ demonstrating regional decoupling, possibly indicating beneficial changes that were limited to the salience, visual and sensorimotor networks. In the current paper, longer term results actually showed maladaptive changes, as the global network coupling increased over five years,

which was related to clinical progression (e.g. worsening cognitive functioning and physical disability). The authors interpret these findings as a constraint of functional connectivity: The damaged structural backbone of the network no longer allows for the normally diverse repertoire of brain function. This concept is further illustrated in Figure 1.

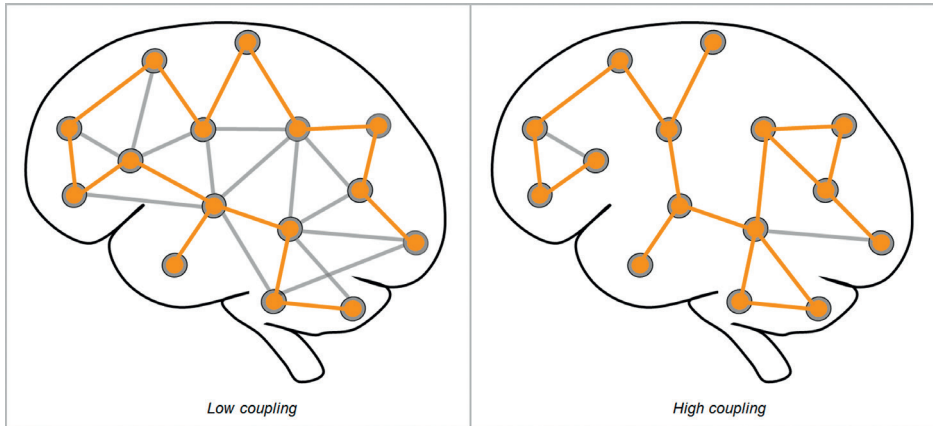


Figure 1. Structure-function coupling in relation to clinical progression in MS.

Structural connections (lines) are indicated between the different brain regions (circles). Functionally, some connections are more commonly used (orange lines) than others (grey lines). Left: Coupling between structural and functional patterns is low at disease onset (i.e. not all connections are orange). The dynamic functional repertoire of the brain is preserved, which allow for complex processing demands if needed. Right: As MS continues to disconnect structural pathways, brain function can no longer express its full dynamic repertoire, limiting possible reconfigurations of the network. Thus, brain function is forced to use the same underlying pathways continuously, and coupling will increase (relatively more connections are orange). This limited repertoire could hamper information processing and induce clinical progression.

There are some limitations to note regarding the work of Koubiyr et al,⁷ however. For instance, the included patients were diagnosed according to the 2010 McDonald criteria, the standard at the time of inclusion. However, when applying the 2017 McDonald criteria, 28 of the 32 patients would actually be diagnosed with definite MS at baseline, which could indicate that even in the current study the earliest changes might not have been captured. Although the study included longitudinal data spanning multiple years, results should be validated in other cohorts with larger sample sizes. Furthermore, within the growing field of network neuroscience, there is little consensus on how best to measure the coupling of structural and functional network characteristics. The current approach only analyzed functional

connections when there was a direct underlying structural tract, even though indirect functional communication might still be important for cognition. In addition, a more complex framework has recently been introduced to study coupling, defined as multilayer network imaging.⁸ This approach calculates network measures across multiple modalities (“layers”) as part of one large network, allowing for a more sophisticated calculation of structure-function interactions.

Another important development in network neuroscience resides in the discovery of so-called “dynamic” functional connectivity. This concept measures the variation of connectivity patterns during a single scan session, which could actually quantify the previously mentioned “repertoire”. The body of literature on dynamic network changes in MS remains limited, but has indeed shown that the dynamic behavior of the brain network is disrupted in early MS,⁹ as well as in cognitively impaired MS patients.⁵ Future work is now needed to further assess the predictive potential of this coupling, especially in the context of “multilayer” and dynamic network imaging. As more studies will hopefully continue to emerge on early MS,¹⁰ it is now crucial to determine how we should approach and interpret network abnormalities in MS to avoid further confusion.

To conclude, the study by Koubiyr et al.⁷ adds important information to the field, as the current lack of data in early MS remains problematic. This disease stage might reveal specific hallmarks related to the coupling between structural damage and functional network changes, indicating an imminent clinical progression. Determining these hallmarks is necessary to understand the mechanism underlying clinical progression in MS and to predict which patients are at risk for a network collapse. In addition, these data might enable us to delineate an optimal window of opportunity to intervene in order to prevent the network from collapsing.

REFERENCES

1. Chard D, Alahmadi A, Audoin B, et al. Mind the gap: From neurons to networks to outcomes in multiple sclerosis. *Nature Reviews Neurology* 2020. In Press.
2. Tewarie P, Steenwijk MD, Brookes MJ, et al. Explaining the heterogeneity of functional connectivity findings in multiple sclerosis: an empirically informed modeling study. *Human brain mapping* 2018; 39: 2541-2548.
3. Koubiyr I, Besson P, Deloire M, et al. Dynamic modular-level alterations of structural-functional coupling in clinically isolated syndrome. *Brain* 2019; 142: 3428-3439.
4. Braun U, Schäfer A, Walter H, et al. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. *Proceedings of the National Academy of Sciences* 2015; 112: 11678-11683.
5. Eijlers AJ, Wink AM, Meijer KA, et al. Reduced network dynamics on functional MRI signals cognitive impairment in multiple sclerosis. *Radiology* 2019; 292: 449-457.
6. Dai Z, Lin Q, Li T, et al. Disrupted structural and functional brain networks in Alzheimer's disease. *Neurobiology of Aging* 2019; 75: 71-82.
7. Koubiyr ID, Deloire M, Brochet, B, et al. Structural constraints of functional connectivity drive cognitive impairment in the early stages of multiple sclerosis. *Multiple Sclerosis Journal* 2020. In Press.
8. Muldoon SF and Bassett DS. Network and multilayer network approaches to understanding human brain dynamics. *Philosophy of Science* 2016; 83: 710-720.
9. Rocca MA, Hidalgo de La Cruz M, Valsasina P, et al. Two-year dynamic functional network connectivity in clinically isolated syndrome. *Multiple Sclerosis Journal* 2020 May;26(6):645-658.
10. Hidalgo de la Cruz M, Valsasina P, Mesas S, et al. Clinical predictivity of thalamic sub-regional connectivity in clinically isolated syndrome: a 7-year study. *Molecular Psychiatry* 2020; Apr 22.