Cumulative evidence for MS as a neural network disconnection syndrome consistent with cognitive impairment mechanisms and the confounding role of fatigue and depression

outlook from the Fourth Nordic MS symposium

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Conclusion: Cumulative evidence for MS as a neural network disconnection syndrome consistent with cognitive impairment mechanisms, and the confounding role of fatigue and depression - Outlook from the Fourth Nordic MS Symposium

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Abstract:
The Fourth Nordic MS symposium served as a platform to present an overview over the rise and impact of cognitive impairment in people with MS, from early stages on, impairing their quality of life. After discussing MS and cognitive impairment symptoms, a review on the pathophysiology underlying cognitive impairment was given, followed by a talk on neuroimaging highlighting cortical reorganization in MS-affected brains. As a conclusion, therapy and treatment options were discussed. The symposium presented several cutting-edge research studies providing or testing working models that appear successful in predicting and explaining cognitive impairment in MS, such as the disconnection syndrome.
The prevalence of cognitive impairment in people with MS is well-known, but several facets of its mechanisms are poorly understood. The disconnection syndrome description of MS characterized by network disruption is one of the most recurring models underlying cognitive impairment and it is thought to be caused by several neurodegenerative processes that start early. Cognitive impairment is already reliably reported in early stages by around half of the MS population, in the form of and in relation to - initially temporary - changes in mood, fatigue, working memory decline and other cognitive deficits [1,2]. An important current debate addresses whether neural changes related to cognitive functioning in MS are adaptive or maladaptive. Even though many neural changes are still referred to as conceivably compensatory, perhaps most neural changes should be assumed to be maladaptive as they are often paired with cognitive impairments. Damage of strategic grey matter areas such as the thalamus - which has many cortical and subcortical connections and shows atrophy already during the earliest disease stages -, may play a distinctive role in cognitive dysfunction [3].

Recently, it has been verified that a very significant protection for cognitive impairment is provided by brain reserve, which can be defined as maximal lifetime brain growth, and cognitive reserve or intellectual enrichment evoked by for example reading and creating [4,5]. Level of education also seems to have a different protective effect on MS [6]. Cognitive impairment in MS cannot be defined as a decline in general intelligence, as current research confirms that one of the key cognitive domains that are first and foremost affected in MS is processing speed [7]. Subsequently other domains such as memory, sustained attention, verbal fluency, and visuospatial learning are affected. Differences between subtypes of MS have been observed; primary progressive MS patients experience most often cognitive decline while often overestimating their cognitive performance. In contrast, relapsing-remitting MS patients experience least often cognitive decline, however they tend to underestimate their cognitive performance [8,2].

The first session addressing cognitive symptoms in MS was opened by Päivi Hämäläinen who presented the effect of rehabilitation techniques on cognitive impairment [9]. Cognitive impairment cannot be explained by the symptom of fatigue, which about 80% of the MS patients experience, nonetheless is cognitive fatigue quite visible during cognitive tasks [10]. The necessity of early intervention is emphasized and can be achieved by an individually tailored program, if necessitated by widespread cognitive impairment through a multimodal neuropsychological approach [11–13].

An overview over neurological changes in relation to MS was given by Gro Owren Nygaard [14]. Neural correlates to MS progression are heterogeneous including lesions, atrophy and damage invisible with conventional imaging techniques such as magnetic resonance imaging (MRI). Cognitive impairment however seems to have correlates in the form of reduced thalamic volume [15] and amount of cortical lesions [16]. Decreased cognitive performance was reported to correlate with decreased thickness or volume of relevant cortical structures [17]. The results were heterogeneous, consistent with heterogeneity of MS patients likely related to their
varying levels of cognitive reserve. Whereas functional reorganization of the MS brain used to be a favorable explanation for the functional activation and connectivity changes observed in the cognitive impaired MS brain, a more contemporary hypothesis suggests that if structural damage is accumulated, it may cause network collapse and thus disrupt network efficiency which promotes in turn a cascade of cognitive impairments [18].

Confounding factors including fatigue, neurological impairments, comorbidities and therapy side-effects that complicate the diagnosis and prognosis of MS were discussed by Emilio Portaccio, who focused on depression as comorbidity [19]. Depression in people with MS can be a symptom either as a cause of, or a reaction on having MS, but it can also be a separable syndrome [20]. Cognitive functioning as well as fatigue – both present but changing factors in MS patients – play a role in the development of MS [20]. Depression directly affects cognitive abilities in people with MS and has a direct relationship with fatigue [21]. A review by Feinstein summarizes how depression in MS may impair cognitive and attentional capacity which impairs working memory and in specific executive functions [22]. Furthermore, a difference in effect of depression on subjective and objective cognitive evaluation has been shown [23]. Overlap of brain regions affected by depression and by cognitive impairment is found in regions such as the hippocampus and frontal regions [20].

Different functional MRI (fMRI) methods may look at activation changes during task, functional connectivity changes between regions of interest during task or rest, or an investigation of network connectivity, either task-based networks or intrinsic brain activity alterations emerging during rest. Rest refers to a state in which a participant is left to his or her own thoughts [24]. Investigating resting state data overcomes for instance the bias of MS patients matching task performance with healthy controls, as no task performance is required. Robustly, intrinsic functionally connected networks spontaneously fluctuate in activity in healthy participants [25]; some of these networks are hypothesized to show altered connectivity in people with MS.

Seed-based functional connectivity analysis calculates connection strength between a region of interest (the seed) with other regions or voxels in the brain. With this method, differences investigating connectivity between specific regions during task were found for people with MS, who exhibited an absent connectivity pattern between the left amygdala and prefrontal cortices, both ventrolateral and medial, unlike healthy controls. However, people with MS had increased activation in ventrolateral prefrontal cortex, perhaps reflecting - and even compensating for - a disrupted network [26].

Iris-Katharina Penner further discussed neural networks, and how a connectivity collapse or disconnection syndrome in key regions for crucial cognitive functions may explain cognitive impairment progresses in people with MS [27–29]. This model can also be applied to explain fatigue, as fatigue may be a result of lesions disrupting frontal and parietal networks [30], but is also related to atrophy in the corpus callosum [31]. Fatigue reports are always subjective due to the lack of objective measurements, however - as discussed above - fatigue symptoms are correlated to,
and thus confounded by, cognitive impairment and depression. It is therefore of importance to use a highly sensitive and specific scale to measure fatigue [32]. To decide about treatment for the patient, the MS decision model was recently developed, which includes neuropsychological aspects such as fatigue and depression in treatment decision making, and better reflects the complexity of the disease even in early stages when other scales cannot [33].

The second session investigating the pathophysiology of cognitive impairment in people with MS was started by Friedemann Paul, who presented some conventional and more specific non-conventional MRI methods [34]. It is known that white matter lesions cannot explain all cognitive impairment, and damage to normal appearing white matter (NAWM) and to grey matter affects cognitive performance as well. Long-term prognosis and disability of MS may be better explained by cortical lesions, grey matter atrophy [35], and by diffuse damage in NAWM, fitting with the aforementioned disconnection syndrome underlying physical and cognitive MS deficits [36,37]. A robust longitudinal study by Calabrese and colleagues investigating pathology in over 300 MS patients underlines the interaction between lesion volumes of white matter and gray matter pathology, relative to the disease duration, in order to predict cognitive function over five years [16]. Of interest is that neurodegeneration such as grey matter atrophy occurs already in the very early stages of MS, before the clinical threshold is reached to diagnose MS based on symptoms [38].

The talk of Thomas Berger aimed to elucidate the effect of immunological processes on cognitive impairment, due to the fact that MS is an inflammatory disease [39]. Inflammation drives all neurodegeneration, and therefore addressing (pre-) inflammatory processes may halt all neurodegeneration. Similarly to processes visible during fever - an immunological reaction with a behavioral response (fatigue, social withdrawal, anorexia, depressed mood, etc.) - the immune system interacts with the brain to alter behavioral processes [40,41]. Moreover, correlations of lymphocytic populations with cognitive functioning have been found in relation to MS [42].

Maria Rocca discussed in the third session on cortical reorganization whether functional reorganization observed in people with MS with the use of fMRI would be adaptive or maladaptive [43]. Several studies show increased recruitment of bilateral cortical regions during cognitive tasks, which is related to T2 lesion load [44] or NAWM or grey matter damage [45]. This leads to the question whether the structural and functional connectivity is affected, and a study by Rocca and colleagues on effective connectivity related to white matter tract integrity found that in benign MS there was a relation between functional connectivity during a Stroop test and damage in white matter tracts, but only in those tracts that were cognitively related to the task [46], indicating a strong connection between structural damage and functional changes in MS. Within MS there are several intra- and inter-network abnormalities observed which favors the adaptation of the disrupted network model explaining cognitive impairment in MS. One of these disrupted networks is the default mode network (DMN), which consistently deactivates when a task is
executed, but surfaces when a participant engages in unguided self-reflective thoughts or 'day-dreaming', and is a robust network observed as one of the fluctuating networks during resting state. Cognitive impairment and structural damage in severe MS showed correlation with reduced connectivity of the anterior node of the DMN. Interestingly, in pediatric MS patients the posterior rather than the anterior node is affected [47]. Graph theory studies that describe the brain and its neural networks as interconnected nodes have identified consistently that cognitive impairment in MS is characterized by a loss of hubs in the frontal lobe [29], similarly is fatigue in MS characterized by a loss of hubs in the frontal lobe, basal ganglia and thalamus. To understand the connectomics and the underlying pathology of MS, the reader can be referred to the recent comprehensive review by Fornito and colleagues [48].

The last session covered evidence-based therapy for cognitive impairment, which is of interest due to the lack of symptomatic treatment for cognitive impaired MS patients [49]. In this session Fredrik Piehl introduced different symptomatic treatments of fatigue and depression [50]. In search for the molecular background, as recent as this year some subthreshold indications were found for lower levels of tryptophan (which would result in less serotonin) in people with MS with depression, together with indications of its neurotoxic effects through byproducts after degradation [51]. There is as of yet not enough evidence to validate an MS-specific anti-depressant treatment of major depression. Fatigue treatment with non-pharmacological interventions exist, but are of uncertain clinical relevance (e.g. [52]), likewise there are no known successful and effective pharmacological treatments of fatigue. However, physical training, even in the form of high-intensity training, has very promising effects on fatigue in MS patients [53,54].

Lastly, Tjalf Ziemssen discussed disease modifying therapies (DMTs) in regard to cognitive function in MS and identified the problems of identifying cognitive functions [55]. This problem arises because compensatory neural adaptations come automatic to the patients, therefore cognitive impairment should be measured by specific tools measuring impairment during specific stages of MS. The current studies leave more questions to be answered before the positive effects of DMTs can be interpreted free from confounding factors [56].

**Conclusion**

There is ample ground to regard cognitive impairment as a result of disrupted cognitive network functionality in MS, this is possibly an effect of a maladaptive strategy of the brain upon gaining white matter and cortical lesions and changes in normal appearing white matter. It is clear that cognitive impairment starts during early stages of MS, following neurodegenerative processes that are invisible but cumulative and damaging. Therefore, intervention has to start early as well. Fatigue and depression in people with MS can obscure cognitive results, but the emerging body of research enables better separation of these components. However, the investigation of the effect of treatment on cognitive abilities is still under development and needs substantial improvements.
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