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Relation between functional brain imaging, cognitive impairment and cognitive rehabilitation in patients with multiple sclerosis

Abstract Cognitive impairment belongs to the core symptoms in MS affecting quality of life, self-esteem, and social as well as occupational functioning. Due to this high impact on patients' well-being efficient treatment concepts are required. Imaging studies on cognition have shown that functional reorganisation takes place spontaneously to compensate for deficits. In mildly to moderately impaired patients these processes may support coping with emerging deficits. However, these compensatory processes seem to be limited as brain activation of cognitively severely impaired patients is characterised by decreased additional recruitment of brain regions. Cognitive rehabilitation concentrates on the question whether induction of brain plasticity is possible for both the support of the spontaneous processes and the initiation of new ones. Combining cognition, brain imaging and cognitive rehabilitation in MS, an intriguing question is whether fMRI can provide further insights into the mechanisms of induced plasticity and serve as objective outcome measures for efficient cognitive intervention.

Key words brain imaging · fMRI · cognition · multiple sclerosis · cognitive rehabilitation

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Introduction

In general, cognitive impairment is defined as a decline in cognitive performance that has an impact on the subject's social and occupational life. The decline can either refer to cognitive subfunctions such as attention, memory, executive functions etc. or can be a global problem where many subfunctions are affected at the same time. One of the main issues, however, is that the subject experiences psychological strain indicating that alternative cognitive strategies are not sufficient to cope with the impairment.

Cognitive impairment in MS

Cognitive decline was already described by Charcot in 1877 [10] to be one of the key features of MS. Surprisingly, research in the following decades focussed solely on the physical components of the disease disregarding psychological and cognitive aspects. This disregard, however, was not due to a lack of interest in psychological aspects but reflects how MS was perceived at the beginning of the 19th century. The obvious and visible symptoms clearly derived from the motor system and the understanding of the disease was directed towards neuropathological changes in the white matter. Cognition, on the other hand, was thought to be exclusively a function of the cortex where white matter tracts and subcortical structures play only a minor role [41]. Today, it is well-known that the fibre integrity of the white matter is essential for cognitive functioning and that cortico-subcortical connections mainly control the information processing speed while fronto-parietal and fronto-temporal connections are mainly responsible for attention, memory and executive processes. Furthermore, cortical demyelination is nowadays also discussed to be one possible feature of tissue destruction in MS. Although three different cortical lesion types were defined

(1. cortico-subcortical compound lesions, 2. small perivascular intracortical lesions, 3. band-like subpial demyeliniation) [8, 21, 36] their contribution to cognitive decline has not yet been clarified. A recently published paper by Kutzelnigg and Lassmann [23] is concerned with the relation of cognitive decline and the different types of cortical lesions. Using sensitive immunocytochemical techniques these specific alterations in the cortex itself are detectable post-mortem. Interestingly, the distribution of cortical lesions might have a direct relation with the cognitive domains mainly affected in MS. However, as imaging techniques are currently not sensitive enough to visualise the different types of cortical lesions, correlative analyses with cognitive test performance are not yet feasible in the living brain. Thus, the scientific focus in MS has changed remarkably by attending to cognitive decline as one of the main symptoms affecting patients with MS. Particularly, this becomes apparent in the high number of emerging publications dealing with cognition and possible correlatives in MS.

Cognitive impairment and structural MRI

Conventional MRI is a well accepted tool in the diagnostic assessment of patients with MS, in characterising lesions and in monitoring disease evolution [26]. However, it is only of low pathological specificity and thus not a powerful correlative for cognitive alterations. This might be one reason for only weak correlations between structure and function in MS [e. g. 9, 17]. Only studies correlating regional lesion volume with specific cognitive functions succeeded in finding better relations [e. g. 42, 46] indicating that a general brain volume decrease can be compensated while destruction of critical and specialised brain regions results in cognitive alterations. These results are in accordance with the hypothesis formulated by Kutzelnigg and Lassmann [23] that the distribution of cortical demyelinated plaques might account for specific cognitive deficits. Disappointingly, a longitudinal study on cognitive dysfunction over 8.5 years [37] showed high correlations between temporal, occipital and frontal lesions and specific cognitive test performances at baseline, but these relations could not be confirmed in the long run. Thus, the increase in the number of regional lesions did not correspond to the evolution of cognitive deficits which means that even local brain pathology can only, in part, explain cognitive changes in MS.

More specific MRI parameters such as whole brain atrophy [1, 5] or atrophy of specific brain regions [4–6, 11, 19], magnetisation transfer [12, 15, 49] and MR spectroscopy [16, 18, 28] show much better correlations with cognitive alterations even in the early phase of MS and even for specific cognitive functions. Thus, brain pathology in terms of irreversible demyelination and axonal loss seems to be related more directly to cognitive impairment although even in this context quantitative and predictive values are still missing.

Cognitive impairment and functional brain imaging

As structural MRI does not provide a satisfying explanation for cognitive decline, functional brain imaging might be a more powerful approach to characterise cognitive alterations in MS. Indeed, changes in functional brain organisation can already be observed in the very early stages of the disease.

PET/SPET

PET and SPET studies on cognitive decline in MS report metabolic changes. Deficits in perfusion, mainly concentrated on the left hemisphere, were reported in the frontal and temporal lobe [31, 39, 40, 44] as well as global and regional reduction in cerebral glucose metabolism [7]. These results indicate that hypometabolism of brain regions related to specific cognitive functions might be one critical factor in the development of cognitive decline in MS.

MR spectroscopy

MR spectroscopy as a method to evaluate axonal integrity has been used sparsely to study cognitive alterations in MS. In a study by Pan et al. [28] lower N-acetyl aspartate (NAA) levels in predefined regions of interest were correlated with specific cognitive functions. Accordingly, a recently published study by Gadea et al. [18] reports lowest NAA/Cr levels in RRMS patients who showed the highest decrease in attention performance. Thus, NAA seems to provide a specific measure for pathological changes in the CNS that are especially responsible for cognitive functioning.

fMRI

In accordance with studies on the motor system [e. g. 29, 43] fMRI data on cognition show significant changes in brain organisation compared to healthy controls. Interestingly, these changes are already evident at the very early stages of the disease, when cognitive deficits are not yet clinically detectable [2, 3]. Additional activation, mainly in the prefrontal cortices during the performance of a working memory task, was interpreted as a compensatory mechanism that contributes to normal

performance. In mildly to moderately impaired patients, increased and additional activation was observed when patients performed the PASAT [25, 47]. In these cases, a measurable mild cognitive impairment was related to a significant increase in brain activation suggesting that the brain uses alternative pathways to perform the cognitive task. At this point, it is open to discussion whether, as a consequence, severe cognitive impairment will be related to even more additional recruitment of functional areas into a compensatory network. Interestingly, this does not seem to be the case as a comparison between mildly and severely impaired MS patients who performed a tonic alertness task clearly demonstrated that the increase in functional brain activation is significantly reduced in severely impaired patients [35].

From the fMRI studies presented so far we can conclude that CIS patients and those with a mild to moderate cognitive impairment recruit additional functional brain areas meaning (1) that functional changes are already present before deficits are clinically detectable and (2) that the increase in brain activation seems to be responsible for the compensation of a deficit. Further, a lack of those compensatory mechanisms might be responsible for severe cognitive impairment where the MS brain is no longer capable to build up new functional networks. If so, then the relation between functional brain activation and cognitive impairment may be expressed by an inversed u-shaped curve where at some stage of the disease the CNS is no longer able to deal with the widespread destruction of the brain tissue on a functional level.

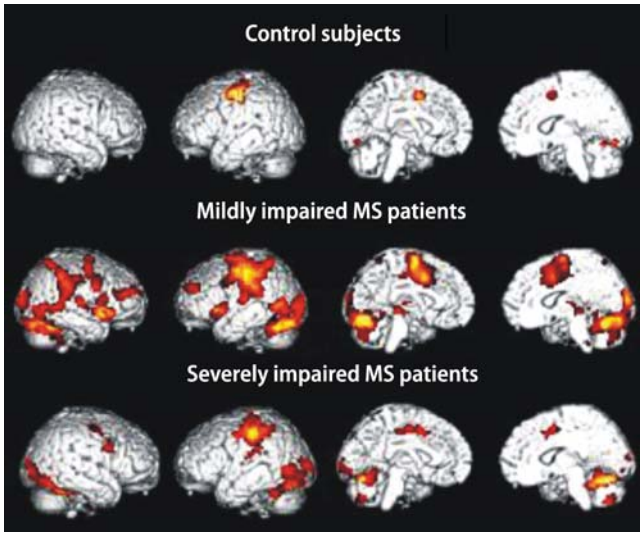

Fig. 1 Functional brain activation patterns for control subjects, mildly impaired MS patients and severely impaired MS patients while performing a tonic alertness task ($p < 0.001$, corrected for multiple comparisons)

fMRI, brain plasticity and cognitive rehabilitation

So far, fMRI studies have shown spontaneous processes of functional reorganisation in the MS brain. The recruitment of additional functional brain regions is assumed to be related to compensatory mechanisms that result in non-pathological behaviour or only moderate impairment. If these mechanisms are powerful enough to keep behavioural performance on a high level then the question arises if it is possible to use this power in cognitive rehabilitation. The rationale would be to identify the cognitive functions mainly affected in a patient, to compose a training procedure for these functions, to stimulate alternative pathways by this training and thereby to improve cognitive functioning. Cognitive rehabilitation can be seen as an intervention aimed at changes in specific neuronal circuits. However, although imaging studies have provided good insight into the mechanisms of recovery and plasticity in MS [2, 3, 25, 35, 47] reliable tools to evaluate the effects of cognitive rehabilitation are still missing [32]. Studies on cognitive rehabilitation in MS are still rare and the results are hardly comparable as cognitive outcome measures, training tools and training procedures differ remarkably [20, 24, 38, 45, 48]. Therefore, the efficacy of cognitive rehabilitation has not yet been proven by using objective readouts. As fMRI provides direct insight into the working brain, one intriguing question is whether this method might be used as a reliable tool to evaluate the effects of cognitive rehabilitation. If cognitive rehabilitation is seen as a procedure to induce plasticity processes in the brain, then fMRI might be useful to verify this assumption. In a first pilot study [33, 34] we tried to determine if a computerised attention training induces alterations in functional brain organisation. For this purpose, cognitively mildly and severely impaired MS-patients were investigated on different attention functions using a computerised attention software and fMRI. For three to four weeks all patients received a computerised training on selective attention. After the

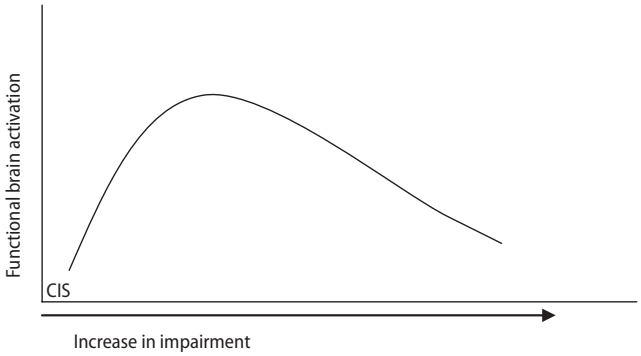

Fig. 2 Schematic illustration of the relation between the evolution of cognitive impairment and the increase in functional brain activation

training interval, all patients were reinvestigated behaviourally and by fMRI. When comparing pre- and post-training fMRI results it became evident that in both groups of patients three attention related structures were activated in addition: the posterior cingulate cortex, the precuneus and the dorsal frontal gyrus [33, 34]. These three structures have specified functions in the attention network including focussing and inhibition [50], attentional shifting and task switching [13, 22, 27] and selection of action [30]. As a clear increase in behavioural performance could be verified one can conclude that the attention training caused recruitment of specific attentional areas that finally resulted in behavioural improvement. However, these findings cannot be generalised, since the study included only 11 patients and behavioural effects were small. Nevertheless, these data should motivate to start cognitive rehabilitation studies on more homogeneous patient cohorts and to define a gold standard for primary outcome measures and training tools. Finally, studies that are aimed at defining the most efficient training interval are needed. At present, it is not known whether a temporally longer and more distributed intervention might be more successful than a short and concentrated one. In a study by Draganski et al. [14] a three month training on juggling even induced changes in grey matter indicating that changes in brain structure are already evident after a short period of time. If we combine these results with those of our pilot study and suppose that structural changes last longer than functional changes we can assume that a powerful training should last at least four to 12 weeks to induce functional changes. However, the uncertainty remains as to how intensive a training procedure has to be to produce an optimal outcome. Studies to clarify these questions are needed to provide efficient rehabilitation tools for MS patients in the future.

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