Cognition and cognitive rehabilitation in adult and juvenile patients with Multiple Sclerosis

Cumulative Dissertation

submitted in partial fulfilment

to obtain the degree of

Doctor of Philosophy of the Department of Psychology, of the University of Basel

by

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Basel, 2015

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Statement of Authorship

I. I, Martina Hubacher, hereby declare that I have written the submitted doctoral thesis "Cognition and cognitive rehabilitation in adult and juvenile patients with multiple sclerosis" without any assistance from third parties not indicated.
II. I only used the resources indicated.
III. I marked all the citations.
IV. My cumulative dissertation is mainly based on three manuscripts, of which one is already published and two are actually under review. I certify here that the articles in this dissertation concern original work. I contributed substantially to the idea and conception of all manuscripts in this dissertation and have been primarily responsible for data collection, analyses, and writing of manuscripts two and three. This characterization of my contributions is in agreement with my co-authors' views.

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Abstract

Multiple sclerosis (MS) is accompanied by cognitive deficits in half of adult patients and in one third of children. These deficits have a serious impact on daily functioning of patients and may influence the ability to achieve educational goals and participate in professional and social life. Therefore, the focus of this thesis is on cognitive deficits, especially the core deficit regarding working memory (WM), and their treatment with cognitive rehabilitation. The present dissertation contains three original manuscripts that target these topics and further investigate A) the importance of cognitive functioning and the utility of neuropsychological testing in MS patients, B) different patterns of response to WM training regarding cognitive and brain function in adults with MS, and C) effects of WM training in juvenile patients with MS.

Contents

Introduction and aim of the thesis

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS) with a highly heterogeneous clinical presentation. On average, the disease onset is between 20 and 40 years of age (Barten, Allington, Procacci, & Rivey, 2010). The incidence rate of MS in children is low, nevertheless juvenile MS is increasingly becoming the focus of research because of the severe impact the disease may have at this young age. After the age of 18, incidence increases reaching a peak between 20 and 40 years, but women are affected earlier than men (2-5 years; Confavreux & Vukusic, 2006). Afterwards, the incidence decreases and MS is rare above ages of 50 years. The prevalence rate of MS in Europe is about 83/100,000 with a mean annual incidence rate of about 4.3/100,000 (Pugliatti et al., 2006). In Switzerland (Canton Berne), the prevalence rate in 1986 was high, with approximately 110/100,000 (Beer & Kesselring, 1994).

Next to the often-described physical disability due to MS, many patients experience cognitive decline. Therefore, after a general introduction to MS, this thesis will in the first part focus on cognitive dysfunction and its impact on daily life in adult as well as in juvenile MS patients. Further, we attempt to underline the relevance that cognitive functioning may have on clinical decisions, including treatment options. We therefore conducted a case study that not only illustrates the impact of MS-related symptoms but primarily highlights the utility of neuropsychological testing, even for guiding treatment decisions in juvenile MS patients:

Study 1 (Appendix A): Penner, I.-K., **Hubacher, M.**, Rasenack, M., Sprenger, T., Weber, P. & Y. Naegelin (2013). Utility of neuropsychological testing for guiding treatment decisions in paediatric multiple sclerosis. *Multiple Sclerosis Journal, 19* (3), 366-368.

In the second part, working memory (WM), a core cognitive function, is described in more detail with regard to the psychological model and the underlying functional brain correlates. Because of the importance of normal cognitive functioning for everyday life, treatment possibilities for cognitive deficits in MS will be described with a focus on cognitive rehabilitation and training approaches. In this domain, literature on the effects of specific WM training is rare and underlying brain plasticity processes have not yet been described. Therefore, a case series assessing the effects of computerized WM training on cognitive functioning and fMRI measured on an individual basis tries to fill this gap in the existing literature by describing different patterns of response:

Study 2 (Appendix B): **Hubacher, M.,** Kappos, L., Weier K., Stoecklin, M., Opwis, K., Penner, I.K (under review). Case-based fMRI analysis after cognitive intervention in MS: A Novel Approach.

To our knowledge, there are no data available on the effects of cognitive rehabilitation in juvenile MS patients. We therefore conducted a second case series to gain first insights into cognitive rehabilitation in adolescents with MS:

Study 3 (Appendix C): **Hubacher, M.**, DeLuca, J., Weber, P., Steinlin, M., Kappos, L., Opwis, K. & Penner, IK. (under review). Cognitive rehabilitation of working memory in juvenile Multiple Sclerosis – Effects on cognitive functioning, functional MRI and network related connectivity.

The last chapter contains a general discussion focusing on three different topics. First, because the two case series were conducted according to the same study design, a comparison between the effects of cognitive training in adult and juvenile MS patient is drawn. Second, factors for response to cognitive rehabilitation approaches are discussed on the basis of the case series and existing literature. The third part describes methodological limitations and implications for further research.

Multiple sclerosis

Aetiology and pathogenesis of MS

In the aetiology of MS various concepts are discussed. Complex genetic traits may influence the possibility of a later MS. Next to twin studies, which demonstrate a higher concordance rate in homozygote siblings (Ebers et al., 1986), and studies describing familial clustering (Robertson, et al., 1996; O'Gorman, Lin, Stankovich, & Broadley, 2013), genome-wide studies have identified a number of associated common variants. Many of these variants implicate genes associated with immunological processes (Sawcer, Franklin, & Ban, 2014). Nevertheless, genetic factors may only be factors for predisposition. The observation that prevalence of MS varies in different geographical regions, with lower incidences in regions near the equator (Simpson, Blizzard, Otahal, Van der Mei, & Taylor, 2011), is one example that strongly supports the involvement of environmental factors. Further, there is growing evidence for a viral contribution to MS (Maghzi et al., 2011; Mecha, Carrillo-Salinas, Mestre, Feliu, & Guaza, 2013). To summarize, there is evidence for both genetic and environmental factors and possible interactions.

MS is defined by the occurrence of widespread plaques or lesions within the central nervous system (CNS). MS lesions can be located in any part of the CNS, but are typically seen in periventricular regions, and can vary in their extension and volume. For many years, MS was regarded as with-matter disease, but new imaging techniques have drawn attention to grey matter lesions.

Two main processes drive MS pathology: Inflammation and degeneration. Inflammation occurs after leakage in the blood–brain barrier, which leads to an influx of immune cells. Whether this immune response is a classic autoimmune reaction (Lucchinetti et al., 2011) or is a secondary reaction to other processes within the brain (Geurts, Stys, Minagar, Amor, & Zivadinov, 2009) remains unclear. The classic autoimmune theory of MS pathology suggests that inflammatory processes lead to focal demyelination, axonal loss and reactive gliosis and thereby to MS lesions (Lassmann, 2004). Of course, the two aspects of inflammation and neurodegeneration are closely related (Frischer et al., 2009), but there is a debate whether neurodegeneration might be a primary process to inflammation (Trapp & Nave, 2008; Nikic et al., 2011) or whether these might even be independent processes (Craner & Fugger, 2011). Neurodegeneration and thereby loss of grey and with matter leads to brain atrophy and to permanent neurological disability (Lisak, 2007; Lassmann, 2007; Klaver, De Vries, Schenk, & Geurts, 2013).

Clinical aspects of MS

During the acute phase of the disease, inflammation leads to neurological dysfunctions. Symptoms of such a relapse can be of a various spectrum dependent on the location of the lesion. In the early stages, these symptoms include visual impairment and orbital pain (e.g., optic neuritis) or sensory and motor disturbances.

Diagnosis of MS is based on the combination of the clinical presentation, cerebrospinal fluid findings as oligoclonal bands or elevated immunoglobulin G index, evoked potentials and visualization of white matter lesions within the CNS by magnetic resonance imaging (MRI). According to the McDonald's Criteria (Polman et al., 2011), typical MS lesions are disseminated in space and time, meaning that patients have lesions in multiple areas of the CNS and have to experience more than one relapse. The criteria for dissemination in space are fulfilled if there has been more than one T2 lesion in at least two areas (periventricular, juxtacortical, infratentorial or spinal cord). Dissemination in time can be demonstrated by either new T2- or gadolinium-enhancing lesions in a follow-up MRI, or T2- and gadolinium-enhancing lesions in one MRI. Patients that do not fulfil the criteria receive the diagnosis of a clinically isolated syndrome (CIS). Of these patients, 30-70 % later convert to clinically definite MS (Miller, Barkhof, Montalban, Thompson, & Filippi, 2005).

MS occurs in three different main clinical disease courses: relapsing-remitting MS (RRMS), secondary progressive (SPMS), and primary progressive MS (PPMS; Stys, Zamponi, van Minnen, & Geurts, 2012; Lublin & Reingold, 1996; Thompson et al., 1997). RRMS is defined by acute relapses, lasting weeks or months, with neurological symptoms and afterwards a remission phase. Especially in the early stages of the disease, remission might even be complete due to regeneration processes. But during the disease course, pathological aspects might exceed regeneration processes and disability accumulates. Of newly diagnosed patients, 85-90% have RRMS. Within 10 years from disease onset, approximately 50% of RRMS patients experience a slow progression of neurological disorientations with fewer relapses. This disease course is usually termed as SPMS. Further, 10-15% of patients have PPMS, a progressive form of the disease from the beginning with several plateaus but without clinical relapses. Progressive forms of the disease are associated with more neurodegenerative and fewer inflammatory processes (Rovaris et al., 2006).

The clinical presentation of MS is highly heterogeneous. Often-described physical symptoms are sensory disturbances such as numbness or prickling (paraesthesia) or muscle-related symptoms such as spasticity or weakness, and problems with coordination, loss of balance and impaired walking can be observed. Further, patients may experience pain in

extremities, vertigo and dizziness, heat sensitivity or disturbance of micturition. For a clinical rating, the Expanded Disability Status Scale (EDSS; Kurtzke, 1983) is used. The scale ranges from 0 to 10 points with an increase of 0.5 points per step and summarizes symptoms regarding eight functional systems defined by Kurtzke (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and "other"). 0.0 refers to a normal neurological examination, scores from 1.0 to 4.5 represent patients with MS who are still able to walk without help or rest for at least 300 meters, and EDSS scores from 5.0 to 9.5 are defined by the impairment to ambulation.

Next to the well-known physical symptoms, patients often experience cognitive and motor fatigue (61-95% depending on disease course and duration of disease; Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Patti & Vila, 2014). Fatigue is a state of either physical or mental exhaustion that is not explained by other factors such as exertion, lack of sleep or depression. Patients often describe being more fatigued after physical or mental strain and needing more rest and time to recover. Furthermore, mood disorders (50-60% Feinstein, 2011) and cognitive dysfunction are frequently reported in MS patients. Cognitive deficits are the scope of the next chapter within this thesis.

Treatment options for MS

Acute inflammatory relapses are treated with intravenous or oral corticosteroids (Burton, O'Connor, Hohol, & Beyene, 2012). If severe relapse symptoms persist, a second cycle may be considered. To influence the disease course, several disease-modifying treatment options, including immunomodulating and immunosuppressing drugs, are available today. First disease-modifying drugs for first-line therapy were approved in the nineties. Interferon beta and glatiramer acetate ameliorate the disease course if patients have relapses. Therefore they are indicated in CIS and RRMS and a few of them are available for treatment of SPMS. They reduce the annual relapse rate by about 30% compared to placebo. There are a few side effects such as flu-like symptoms or immediate postinjection systemic reaction, injection site reactions and elevated liver enzymes (McGraw & Lublin, 2013). New oral drugs have emerged in the past few years. Fingolimod, which only in Switzerland is approved as first-line treatment (Kappos et al., 2010), teriflunomide (O'Connor et al., 2011), and dimethyl fumarate (Gold et al., 2012) are described to be similar or more effective than older treatment options, but there are no data available for long-term treatment.

If patients do not respond to these first-level treatment options, escalation of therapy might be considered. These drugs are considered to be more potential than first-line drugs, but

more serious side effects may occur. Escalation therapies in MS are for example the immunosuppressive mitoxantrone and natalizumab.

The decision to escalate therapy is today mainly based the occurrence of relapses, disease progression indicated by EDSS worsening, and the enlarging of existing MS lesions or occurrence of new lesion in MRI. Today, there are efforts to include further parameters such as "soft signs" to assess the disease course and thereby support treatment decisions. One example is the recently proposed Multiple Sclerosis Decision Model (MSDM; Stangel et al., 2013; Stangel, Penner, & Kieseier, 2014). Disease course is thereby assessed by the frequency and severity of relapses and MRI criteria, as in previous models, and additionally by cognitive and neuropsychological tests. To rate disease progression, the authors recommend using a modified version of the Multiple Sclerosis Functional Composite (MSFC) instead of the EDSS, because the EDSS might not be sensitive enough to rate changes, especially early in the disease course. The modified MSFC assesses upper and lower limb function, the visual system, and cognitive functioning (processing speed). Additionally to previous models, the MSDM includes neuropsychological factors such as fatigue, depression, anxiety and quality of life. Approaches such as the MSDM reflect the ongoing move away from a focus on physical disease progression and relapse rate towards a more integrative view of the disease.

MS in juvenile patients

Today research focuses increasingly on children and adolescents with MS; however, cases of juvenile MS were already being reported more than 130 years ago. In his review, Marie (1883) described 14 cases. Later, Nolda (1892) collected 25 cases from the literature and in 1904 Müller (1904) reviewed 139 cases in total. It is interesting that even in older descriptions, one can find hints of school problems in these children and cognitive impairments, mainly regarding focusing their attention (Eichhorst, 1896). Of course, it is debatable whether these cases represent children with MS or whether these children were misdiagnosed, because diagnosis was made according to clinical presentation and post-mortem confirmation was rarely obtained. A discussion arose in these times as to whether MS occurs in children.

Today, the diagnosis of juvenile MS is still difficult. For diagnosis of MS in children and adolescents, as in adults, the McDonald Criteria (Polman et al., 2011) can be applied. The most common differential diagnosis is acute disseminated encephalomyelitis (ADEM). ADEM has its peak incidence in children aged about six years and it is more frequent in children younger than ten years than in adolescents (Torisu et al., 2010). ADEM is considered to be a typically monophasic event, often following a previous infection and associated with

symptoms not typical for MS, such as encephalopathy and seizures. Next to these symptoms, neurological symptoms are often comparable to MS (Eckstein, Saidha, & Levy, 2012).

In about 3-5% of MS cases, the disease manifests during childhood or adolescence (Renoux et al., 2007; Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007). MS in children presents itself analogous to adult MS with some slight differences: Most children have a RR onset of the disease (Banwell, et al., 2007; Yeh & Weinstock-Guttman, 2009), with a first event comparable to adult CIS, but relapse rate seems to be elevated in children (Gorman, Healy, Polgar-Turcsanyi, & Chitnis, 2009). Lesion burden is higher in children than in adults (Yeh et al., 2009), reflecting a more inflammatory disease course in children (Chitnis et al., 2012). In younger patients (<11 years), lesions appear to be larger and more ill-defined than in adolescents (Chabas et al., 2010).

In summary of this chapter, MS is highly heterogeneous in its clinical presentation. Its origins lie in inflammatory and neurodegenerative processes within the brain and therefore affect physical, emotional and cognitive functioning. Further, a small number of patients have a disease onset during childhood or adolescence. These juvenile patients are more affected by the disease than patients with adult-onset.

Cognitive deficits in MS

Half of MS patients are affected by cognitive deficits (Amato, Ponziani, Siracusa, & Sorbi, 2001; Rao et al., 1991). Cognitive deficits in MS are as heterogeneous as the clinical presentation of MS patients and can involve multiple cognitive domains. Deficits in attention functions and concentration, executive functions, visuospatial skills, language and cognitive flexibility have been described (Amato, Zipoli, & Portaccio, 2008; Chiaravalloti & DeLuca, 2008; Litvan, Grafman, Vendrell, & Martinez, 1988; Rao, 1986; Prakash, Snook, Lewis, Motl, & Kramer, 2008; Zakzanis, 2000). These deficits can be observed in many MS patients, nevertheless, more frequent are cognitive deficits regarding memory or new learning (Benedict, Cookfair, et al., 2006; Thornton, Raz, & Tucke, 2002), working memory (WM); (Amato et al., 2010; Lengenfelder et al., 2006), and information processing speed (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Goverover, Genova, Hillary, & DeLuca, 2007; Stoquart-ElSankari, Bottin, Roussel-Pieronne, & Godefroy, 2010). These domains are regarded as core cognitive deficits in MS (Calabrese, 2006; Rogers & Panegyres, 2007).

Memory deficits in MS can be observed regarding new learning as well as retrieval (Chiaravalloti & DeLuca, 2008; Thornton, et al., 2002). But there is evidence that a primary deficit in new learning may lead to secondary deficit in retrieval functions because effects regarding delayed recall vanish when controlling for initial learning (Demaree, Gaudino, DeLuca, & Ricker, 2000).

Processing speed, the cognitive domain with the fastest decline in patients with MS (Denney, Lynch, Parmenter, & Horne, 2004), is closely related to WM and their relation has been the subject of intense discussion (DeLuca, et al., 2004; Parmenter, Shucard, & Shucard, 2007). There is evidence that processing speed dysfunctions might to some extent underlie WM deficits in MS patients (Genova, Lengenfelder, Chiaravalloti, Moore, & DeLuca, 2012; Kalmar, Gaudino, Moore, Halper, & Deluca, 2008), because patients are able to increase their accuracy in performance when they receive more time to solve the task (Leavitt, Lengenfelder, Moore, Chiaravalloti, & DeLuca, 2011).

Cognitive deficits may occur from the beginning of the disease. In CIS, deficits regarding memory, information processing speed, attention and executive functions have been described (Feuillet et al., 2007; Khalil et al., 2011; Uher et al., 2014). In early RRMS the same spectrum of cognitive deficits has been observed (Olivares et al., 2005). Further, cognitive dysfunction seems to be more pronounced and severe in the progressive stage of the disease (Denney, Sworowski, & Lynch, 2005; Bergendal, Fredrikson, & Almkvist, 2007).

There are also reports about stability of cognitive functions over time in MS patients (Kujala, Portin, & Ruutiainen, 1997; Rosti, Hamalainen, Koivisto, & Hokkanen, 2007; Sperling et al., 2001); cognitive functions seem to decline (Amato, et al., 2001; Amato, Portaccio, et al., 2010; Feinstein, Kartsounis, Miller, Youl, & Ron, 1992; Reuter et al., 2011) especially core deficits such as memory or processing speed (Strober, Rao, Lee, Fischer, & Rudick, 2014).

The formation of cognitive deficits in MS may go back the multiple pathological processes. T2 lesion load is to some extent associated with cognitive performance (Lazeron et al., 2000). Grey matter pathology has been proposed as better predictor for cognitive functioning (Rovaris, Comi, & Filippi, 2006). RRMS patients with cognitive impairment have a higher cortical lesion burden than patients without cognitive impairment (Calabrese et al., 2009). Memory functions and processing speed, especially, seem to correlate with number of grey matter lesions (Mike et al., 2011; Roosendaal et al., 2009). Nevertheless, Papadopoulou and colleagues (2013) found no predictive value of cortical lesions for cognitive functioning, whereas white matter lesions were a significant predictor for processing speed.

Integrity of fiber tracts in normal-appearing white matter, assessed with diffusion tensor imaging (DTI), seems to contribute to the cognitive deficits (Benedict et al., 2013a; Bester et al., 2013). Cognitive-impaired patients thereby have, compared to cognitive-preserved patients, additional white matter integrity damage in the thalamus, the uncinate fasciculus, juxtacortical areas, brainstem, and cerebellum (Hulst, Steenwijk, et al., 2013). Lesions and diffuse changes in white matter interrupt afferent and efferent connections between brain regions and thereby lead to a disconnection syndrome affecting several cognitive domains (Dineen et al., 2009; Calabrese & Penner, 2007).

Further, whole brain (Deluca, Leavitt, Chiaravalloti, & Wylie, 2013; Zivadinov et al., 2001) as well as cortical and subcortical brain atrophy is associated with cognitive deficits (Amato et al., 2007; Benedict, Bruce, et al., 2006; Riccitelli et al., 2011; Hulst, Gehring, et al., 2013). Thalamus alterations thereby seem to be associated with cognitive decline (Minagar et al., 2013). Thalamus atrophy and subtle thalamus pathology as assessed by DTI are predictors for cognitive status in MS patients (Benedict et al., 2013b). In a study by Schoonheim et al. (Schoonheim et al., 2015), thalamus structure and thalamus function were identified as independent predictors for the severity of cognitive dysfunction.

There is no direct relationship between cognitive deficits and physical disability (Amato, Zipoli, et al., 2008; Amato, Portaccio, et al., 2008) and cognitive deficits are hardly predictable, but several symptoms are associated with their presentation. Depressive symptoms and fatigue are factors related to cognitive decline (Arnett, Higginson, Voss,

Randolph, & Grandey, 2002; Diamond, Johnson, Kaufman, & Graves, 2008). There is evidence that cognitive deficits lead to higher and faster exhaustion (Parmenter, Denney, & Lynch, 2003) and increased fatigue (Krupp & Elkins, 2000). Cognitive impairment has an impact on the activities of daily living (Kalmar et al., 2008). Furthermore, cognitive deficits are associated with quality of life (Simioni, Ruffieux, Bruggimann, Annoni, & Schluep, 2007) in early RRMS. After correcting for depressive symptoms, Glanz and colleagues (2010) found a relationship between processing speed measures and health-related quality of life in patients with early RRMS and CIS. Ruet et al. (2013) reported that processing speed and memory dysfunction in the early stage of MS are associated with health perception and, furthermore, that cognitive impairment is predictive for later vocational status. Others found no connection between quality of life and cognitive deficits, but cognitive deficits were a predictor for work capacity (Benedict et al., 2005). Further cognitive deficits seem to be associated with response to rehabilitation programs (Langdon & Thompson, 1999).

In the last few years, protective factors for cognitive decline have also been discussed. One concept thereby is “cognitive reserve”. The concept of cognitive reserve postulates that intellectual enrichment is associated with higher cerebral efficiency and that patients with higher cerebral efficiency are able to better withstand brain damage because of the usage of other pre-existing cognitive processes or compensatory mechanisms (Stern, 2002; Stern, 2009) Cognitive reserve thereby results from several factors such as higher premorbid intelligence or higher education. Further, premorbid leisure activities are discussed as factors for cognitive reserve (Sumowski, Wylie, Gonnella, Chiaravalloti, & Deluca, 2010). Cognitive reserve in MS seems to reduce the effect of brain atrophy on cognition (Sumowski, Wylie, Chiaravalloti, & DeLuca, 2010; Amato et al., 2013). Nevertheless, research on protective factors for cognitive decline in MS is in its infancy and future data are needed to prove the concept of cognitive reserve and identify addition protective factors.

Assessment of cognitive deficits in MS

Cognitive decline may severely impact daily life of patients with MS. Nevertheless, cognition functions still rarely are assessed in clinical practice. Because a wide spectrum of cognitive deficient functions may appear in MS, screening batteries for cognitive functions should be used. Many studies use the Brief Repeatable Battery of Neuropsychological Test (BRB-N; Rao, 1990) that assesses verbal and visual memory, information processing speed and executive functions with duration of approximately 40 minutes. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012) is a consensus

approach to make cognitive screening more applicable for clinical practice. It includes a test for processing speed as well as for verbal and visual memory and takes only 15 minutes. The authors advise administering at least the Symbol Digit Modalities Test (SDMT; Smith, 1973) once a year in MS patients.

Processing speed is often measured with tests that also require WM functions. One example is the SDMT, which is widely applied to MS patients and is included in the BRB-N, the BICAMS, and in the modified version of the MSFC within the MSDM. Participants thereby receive nine simple symbols with corresponding numbers from one to nine. In the oral version of the test, participants then have to name as many symbols with the corresponding number as possible within 90 seconds. To do so, processing speed as well as WM functions are required.

A more pure measure of processing speed might be reaction times during alertness tasks (for example within the Testbatterie zur Aufmerksamkeitsprüfung: TAP; Zimmermann & Fimm, 1992). Alertness can be divided into a tonic and a phasic state. The tonic aspect is related to sustained attention and speed of response (press button when target cue appears). The phasic aspect is the ability to profit from a cue before the target appears, which facilitates a faster reaction.

For visual and verbal aspects of WM, Corsi Blocks backward and Digit Span backward from the Wechsler Memory Scale-Revised (WMS-R; Haerting et al., 2000) can be applied. During the Corsi Blocks test, participants have to remember a sequence of blocks presented by the investigator and afterwards reproduce this sequence in reverse order. During the Digit Span test, on the other hand, participants hear a digit sequence and, again, have to reproduce this sequence in reverse order.

A further task for the assessment of WM is the N-Back task. This test is applicable in functional brain imaging studies. In our case series, we used a modified version of the N-Back task included in the TAP (Zimmermann & Fimm, 1992). Sequences of pseudo-randomized digits were continuously presented on a screen. Participants had to press a button as fast as possible whenever the target appeared. A target is thereby a digit that is identical to the immediately preceding digit (1-back), the second to last digit (2-back) or the third to last digit (3-back).

Cognition in juvenile MS patients

Cognitive dysfunction function can be observed in one third of juvenile MS patients (Banwell & Anderson, 2005; MacAllister et al., 2005; Amato, Goretti, et al., 2008; Amato et al., 2014).

As in adults, affected cognitive domains are verbal memory, working memory, and attention. Additionally, 20-40% of children and adolescents show language problems (Amato, Goretti, et al., 2008). Cognitive deficits seem to disorient during the disease course (Amato, Goretti, et al., 2010) in some patients, whereas in others stability or even improvement of cognitive functioning may be observed (Amato et al., 2014). Cognitive dysfunction has also been observed in juvenile patients with CIS (Julian et al., 2013).

Of course, cognitive deficits have severe effects on adults with MS, but in juvenile patients impact on everyday functioning is even more prominent. Of juvenile MS patients, 30-40% are affected regarding their school and everyday activities (Amato, Goretti, et al., 2008) and MS may hamper expected age-related cognitive gains (Charvet et al., 2014). Apparently, cognitive deficits may have a big impact on their participation in school and thereby their further academic career and psychosocial development.

To illustrate the importance of cognition in juvenile MS and the utility of neuropsychological testing in these patients, we conducted a case study (study 1: Penner et al., 2013; Appendix A). A 16-year-old patient with RRMS came to our clinic because of MS-related fatigue and school problems. In retrospect, at the age of 11 years, the boy had initial symptoms indicating a demyelinating event of the CNS. He experienced several relapses with incomplete remission, always accompanied by extreme physical and mental exhaustion. He therefore frequently missed school and could not participate in social events. Because of the severe disease progression, treatment was escalated from interferon-beta 1a to natalizumab, but the feeling of extreme physical and mental exhaustion remained and problems at school increased.

To further evaluate the described symptoms of exhaustion and their relation to school problems, he underwent a neuropsychological assessment including questionnaires for fatigue, quality of life and depressive symptoms, a broad cognitive testing and an intelligence scale. He had clinically relevant elevated fatigue and decreased quality of life. Depressive symptoms were present, but below clinically relevant cut-off. Cognitive testing revealed no pathological findings and his intelligence was high.

At a second neuropsychological testing, two weeks later, he reported not feeling well, being more exhausted and having minor balance problems. Fatigue and depressive symptoms were elevated compared to baseline and cognitive testing revealed minimally decreased cognitive performance, but a clinically meaningful decrease in alertness task in the TAP (basic attention). Higher reaction times during this task indicate slowed information processing. EDSS was stable but MRI showed four new T2 lesions compared to four months

earlier, without contrast-enhancement. We decided to regard the experienced exhaustion, the balance problems and severe cognitive slowing as symptoms of a new relapse. Three weeks after treatment with methylprednisolone, EDSS was stable, balance problems had disappeared, and the boy reported improvement of his physical and mental condition. His cognitive performance improved; however, performance during the alertness task remained decreased. In a follow-up assessment, three months after relapse, all cognitive domains were back to baseline level except for decreased alertness. Alertness performance from baseline, testing during relapse, one month after relapse and three months after the training are displayed in Figure 1.

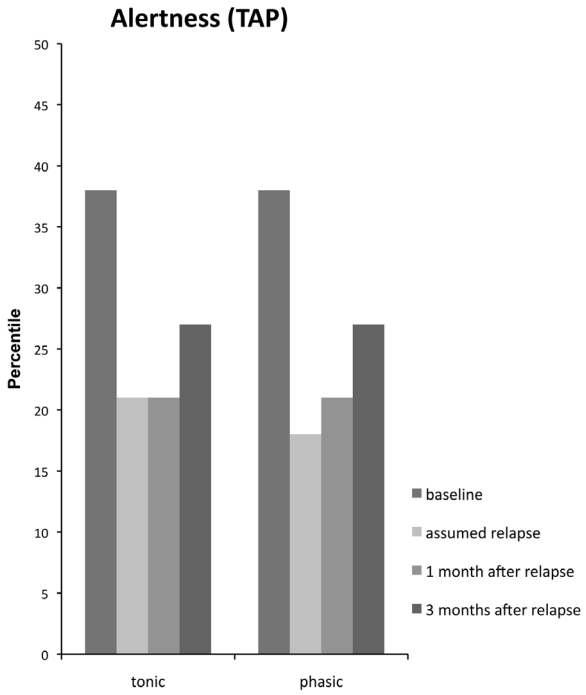

Figure 1. Percentile rank for a 16-year-old boy's performance during a tonic and phasic alertness task. Two weeks after the first neuropsychological assessment, the boy's alertness performance severely decreased. One month after relapse, his performance was stable and at follow-up a slight increase was observed (from study 1: Penner et al., 2013; Appendix A).

This case study clearly illustrates several aspects that are relevant in juvenile (and to some extent also adult) patients with MS. Because of disease activity and symptoms of exhaustion, he repeatedly missed school. Therefore, he had problems achieving educational objectives, which were intensified by his slowed information processing speed and fatigue symptoms. Missing school and not being able to attend social events further led to some kind of isolation and increased depressive symptoms.

The absence of classic neurological symptoms during relapse in this case and presentation with cognitive decline, exhaustion and depressive symptoms illustrate that

relapses in MS might present with diffuse or subclinical symptoms. Of course, one might argue that this event was not an actual relapse, but the boy's response to methylprednisolone oppugns this. Relapses with the main impact on cognitive functions are currently subject of discussions. "Cognitive relapses" have been reported in other case studies (Coebergh, Roosendaal, Polman, Geurts, & van Woerkom, 2010; Larner & Young, 2009). Recently, Pardini and colleagues (Pardini et al., 2014) defined an "isolated cognitive relapse" as an event with a transient objective significant cognitive decline, without clinical or subjective evidence of other new neurological signs and symptoms, or associated contrast-enhancing lesions. Our case would not meet these criteria, because of the lack of contrast-enhancing lesions and the patient's report of minor balance problems. Nevertheless, decline in processing speed was one of the main symptoms during relapse.

Described relapse was primarily associated with "soft signs" such as increase in depressive and fatigue symptoms and cognitive decline. These factors essentially contributed to the treatment decision. Further, three months after relapse, the boy's processing speed performance had not yet fully recovered, whereas other symptoms had improved. Decline in processing speed was not only one of the main symptoms during relapse but also the symptom with the slowest recovery. This further illustrates the importance of assessing neuropsychological symptoms and cognitive functions on a regular basis to observe general disease course and thereby supports approaches—such as the previous described MSDM—that aim to additionally include neuropsychological factors such as fatigue, depression, quality of life and cognitive functioning for the assessment of disease course and to support treatment decisions (Stangel et al., 2013).

In summary, this chapter illustrates that cognitive dysfunction in MS patients affects a wide range of cognitive domains, but that core cognitive deficits in MS include memory, WM, and information processing speed. Cognitive deficits are hardly predictable by factors related to the disease course and severely affect the daily life of MS patients. The importance of cognitive functioning and the utility of frequent neuropsychological testing, especially in juvenile MS patients, are further highlighted by the single case described here.

Working memory (WM)

As previously described, one core deficit in MS may concern WM performance. WM describes a system that enables us to store information for a short period of time and to manipulate this information by linking and thereby refreshing new incoming information with information in long-term memory (LTM). Several models exist for WM, but the one that has been most extensively investigated was proposed by Baddeley and Hitch (1974). It consists of a central executive, which controls incoming information and integrates stored information, and two domain-specific slave systems: The phonological loop is a subsystem for storing verbal information, whereas the visuospatial sketchpad is responsible for visual input. Later, a third slave system was added, the episodic buffer, which describes a system for intermediate storage of integrated information that is connected with LTM (Baddeley, 2000, 2003a, 2003b).

In patients with MS, dysfunction of both slave systems (Litvan et al., 1988; Rao et al., 1993) and the central executive system (D'Esposito et al., 1996; Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994; Kennedy, & Taylor, 1994) has been observed. Furthermore, impairments regarding the central executive system might be the cause of memory dysfunction in MS patients (John DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998 Christodoulou, & Engel, 1998).

Baddeley's description of the WM as a cognitive system for timely limited storage and manipulation of the remembered information highlights the strong relation of WM with other cognitive functions: to choose relevant information, attention functions such as alertness or salience are necessary. Further, WM is connected to LTM by the episodic buffer, which retrieves relevant information from LTM and later stores manipulated information (Baddeley, 2003b). The relation to short-term memory (STM) is underpinned by the fact that in literature these two concepts of cognitive functions are often treated as synonymous. But whereas the term of STM should refer to the pure storage of information, WM includes content manipulation and interaction between inputs and outputs (Engle, Tuholski, Laughlin, & Conway, 1999). It can be seen that WM is a fundamental set of processes and a main component supporting many other cognitive functions from selective attention to complex decision making (Baddeley, 1986). Further, in children WM is one of the strongest predictors of subsequent school achievements, such as mathematics and reading (Gathercole, Pickering, Knight, & Stegmann, 2004; Dumontheil & Klingberg, 2012).

Imaging WM

Neuroimaging studies using functional MRI (fMRI) are very popular to assess brain activation during a task. fMRI is based on the change in magnetization between oxygen-rich and oxygen-poor blood. This blood-oxygen-level-dependent (BOLD) signal is thought to be coupled with the underlying neuronal activity. Neuroimaging studies assessing BOLD signal change during WM tasks have helped to identify several areas in frontal and parietal cortices that are associated with WM functions (Owen, McMillan, Laird, & Bullmore, 2005).

Within the frontal cortex, verbal information, especially rehearsal processes, activates left Broca's area (Brodmann's area (BA) 44) and left-hemisphere supplementary and premotor cortex (BA 6), whereas spatial information results in activation of the right premotor cortex (Smith & Jonides, 1999). Prefrontal cortex is associated with organization and contextualization of incoming information, functions of the central executive of the WM (Baddeley, 2003; D'Esposito et al., 1995). More precisely, executive processes such as selective attention and task management frequently activate the anterior cingulate and the dorsolateral prefrontal (BA 9/46) cortex (Smith & Jonides, 1999). The dorsolateral prefrontal cortex is thereby thought to maintain information by directing attention to internal representations of stimuli that are stored in posterior areas (Curtis & D'Esposito, 2003) or top-down control of sensory regions (Sreenivasan, Curtis, & D'Esposito, 2014). Parietal regions (BA 7/40) are activated during all WM tasks. Activation occurs more parietally for items where spatial position is important versus more inferior temporal activation for items with patterns (Cabeza & Nyberg, 1997). These relations of brain regions are to some extent also supported by lesion studies (Müller & Knight, 2006).

WM undergoes a maturation process during childhood and adolescence (Gathercole, Pickering, Ambridge, & Wearing, 2004; Westerberg, Hirvikoski, Forssberg, & Klingberg, 2004). Myelination, synaptic strengthening and synaptic pruning are processes underlying the maturation (Edin, Macoveanu, Olesen, Tegnér, & Klingberg, 2007 Tegnér, & Klingberg, 2007). Higher WM performance is associated with higher activation in above-described areas in children and increase in WM capacity during development is associated with increases of activation (Ullman, Almeida, & Klingberg, 2014). Younger children show less activation in core working memory areas and rely more on activation in the ventromedial cortex; during adolescence, the WM activation becomes more complex. In adults, the WM-associated activation pattern is even more specialized (Scherf, Sweeney, & Luna, 2006).

In adult patients with MS, differences were found in comparison to healthy adults in activation during WM tasks. A recent meta-analysis indicated decreased activation in bilateral

inferior parietal, bilateral dorsolateral prefrontal and the right ventrolateral prefrontal cortex and increased activation in the left ventrolateral prefrontal cortex in patients with MS compared to healthy controls (Kollndorfer et al., 2013). MS patients with cognitive impairment showed higher activation of the right dorsolateral prefrontal cortex during WM processes compared to cognitive-preserved patients. With higher WM load, cognitive-impaired patients showed reduced activation across all WM-associated brain regions compared to healthy controls and cognitive-preserved patients (Rocca, Valsasina, Hulst, et al., 2014); however, patients without cognitive impairment showed altered activation during WM tasks compared to healthy controls (Amann et al., 2011).

A network perspective of WM

The observable activation pattern during fMRI studies with WM paradigms represents a network of several clusters in the brain. The network perspective has gained in importance in recent years. In today's research, the human brain does not have the status of a set of simple isolated functional clusters but a highly interconnected system of large-scale networks (Bressler & Menon, 2010). The human connectome is investigated with a wide range of techniques assessing structural as well as functional connections within the brain. The term functional connectivity refers to the temporal correlation of BOLD-signals between different areas in the brain and can be assessed with fMRI data collected during task-solving or during rest. Next to using simple correlation approaches with regions of interests that require a priori knowledge of the distribution of a network, model-free techniques such as the Independent Component Analysis (ICA) are widely used. Thereby, fMRI data are decomposed into spatially independent patterns and time courses.

WM processes are primarily associated with a fronto-parietal network (fpNW) resembling the activation pattern during WM tasks observed in classic fMRI studies. MS patients seem to have decreased connectivity within the WM network even at the earliest stages of the disease (Au Duong et al., 2005). When assessing this network by ICA, the fpNW is divided into a right and left part. For illustration purpose, components for this network from an ICA is displayed in Figure 2. Nevertheless, the functionality of the fpNW depends on and is supported by its interaction with other functional brain networks. It is closely related to the Default-Mode Network (DMN), which is thought to support other cognitive networks, and to the anterior Salience Network (aSN) which facilitates the switch between the fpNW and the DMN. These two networks are described in more detail in the paragraphs below.

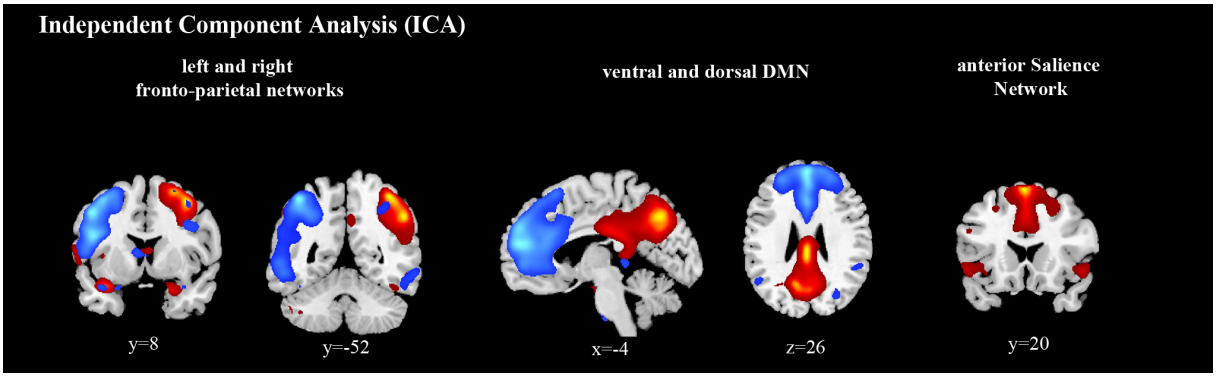

Figure 2. Illustration of ICA - functional networks relevant for working memory performance: the left (red) and right (blue) fronto-parital networks, the ventral (red) and dorsal (blue) DMN and the anterior salience network of 5 participants with juvenile MS (from Hubacher, DeLuca et al.; under review; Appendix C).

The Default-Mode Network.

A second network, which supports cognitive functioning, is the Default-Mode network (DMN). It includes regions in the posterior cingulate cortex, parts of the medial frontal gyrus, the anterior cingulate cortex, the retrosplenial cortex and precuneus (Mazoyer et al., 2001; Buckner, Andrews-Hanna, & Schacter, 2008). Using an ICA to assess this functional network, it often appears divided into a ventral and dorsal part. The ventral network is located in the retrosplenial cortex and precuneus with extension to the medial temporal lobe. The dorsal part consists of two main clusters in the medial prefrontal cortex and the posterior cingulate cortex (Figure 2).

The DMN is typically more activated during rest than during cognitive tasks (Raichle et al., 2001) and its activation is anti-correlated to other cognitive networks. It is associated with introspection and autobiographical processes and activated during sleep and sedation (Horovitz et al., 2009; Sämann et al., 2011; Spreng & Grady, 2010). Further, the DMN is thought to facilitate or monitor other cognitive processes. Strength of connection between DMN (medial frontal gyrus/anterior cingulate) and the dorsolateral prefrontal cortex as part of the WM network is related to cognitive functioning (Hampson, Driesen, Roth, Gore, & Constable, 2010). Further, within the DMN, strength of functional connection between the sub-nodes, posterior cingulate cortex, the medial frontal gyrus and ventral anterior cingulate cortex is positively associated with WM performance during rest and during WM tasks (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006).

DMN alterations are described in many psychiatric and neurological diseases such as major depression, schizophrenia, Alzheimer's disease or epilepsy (Broyd et al., 2009; Greicius et al., 2007; Kim et al., 2009; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005; Oser et al., 2014). In patients with MS (Basile et al., 2013; Bonavita et al., 2011),

alterations have been described across all the disease's courses from CIS (Roosendaal et al., 2010) to progressive forms (Rocca et al., 2010). Cognitive-impaired MS patients show less deactivation of the DMN during WM tasks compared with cognitive-preserved patients and healthy controls (Rocca, Valsasina, Hulst, et al., 2014), but also patients without cognitive impairment show altered deactivation compared to healthy controls (Amann et al., 2011).

During resting-state fMRI patients with early MS show increased connectivity within the DMN and the executive network, but decreased connectivity between these two networks compared to healthy controls (Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011). A recent study comparing paediatric MS patients and healthy controls reports changes both within several networks and between networks (Rocca, Valsasina, Absinta, et al., 2014). Among other network alterations, paediatric patients had decreased functional connectivity within the fpNW and the DMN and increased connectivity within the attention network. Further functional connectivity between the left fpNW and the DMN was decreased. Connectivity alterations in these patients also contributed to their cognitive status. Further, structural and functional alterations of the posterior DMN are associated with cognitive performance in juvenile MS (Rocca, De Meo, et al., 2014).

The Salience Network.

The aSN (displayed in Figure 2) includes mainly the anterior part of the insula and the dorsal anterior cingulate cortex (Seeley et al., 2007), paralymbic structures that are associated with autonomic introspective processes (Critchley, 2005). This network is co-activated during salience processes (such as empathy of pain or listening to enjoyable music; Blood & Zatorre, 2001; Singer et al., 2004), and is therefore described as a network for guiding attention to a broad spectrum of intra- and extrapersonal events (Bressler & Menon, 2010; Eckert et al., 2009). The aSN seems to be essential for the functionality of the fpNW and the DMN. During cognitive tasks, these networks have a close interaction. Thereby, the switch between these two networks is mediated by the aSN (Sridharan, Levitin, & Menon, 2008). In patients with MS, there is scant knowledge about functionality of the aSN. One study indicates altered inter-network connectivity between the aSN and an "executive network" but not with other cognitive brain networks (Rocca et al., 2012). Further, Faivre and Colleagues (2012) describe several networks that are correlated with the MSFC score. One of them is a network including the anterior part of the insula.

In summary of this chapter, WM is an essential cognitive function for everyday life,

with close interaction with other cognitive systems on a behavioural as well as a neural level. WM depends on a brain network with clusters in mainly frontal and parietal regions and its interaction with the DMN and the aSN. MS patients show alterations regarding the fpNW but also alterations in networks supporting WM function and their interconnection. Interruption in connectivity of these widespread networks by MS lesions has a serious impact on their functionality and might to some extent explain cognitive dysfunction in MS patients.

Treating cognitive deficits in MS

Because of the impact of cognitive deficits on daily life and normal functioning in MS patients, effective treatment options for these symptoms are absolutely mandatory. Disease-modifying treatment in MS has only limited effects on neuropsychological functioning and most of the existing studies were never designed to assess this domain, because in most studies cognition is a secondary or tertiary outcome measure (Patti, 2012). Among disease-modifying treatment options, there is most evidence for effects of interferons on cognition (Fischer et al., 2000; Flechter, Vardi, Finkelstein, & Pollak, 2007; Patti et al., 2013). Thereby a treatment early in the disease course seems to have a more positive impact on cognitive functioning than a delayed treatment (Penner, Stemper, et al., 2012). For glatiramer acetate mixed results exist, with studies showing both negative (Schwid et al., 2007; Weinstein et al., 1999) and positive (Ziemssen et al., 2014) results for effects on cognitive functioning. Further, there is some evidence for positive effects of natalizumab (Iaffaldano et al., 2012; Weinstock-Guttman et al., 2012).

Because standard treatment in MS has only limited effects, additional symptomatic pharmacological treatment options may be considered. But acetylcholinesterase inhibitors, such as donezepil and rivastigmine show few to no effects on cognition in MS (Krupp et al., 2004; Krupp et al., 2011; Mäurer et al., 2012). One trial, assessing the effects of memantine on cognitive functioning in patients with MS, was stopped after worsening of neurological symptoms (Villoslada, Arrondo, Sepulcre, Alegre, & Artieda, 2009) and second study showed no evidence for positive effects (Lovera et al., 2010). Only stimulants such as l-amphetamine, modafinil and armodafinil seem to have effects in MS on some cognitive domains (Morrow et al., 2009; Sumowski et al., 2011; Möller et al., 2011; Bruce et al., 2012); however, overall, results are not convincing for substantial effects of pharmacological treatments on cognitive functioning in MS.

Therefore, it is obvious that pharmacological treatment options for cognitive impairment in MS are not sufficient. Several concepts for non-pharmacological treatment have been proposed. There is some evidence for effects of aerobic training on processing speed (Motl, Gappmaier, Nelson, & Benedict, 2011) and memory (Leavitt et al., 2013) in patients with MS. A Cochrane review (Thomas, Thomas, Hillier, Galvin, & Baker, 2006) inspected the effectiveness of several psychological interventions in MS on factors such as quality of life, psychiatric symptoms, psychological factors such as emotions, self-efficacy and self-esteem and neurological disability (including cognitive functions). Cognitive behavioural therapy and psychotherapy thereby seem to improve symptoms of depression and

may help people cope with their disease, whereas cognitive rehabilitation mainly improved cognitive symptoms. Cognitive rehabilitation is at present the most promising approach to treat cognitive deficits in MS. This will be described in more detail in the following paragraph.

Cognitive rehabilitation

Cognitive rehabilitation approaches are based on retraining of cognitive functions by exercise, adaption and implicit or explicit learning of coping strategies. Approaches thereby use paper-pencil material or computerized tools in single or group sessions with high variance in intensity and duration of the training sessions. Cognitive training is effective in patients after traumatic brain injury or stroke (Bowen & Lincoln, 2007; Cicerone et al., 2000; das Nair & Lincoln, 2007; Lincoln, Majid, & Weyman, 2000) and has gained more attention in the field of MS research during recent years. In a meta-analysis, memory rehabilitation using various memory retraining techniques, such as computerized programs or training on memory aids, showed no short- and long-term effects on memory performance (das Nair, Ferguson, Stark, & Lincoln, 2012). The authors nevertheless concluded that this lack of evidence might result from low methodological quality of some of the included studies. Newer studies that have tried to address some of these methodological issues demonstrated significant improvement on memory functions in MS patients receiving a cognitive rehabilitation program compared to a control group (Brissart, Morele, Baumann, & Debouverie, 2012; Chiaravalloti, Moore, Nikelshpur, & DeLuca, 2013). Rosti-Otajärvi & Hämäläinen (2014), in an update of their Cochrane review from 2011 on neuropsychological rehabilitation approaches in MS, report low but nevertheless positive evidence for effects in general. The applied trainings thereby affected mainly memory span and WM. Further, they reported that when cognitive training was combined with other neuropsychological rehabilitation methods, attention and delayed memory were improved.

Nevertheless, studies included in meta-analyses have a high variation regarding applied methods, training approaches and outcome measures, which hinders comparison. Therefore, clear evidence on the effectiveness of cognitive training in MS is still missing. In healthy adults, controversial results regarding the effects of cognitive training approaches also exist. There are even studies using the same training approach that report no effects or transfer effects (Anguera et al., 2012; Holmes, Gathercole, & Dunning, 2009; Jaeggi et al., 2010; Redick et al., 2013). Different stages of transfer effects can thereby be observed. Near-transfer, for example, describes an improvement on cognitive tasks that need similar cognitive processes such as the trained task. This means that if for example WM was trained with an N-

Back task, effects on other cognitive tests on WM such as Corsi Blocks backward, Digit Span backward or the SDMT will be observed. On the other hand, far transfer effects, which may result from adaptive training approaches (Takeuchi, Taki, & Kawashima, 2010), describe effects of training that are generalized to other cognitive domains.

One further aspect of the effectiveness of cognitive rehabilitation is maintenance of effects after training. Several studies including follow-up visits report long-term effects of cognitive rehabilitation approaches on objective or perceived cognitive deficits in patients with MS (Chiaravalloti et al., 2013; Plohmann et al., 1998; Rosti-Otajarvi, Mantynen, Koivisto, Huhtala, & Hamalainen, 2013). Nevertheless, data on long-term effects of cognitive training are limited and need further inspection.

fMRI studies try to address the mechanisms behind reported training effects. Neuronal plasticity, a fundamental function of the CNS during development across the lifespan, is thought to underlie the observed behavioural changes. Different plasticity processes may follow after brain injury. For example, after acute inflammatory demyelination, remyelination is an important mechanism (Crawford, Mangiardi, Xia, Lopez-Valdes, & Tiwari-Woodruff, 2009). Clinical recovery over time, on the other hand, seems to be induced by adaptive functional reorganization (Mezzapesa, Rocca, Rodegher, Comi, & Filippi, 2008; Wegner et al., 2008). The integrity of the normal-appearing brain tissue is thereby important for network plasticity (Giorgio et al., 2010).

Plasticity processes take place spontaneously in MS patients (Pantano, Mainero, & Caramia, 2006). Patients with MS and mild to moderate cognitive deficits activate additional brain regions compared to healthy controls, whereas severely impaired patients showed less activation (Penner, Opwis, & Kappos, 2007). The increase in activation in patients with mild deficits is thereby thought to reflect a compensational mechanism. A comparable observation can be made in data reported by Louapre and colleagues (2014) regarding functional connectivity of intrinsic brain networks. They compared healthy controls with cognitive-preserved and cognitive-impaired patients with early RRMS. Connectivity within brain networks was increased in patients without any cognitive impairment compared to healthy controls and cognitive-impaired patients. Connectivity within DMN and an fpNW of patients with cognitive impairment was lower than in healthy controls. In patients with early MS, increased connectivity within the DMN and the executive network was accompanied by decreased connectivity between these networks compared to healthy controls (Hawellek et al., 2011), which indicates less interaction between different cognitive networks. Therefore, increased activation and connectivity within a network might reflect a compensational

mechanism for decreased interaction between different cognitive networks. These observations indicate that neuroplasticity processes in patients with slight or no observable cognitive deficits compensate the effects of MS pathology on brain function by increased and more widespread activation of brain networks and higher connectivity within specific networks. Patients with higher impact of the disease and therefore less non-affected brain tissue (Schoonheim, Geurts, & Barkhof, 2010) might at some point no longer be able to compensate, which results in decreased functional activation and behavioural cognitive deficits.

Next to spontaneous plasticity processes after brain injury, training can induce plasticity processes. Kelly, Foxe, and Garavan (2006) describe four different patterns of changes in brain functionality after practice of WM tasks:

1) Studies examining short-term practice effects in healthy humans often report *decreased* activation after training. The mechanism thought to underlie this effect is higher neural efficacy within a network. A certain sharpening of the response within neural networks thereby requires fewer neurons to fire strongly in response network-related tasks. Decreased activation might therefore reflect more efficient information processing within the brain.

2) *Increase* in extent or intensity of activation occurs after extensive training of motor, sensory or cognitive tasks. Increase in *extent* of brain activation thereby reflects additional recruitment of brain areas, whereas increase in *intensity* goes back to a strengthening of response within one region.

3) Further, *redistribution* of brain activation in the healthy brain is defined by mixed increases and decreases of brain activation within one network. The activation pattern itself thereby remains the same. Decreases due to practice are thought to be located in areas associated with cognitive control and attention, whereas increases of activation occur in task-specific areas. The same cognitive process is used to solve the task, but due to practice and learning less attentional control is needed and task-specific processes are more involved.

4) In contrast to redistribution of brain activation, *reorganization* mainly occurs in clinical populations. As with redistribution, reorganization includes increases and decreases of brain activation but reorganization also includes activation of additional anatomical brain regions after practice or training. Shift of brain activation to other cortex regions thereby reflects usage of different cognitive processes.

Regarding effects of cognitive rehabilitation approaches on brain function in MS, most studies assessing this aspect notify increased and more widespread brain activation within the trained network after training (Cerasa et al., 2013; Filippi et al., 2012; Mattioli et al., 2010;

Penner, Kappos, Rausch, Opwis, & Radü, 2006; Sastre-Garriga et al., 2011). Whereas patients receiving cognitive training show increased activation, untreated patients often show a decrease over time (Chiaravalloti, Wylie, Leavitt, & DeLuca, 2012). However, a small trial, with only four participants with MS receiving cognitive training, reported increased activation in posterior regions but decreased activation in frontal areas of the brain (Ernst et al., 2012).

Studies using resting-state fMRI measures to assess effects of a training report higher connectivity within networks underlying the trained function, which correlates with behavioural improvements due to the training (Parisi, Rocca, Valsasina, et al., 2014) and higher connectivity within the DMN (Bonavita et al., 2015; Filippi et al., 2012; Leavitt, Wylie, Girgis, DeLuca, & Chiaravalloti, 2014). Training may further lead to higher or stable connectivity within the SN and the executive network, whereas in untrained patients connectivity within these networks decreases over time (Filippi et al., 2012).

Cognitive rehabilitation approaches applied in MS have targeted different cognitive domains such as attention (Cerasa, et al., 2013; Mattioli, et al., 2010; Penner, Kappos, et al., 2006; Solari et al., 2004) or memory (Chiaravalloti, DeLuca, Moore, & Ricker, 2005; Lincoln et al., 2002) or have used non-specific neuropsychological treatments. Because core deficits in MS concern WM and processing speed, specific treatments for these cognitive domains may be worthwhile and are therefore discussed further.

Training of WM in adults

WM training in healthy adults leads to increased WM performance, not only on the trained task, but also other tasks relying on WM functions (near-transfer) and plasticity within the WM brain network (Klingberg, 2010). Few studies on the effects of specific WM trainings in MS are available. Vogt and colleagues (2008) used the computerized training tool BrainStim to train WM function in patients with MS. After training, MS patients had improved WM performance and higher processing speed. Additionally, fatigue scores improved. Vogt et al. (2009) further compared effects of high intensity training (16 sessions within 4 weeks) with a distributed training condition (16 session within 8 weeks) in MS patients. Both groups showed similar effects regarding fatigue, WM and processing speed. In contrast, in healthy adults, distributed training with BrainStim has a beneficial effect regarding WM, verbal STM and processing speed compared to intense training (Penner, Vogt, et al., 2012).

A meta-analysis from Buschkuehl, Jaeggi, and Jonides (2012) regarding neuronal effects of WM training in healthy adults concluded that there is no clear pattern of results that would single out one specific underlying neuronal plasticity process. They described the same

patterns of response for training of WM as Kelly, Foxe, and Garavan (2006) after practice of a task: activation decrease in trials with short-term trainings (Garavan, Kelley, Rosen, Rao, & Stein, 2000; Landau, Garavan, Schumacher, & D'Esposito, 2007), activation increase (Jolles, Grol, Van Buchem, Rombouts, & Crone, 2010), and redistribution (Dahlin, Neely, Larsson, Backman, & Nyberg, 2008; Olesen, Westerberg, & Klingberg, 2004). There is no evidence for WM reorganization in healthy adults, what is in line with the assumption that reorganization processes occur due to pathological processes within the CNS. In patients with MS, there are no studies investigating different patterns of response to specific WM trainings and their relation to cognitive functioning. We therefore present study 2, a case series assessing the effects of WM training on changes in brain activation during fMRI and corresponding changes in WM and processing speed in patients with early RRMS (Hubacher, Kappos, et al., under review; Appendix B). This study is described in more detail in the paragraphs below.

Similar to previous studies, we used BrainStim (Penner, Kobel, & Opwis, 2006 2006) to train the WM function of participants. This is a computerized training tool based on the WM model of Baddeley described previously in this thesis. It consists of three different modules targeting both verbal and visuospatial aspects and the central executive component of WM (for further details of the training tool, please see the method sections of Appendices B and C). BrainStim is designed to ensure training is based not only on repetition and practice but also on the development and consolidation of strategies. Therefore, stimuli of the modules are presented randomized and the order of the modules is changed during each session. Level of difficulty adapts automatically to the participant's performance. After several correct answers, the level of difficulty increases. If the participant fails to solve a specific number of tasks, the level of difficulty decreases again. BrainStim has been used to train not only MS patients and healthy adults but also elderly healthy adults (Penner, Kobel, Stoecklin, Opwis, & Calabrese, 2007), patients with Parkinson's disease (Adamski et al., in preparation), anorexia nervosa (Adamski et al., in preparation) and chronic schizophrenia (Hubacher, 2013 #4695).

Ten participants with CIS or early RRMS (<10 years), all under treatment with interferon-beta 1b, were randomly assigned to either the treatment group (TG; *N*=6), receiving 16 sessions training with BrainStim during four weeks (four times a week, for 45 minutes), or a waiting list control group (CG; *N*=4). For baseline, neuropsychological assessment for WM function and processing speed (alertness measure and SDMT) was done twice within two weeks to obtain a more stable measure of baseline cognitive functions. Additionally, at the

second baseline visit, structural MRI measure and fMRI with a WM paradigm (N-Back) were obtained. After four weeks of training for the TG (16 sessions within four weeks, participants trained at home and were supervised once a week) or four weeks without any additional treatment (CG), participants again underwent neuropsychological testing and received an MRI. The study design is displayed in Figure 3.

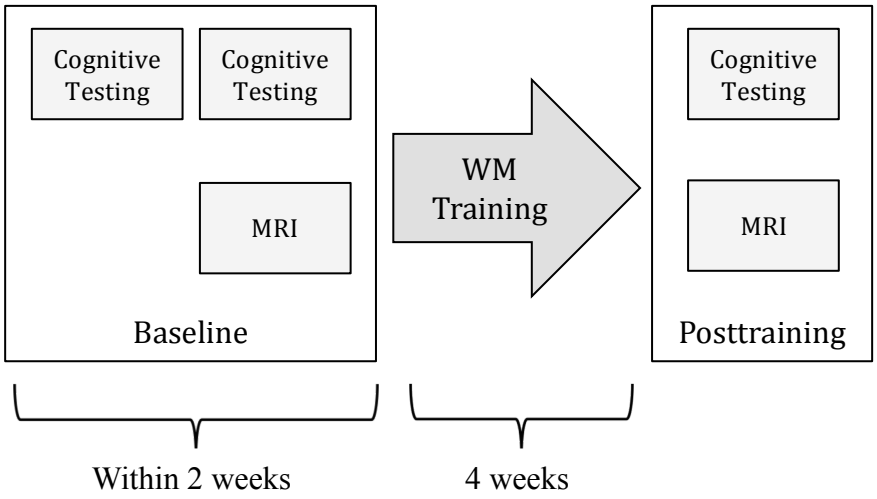

Figure 3. Study design from study 2 (Hubacher, Kappos et al., under review; Appendix B) included a double baseline for cognitive testing to receive a more stable baseline measure. At the second baseline visit structural and functional MRI was performed. After four weeks of training for the treatment group or without WM training (control group), cognitive and brain function was reassessed.

To assess possible patterns of response, the data were analyzed in a case-based manner. We used a triangulation approach derived from quantitative research to identify responding participants. This procedure claims more than one method (qualitative or quantitative) to verify that the variance in the outcome measure reflects a real training effect (Denzin, 1978). Therefore, for this study, response to treatment was defined as observable changes in brain activation during WM fMRI and related effect within cognitive functions (WM or processing speed).

Case-based inspection of the effects of training revealed a highly heterogeneous pattern of response (for more detail, please see Appendix B). Only two participants in the TG showed intense changes in brain activation during the N-Back task after the training and improvement of cognitive performance and thereby fulfilled the responder criteria. One had an intense decrease in brain activation within the WM network accompanied by increases in processing speed (alertness and SDMT). The second participant, fulfilling the responder

criteria, had increased brain activation in frontal, parietal and temporal regions after the training and higher processing speed and WM measures. As participants of the control group, the four remaining participants in the TG showed only slight changes regarding brain activation. Changes of brain activation from baseline to after the training are displayed in Figure 4. The best behavioural measure to distinguish participants in the TG from the CG was the SDMT. Four of six participants in the TG performed higher on this test after the training, whereas no participants in the CG had meaningful changes during this time.

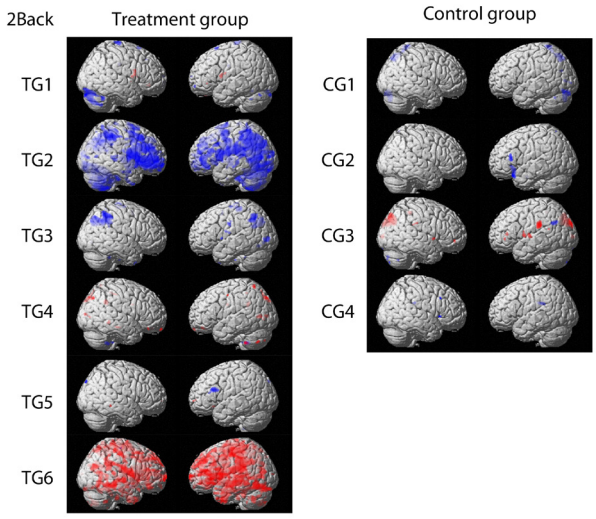

Figure 4. Changes in brain activation from baseline to posttraining for each participant in the treatment and control group ($p < .001$ uncorrected, TH=10). Two participants show intense changes in brain activation (from study 2: Hubacher, Kappos, et al., under review, Appendix B).

As with previous studies, this case series demonstrates that WM training can improve WM and processing speed in patients with early RRMS and that pattern of response in fMRI is highly heterogeneous. This case series demonstrated two different patterns of response in brain activation in MS patients:

A) One participant had decreased brain activation within the WM network after the training. According to Kelly, Foxe, and Garavan (2006), this decrease in brain activation might reflect more efficient information processing within the brain. The increase in processing speed after the training in this participant might therefore be the behavioural expression of this process.

B) The second participant who responded to the training had increased brain activation within the WM network (frontal and parietal regions) and additionally, increased brain

activation in temporal regions. On a behavioural level, this participant had higher processing speed and visual WM performance after the training. The additional recruitment of temporal brain regions probably reflects a reorganization process according to Kelly, Foxe, and Garavan (2006). Further, because the increase in activation was more prominent on the left hemisphere, the usage of a more verbal strategy to solve the task might underlie this effect.

Training of WM in children and adolescents

In a pilot study with 12-year-old healthy children and healthy young adults, Jolles, van Buchem, Rombouts, and Crone (2012) described improvements of WM, which lasted for six months. The 12-year-old children showed immature brain activation during fMRI in fronto-parietal regions. After training the activation pattern in children resembled more the pattern of adult participants. A further pilot study (Jolles, van Buchem, Crone, & Rombouts, 2013; Experiment 2), assessing effects of WM training on the fpNW and the DMN in healthy children, showed no changes in within-network connectivity due to the training.

WM training is often applied in children with attention-deficit/hyperactivity disorder (Beck, Hanson, Puffenberger, Benninger, & Benninger, 2010; Green et al., 2012; Klingberg et al., 2005) or children with poor WM (Holmes, et al., 2009) and seems to be a good tool for treatment of cognitive functions in children. In children with developmental diseases, training leads to normalized brain functions (Shaywitz et al., 2004; Temple et al., 2003). In children with MS, there are no data on the effects of WM or general cognitive trainings on cognitive and brain function. We addressed this issue in study 3, described in the following paragraphs (Hubacher, DeLuca, et al., under review; Appendix C).

Five children (two boys and three girls) between 12 and 17 years with RRMS participated in the study. We used the same study design as described above (Figure 3) but added a follow-up after nine months. Participants trained with BrainStim under the same conditions as adults: four times a week for 45 minutes during four weeks. Participants trained at home on their home computer and were supervised once a week. Because of the small number of juvenile MS patients in Switzerland, we did not include a control condition without training and again avoided statistical comparison. Additional to cognitive functions (processing speed and WM) and conventional fMRI as outcome measures, we acquired a resting-state fMRI sequence and extracted spatially independent networks using an ICA. On the basis of the previously described close interaction between the WM-related fpNW, the DMN and the aSN, these networks were chosen as targets for a later internetwork connectivity analysis for each subject.

All participants improved regarding the SDMT. Two participants performed higher on all cognitive tests after the training and showed corresponding increases in brain activation within the WM network and less deactivation in other areas. One participant increased in processing speed (alertness and SDMT) but not in WM and showed no changes in brain activation during the WM paradigm. The two responding participants additionally showed strengthening of internetwork connectivity between the fpNW and the dorsal and ventral DMN. In the follow-up visit, nine months after the training, effects in functional fMRI and internetwork connectivity had vanished, whereas behavioural effects remained stable.

We further assessed possible factors for treatment response in juvenile MS cases by comparing baseline characteristics of participants (Table 1). There were two distinguishing factors between responding and non-responding participants: A) In responders, time since last relapse was lower than in non-responders, indicating a lower disease activity at the time of the study. B) Responders achieved higher scores in a test for general intelligence at baseline. This leads to the assumption that response to WM treatment might be related to cognitive reserve. This case series gives first insights into WM training in patients with juvenile MS and might serve as jumping-off point for further studies with larger sample sizes.

Table 1. Baseline characteristics and possible factors for treatment response (adapted from study 3: Hubacher, DeLuca et al., under review; Appendix C). Marked in grey are measures for disease activity (last relapse prior to study) and general intelligence (raven matrices), two factors that distinguish between responding and non-responding participants.

	Case 1 Non-responder	Case 2 Responder	Case 3 Responder	Case 4 Non-responder	Case 5 Non-responder
Gender	male	male	female	female	female
Age	16	14	17	16	12
Disease onset	15 y (11 y)	11 y	13 y	14 y	9 y
Therapy	natalizumab	(Vit D)	natalizumab	INFB-1a	INFB-1a
Relapses	3	1	4	3	1
Last relapse prior to study	3 months	2.5 y	2 y	3 months	3 y (new Gd enhancing lesions 4 months)
Raven matrices	77 PR	93 PR	85 PR	36 PR	1 PR
Cognitive fatigue	moderate	no	moderate	severe	no
Motor fatigue	severe	no	moderate	severe	no
Depressive symptoms	no	no	no	no	no
T2 lesion volume (ml)	4.224	5.379	5.996	0.085	9.075

Note. PR: percentile rank

General discussion

Cognitive dysfunction can be observed in half of MS patients and is one of the major symptoms besides physical disability and fatigue. The impact of MS and the importance of cognitive functioning become even more evident in juvenile patients. Disease-related symptoms (relapses but also fatigue or depressive symptoms) lead to missed days in school and combined with cognitive problems, achievement of educational goals is hindered. Further symptoms may lead to problems in the social environment. Frequent cognitive testing in patients may be helpful for observation of the disease course. Cognitive decline may indicate a relapse even in the absence of clear neurological signs and can therefore influence treatment decisions.

Core cognitive deficits in MS concern WM and processing speed, functions that closely interact. Cognitive problems in MS are only minimally impacted by disease-modifying or symptomatic pharmacological treatments, but a promising approach is cognitive rehabilitation. There is evidence for its efficacy in patients with MS during different stages of the disease course. Next to effects on cognitive functioning, changes regarding brain activation after training have been observed, indicating underlying plasticity processes. Because WM is a core deficit in MS, specific training of this cognitive domain may be worthwhile. Training with the computerized training tool BrainStim leads to higher cognitive performance especially regarding WM and processing speed in healthy adults and patients with MS. To assess brain activation patterns related to these effects on cognitive performance, we presented a case series (study 2) including adult participants with early RRMS trained with BrainStim. We thereby identified two different patterns of response to cognitive training, that were earlier described in meta-analyses on effects of cognitive training: A) First pattern was a *decrease* in activation of the WM network and increased processing speed performance that might reflect more efficient information processing within the brain. B) Second pattern was a *reorganization* process, with additional activation of temporal regions. This was accompanied by increased processing speed and WM performance.

A comparable case series (study 3) with five juvenile patients with RRMS presents first data on training effects in juvenile MS. We found effects on cognitive performance and increased activation of the WM network in two participants. These changes were associated with changes in resting-state functional internetwork connectivity, mainly between the fpNW and ventral and dorsal DMN, indicating a training effect on interaction between these networks. Cognitive improvement was maintained after nine months, whereas change in brain

activation and connectivity vanished. In this case series, we identified two possible factors for treatment-response: A) disease activity and B) cognitive reserve.

Of course, presented case series only provide limited evidence for the effects of WM training in juvenile and adult MS patients. Nevertheless, they give us the opportunity to compare effects of WM training in adult and juvenile MS patients for the first time and allow discussion of possible underlying neuronal effects. They further illustrate some of the possible factors that influence the outcome of cognitive rehabilitation. These points are presented in more detail in the paragraphs below, followed by a discussion of methodological aspects regarding these case series and cognitive rehabilitation in general.

Comparing WM training in adult and juvenile cases

The two case series, described in detail previously, in adult and juvenile participants with MS both used the same study design and outcome measures regarding WM and fMRI. This allows a comparison of effects in juvenile and adult patients. In children, the effects were more evident than in adults, because both responders in the childhood group showed higher performance on all WM and processing speed measures and increased brain activation of the WM network, whereas in adults pattern of response was more heterogeneous, with one participant with decrease in brain activation and one participant with reorganization of brain activation.

The clearer effects in juvenile participants may point to higher plasticity in this age group. Of course, the literature clearly indicates trainability of WM during all developmental stages (Jolles et al., 2012; Buschkuehl et al., 2012; Penner, Kobel, Stoecklin, Opwis, & Calabrese, 2007) and immaturity of the brain was even regarded as limiting factor for the chance of effects of cognitive training primarily in frontal structures (Jolles & Crone, 2012). Nevertheless, plasticity processes may be higher or more easily initiated in younger participants, where brain maturation is not yet completed. This assumption is supported by a study on the differences of the effects of WM training in healthy adults and children (Jolles, et al., 2012). Before WM training, children activated less than adult participants during WM fMRI. After six weeks of practice for both groups, the activation pattern of children no longer differed significantly from that of the adults. In patients with MS, especially in children, WM training might be a good approach to treat cognitive deficits, support plasticity processes and help children to achieve age-expected educational goals. Therefore cognitive training should be considered early during the disease course.

Different patterns of response to training in fMRI could be observed. A decrease and

reorganization of brain activation in adult participants and an increase within the WM network in juvenile participants were observed. Reorganization is a pattern that has already been described in clinical populations. Therefore, this pattern might reflect an adaptive process induced by training to compensate for MS-related pathology. In healthy adults, activation decrease (Garavan, et al., 2000; Landau, et al., 2007) and activation increase (Jolles, et al., 2010) were reported as effects of WM trainings. Activation decrease thereby was associated with short-term trainings whereas longer trainings resulted in activation increase. Therefore, these different processes may also reflect different stages during the rehabilitation course: During rehabilitation, in a first stage, brain activation might decrease, reflecting a more efficient information processing within the brain accompanied by effects regarding processing speed. In a later stage, brain activation increases above baseline level and is accompanied by higher performance in WM, which might reflect usage of implicit WM strategies, or, in the case or reorganization, the usage of alternative processes. Applying this to our results, participants that show different patterns of response might be in different stages of the rehabilitation process. Of course, this is highly speculative considering the small amount of data available. Future longitudinal studies with several time points with fMRI measures during the rehabilitation process might give insights into the time-dependent course of plasticity processes.

Factors for effective WM training in MS

In study 3, we presented first data on cognitive training in juvenile patients with MS. Additionally we tried to identify baseline characteristics that distinguished between responding and non-responding participants. We found two possible factors for response to cognitive training:

A) One factor that was associated with rehabilitation outcome was disease activity. Juvenile participants that responded to treatment had a longer time since last relapse. Non-responding participants had a relapse or disease activity in MRI three to four months prior to the study. The assumption that brain function is still affected three months after a relapse is further supported by the above-described juvenile single case (study 1). Three months after the relapse, the patient still showed a decreased performance in processing speed compared to baseline (two weeks prior to assumed relapse). In adult patients, the effects of relapses on cognition seem to disappear after three months (Benedict et al., 2014). Nevertheless, other studies assessing cognitive functioning temporarily close to relapses showed slight differences in SDMT and especially perceived cognitive deficits three months after relapse (Morrow,

Jurgensen, Forrestal, Munchauer, & Benedict, 2011). Pardini and colleagues (2014) described that patients with a possibly isolated cognitive relapse had significantly lower SDMT scores six months and one year after the assumed relapse. This factor might further be a cause of the low responder-rate in our case series with early adult RRMS patients, because participants in the treatment group had relapses three to nine months prior to study inclusion.

B) A second baseline characteristic with possible association to treatment response identified in the juvenile case series was cognitive reserve. Responding participants had achieved higher scores in a test for general intelligence than non-responding adolescents. Higher premorbid intelligence is one expression of higher cognitive reserve. Patients with higher cognitive reserve are thought to better withstand brain damage because of the usage of other cognitive processes or compensatory mechanisms (Stern, 2009). In terms of response to cognitive training, the higher intelligence level might help participants to profit more from cognitive training by faster or more efficient learning of implicit strategies.

Further possible factors for response to cognitive rehabilitation have been identified. Described plasticity processes due to WM training might be related to the dopamine system in the human brain. The dopamine system is related to WM processes (Luciana, Depue, Arbisi, & Leon, 1992; Müller, von Cramon, & Pollmann, 1998) and variations in dopamine regulating genes influence the activation of the WM network during fMRI (Bertolino et al., 2006). In healthy adults, polymorphism of the DAT-1 receptor influences the outcome of cognitive training (Brehmer et al., 2009). However, this association is “bidirectional” because WM training itself impacts cortical D1-receptor density (McNab et al., 2009) and the mean diffusivity in the dopaminergic system (Takeuchi et al., 2014).

In MS patients, Parisi et al. (2014) identified changes in network connectivity as a possible predictor of treatment outcome. Further, patients’ rating of the relation between client and therapist, their agreement on goals as well as the utility and efficacy of rehabilitation were identified as possible factors for outcome regarding fatigue and the achievements of goals (Rosti-Otajarvi, Mantynen, Koivisto, Huhtala, & Hamalainen, 2014). This factor might be less important in rehabilitation trials with computerized cognitive training tools. Nevertheless, the effect of psychosocial factors on rehabilitation outcome should not be underestimated. As in healthy adults (Jaeggi, Buschkuehl, Shah, & Jonides, 2014), further factors such as motivation, need for cognition, preexisting ability, and implicit theories about intelligence might have an influence on the outcome of cognitive rehabilitation approaches. In conclusion, identification of factors for response to cognitive rehabilitation is in its infancy and has to be investigated in larger trials especially designed for this purpose.

Methodological issues

There is no doubt that evidence from case studies is relatively low and that they have several limitations. Nevertheless such detailed inspection of cognitive training might serve as jumping-off point for clinical hypotheses in larger trials on rehabilitation outcome. The presented case series further highlights several methodological aspects that might be considered in later trials. The importance of the inclusion criteria, the specificity of the training and the importance of identifying the right outcome measures are discussed in the following paragraphs.

Inclusion criteria.

Reducing heterogeneity is one of the major issues in clinical trials, especially in highly heterogeneous diseases such as MS. We tried to address this in the adults case series (study 2) by applying relatively strong inclusion criteria: a diagnosis of CIS or RRMS, time since diagnosis less the 10 years, EDSS below 6.0, no relapses three months prior to the baseline visit. Specifying a disease-duration of less than ten years and a particular treatment reduced the number of patients able to participate in the study.

One major concern regarding our two case series presented above is the inclusion of patients regardless their objective cognitive status. Several participants showed no objective deficits in the applied cognitive tests compared with normative data. This might minimize the possibility to observe a treatment effect, by for example the occurrence of ceiling effects, and might negatively impact study results. Nevertheless, applying a cognitive training to patients without objective cognitive deficits might have several rationales:

A) Perceived deficits do not reflect an actual deficit compared to a norm group. It may rather reflect a decline in cognitive functions and cognitive efficiency observed by the patient. We would only detect such a decline by assessing cognitive function on a regular basis. However, such a cognitive decline might already have an impact on the patient's daily functioning: It forces patients to use compensatory strategies or mechanisms to account for less efficient cognitive performance, which results in more effort to participate in daily life. Therefore, the inclusion of participants without objective cognitive deficits might be reasonable.

B) Second, in healthy children Ullman, Almeida, and Klingberg (2014) showed that structural and functional MRI parameters correlated with WM capacity two years later. Here especially, structure and function of the basal ganglia and thalamus predicted later cognitive

status. Further, brain activation may also predict later arithmetic performance level (Dumontheil & Klingberg, 2012). Taking this into account, support of brain function by an appropriate WM training might prevent later cognitive problems, maybe by increasing cognitive reserve. If this concept is applicable to patients with MS, analogous to observed effects of disease-modifying treatment on cognitive functions (Penner et al., 2012), treatment of cognitive decline should be considered early in the disease course and before cognitive decline reaches a clinical cut-off.

Specificity of training.

We applied a WM training that has shown a specific effect on WM and processing speed in MS patients, because WM is one of the core cognitive deficits in MS patients and WM is essential for every-day functioning. Because WM has a close interaction with other cognitive functions, higher effectiveness of WM processes might prevent or ameliorate other cognitive deficits. Nevertheless, whereas some authors describe general cognitive enhancement after WM training (Morrison & Chein, 2011), it has to be noted that others have doubted the effectiveness of WM trainings and found no convincing evidence for transfer effects to other cognitive domains (Melby-Lervag & Hulme, 2013).

Of course, WM might not be the only reasonable target of cognitive interventions. Approaches that identify deficits for each participant and therefore train each participant individually are interesting for clinical practice, but they are not applicable for research on the processes of cognitive rehabilitation and underlying plasticity processes, because they further increase heterogeneity in the sample.

Another interesting approach is the usage of a meta-cognitive training, which has proven its effect on fatigue, mood and self-efficacy in MS patients (Pöttgen, Lau, Penner, Heesen, & Moritz, 2014). Patients thereby learn about their cognitive strengths and weaknesses and explicit coping strategies. Combined with an implicit cognitive training such as BrainStim, this might be a promising approach, especially for clinical practice.

Outcome measures.

The importance of selection of appropriate outcome measures is often underestimated. Because of the specificity of BrainStim on WM and processing speed, we decided to include WM and processing speed as well as brain activation during a WM task as main outcome measures.

In the adults' case series (study 2), changes in SDMT distinguished best between trained and untrained patients and trained juvenile patients (study) all improved regarding this test. Therefore, the SDMT might be a good outcome measure to assess the effects of cognitive rehabilitation in general. Nevertheless, SDMT did not distinguish between patients with or without response regarding brain activation of the WM network. This might be due to the fact that SDMT is a combined measure of WM and processing speed. Higher performance in processing speed or WM might thereby both (independently) result in a higher outcome in this test. WM training with BrainStim has an impact on both domains but these effects might occur during different time points of the rehabilitation process, as described above.

fMRI as outcome measure in rehabilitation trials seems to be problematic, because we do not fully understand the underlying mechanisms of activation increase and decrease after cognitive training. In MS, studies using group level statistics report increased and more widespread activation after training and one small trial reports increased activation in posterior regions and decreased activation in frontal areas of the brain (Ernst et al., 2012). But the detailed inspection of single cases indicates that there are several patterns of response to the same cognitive training. Including different and especially opposed patterns in one group analysis may result in no observable statistical differences. Especially in clinical research, such trials may often not be published. Therefore, fMRI might not be the right outcome measure for rehabilitation studies, when applying simple group statistics. Further studies should assess different plasticity processes induced by cognitive training in MS patients in more detail. fMRI data of rehabilitation trials in MS should be assessed on an individual basis to describe which patterns of response are present. In a next step, patients with different patterns could be compared to gain further insight in mechanisms and factors of cognitive rehabilitation.

It is a valid objection that observed effects in trials on cognitive training might be a result of events occurring during the training period or a result of non-specific factors (general activation of the participant, change in motivation or mood). This, of course, may occur in every study, but in larger samples a single outlier has less impact. Two principles can help to divide possible training effects from other variations: inclusion of a control group (A) and ensuring that assessment of response to treatment relies on more than one outcome measure (Triangulation approach, B).

A) The inclusion of a control group is highly recommended when assessing rehabilitation outcome. We tried to address this issue for both case series, but because the number of patients available for such a time-consuming study is low, we only acquired a

small control group for the adult case series (study 2) and did not include one in the juvenile cases (study 3). Nevertheless, in adult controls only few changes in cognitive functioning were found after four weeks (tonic alertness even decreased in three out of four participants) and no meaningful changes of brain activation of the WM network were observed.

B) To assess effects of WM training in the presented case series, we used the triangulation approach derived from qualitative research (Denzin, 1978). Thereby, the object or effect of interest is assessed with more than one outcome measure. In rehabilitation research this means that response to treatment has to be observable on several predefined training-related outcome measures. Traditionally, this means using more than one test to assess, for example, one cognitive function but this approach can be extended to physiological or brain-imaging measures. We therefore defined response to treatment as when behavioural changes and changes in brain functionality were observable.

These two principles may not fully rule out the possibility that observed changes during the rehabilitation period go back to other processes during this time, but they minimize the risk of misidentifying responding participants. Combining these principles may be helpful in future studies in this field.

Final conclusion

Cognition has a high impact on daily activities and life of MS patients and treatment of these deficits is mandatory. Cognitive rehabilitation approaches have shown their efficacy in several studies but meta-analytic analyses often find only low evidence over all. This might be due to the heterogeneity of study designs possibly also the heterogeneity of the underlying adaptive processes. The presented case series showed that WM training is useful to some extent in adult and juvenile patients with MS. Nevertheless they also highlight that more trials on the effects of cognitive rehabilitation approaches in general and of specific trainings are needed in the future. Such studies should especially address patterns of response regarding fMRI and cognition in MS patients as well as plasticity processes underlying the observed changes and their time dependency. Further, factors for treatment response should be replicated and assessed in more detail. Thereby, in future, we could support our patients more efficiently by applying the right cognitive intervention in the most promising state of the disease, individually.

Acknowledgments

I would like to thank many people inside and ouside academia, who supported me on my journey to complete this thesis. First of all I would like to thank my supervisor, Iris-Katharina Penner, for her invaluable support and advice throughout the last four years and I would like to thank the doctroral committee kindly agreeing to evaluate the present thesis. Further, I would like to thank my co-authors for their contributions to the manuscripts.

Also, I would like to thank my dear colleagues at the Division Cognitive Psychology and Methodology. I am especially grateful to Klaus Opwis and Markus Stöcklin for all their scientific input, and Natalia Adamski and Silvia Heinz, for all their personal support and encouragement. Further, my thanks go to Laura Wiles for helping me with the English proofreading. I would like to thank the Freiwillige Akademische Gesellschaft (FAG) for their finacial support to finish this thesis. My deepst thanks go to the people participating in the studies for their time and patience.

Finally, I would like to thank those people who made rainy days sunnier and brought some color in my life: My friends and family. My thanks go to Donja Rodic, Eva Unternährer and Yasemin Meral for the greatest dinners and evenigs ever. Special thanks go to Michael Meyer for his love and patience. Further I would like to thank my parents Brigitte and Andreas Hubacher-Plüss and my brother, Christian, for their love and support during my whole life.

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Appendices A to C

Appendix A

Penner, I.-K., **Hubacher, M.**, Rasenack, M., Sprenger, T., Weber, P. & Y. Naegelin (2013). Utility of neuropsychological testing for guiding treatment decisions in paediatric multiple sclerosis. *Multiple Sclerosis Journal, 19* (3), 366-368.

Appendix B

Hubacher, M., Kappos, L., Weier K., Stoecklin, M., Opwis, K., Penner, I.K (2015). Case-based fMRI analysis after cognitive intervention in MS: A Novel Approach. *Frontiers in Neurology, 6.*

Appendix C

Hubacher, M., DeLuca, J., Weber, P., Steinlin, M., Kappos, L., Opwis, K. & Penner, IK. (2015). Cognitive rehabilitation of working memory in juvenile Multiple Sclerosis – Effects on cognitive functioning, functional MRI and network related connectivity. *Restorative Neurology and Neuroscience, Preprint.*

Case Study

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–3

DOI: 10.1177/1352458512450355
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Utility of neuropsychological testing for guiding treatment decisions in paediatric multiple sclerosis

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Abstract

In the past years, there has been growing awareness about childhood onset multiple sclerosis (MS) and the relevance of psychosocial aspects such as cognitive disturbances, fatigue and depression in this population. We describe a case of a 16-year-old patient with relapsing–remitting multiple sclerosis (RRMS) who presented at our clinic with severe fatigue symptoms and who underwent repeated neuropsychological examinations. A sudden significant slowing indicated a new relapse while neurological examination did not. This case highlights the high sensitivity and clinical relevance of neuropsychological testing in patients with juvenile MS even in the context of treatment decisions.

Keywords

Juvenile multiple sclerosis, paediatric multiple sclerosis, cognition, neuropsychology, relapse

Date received: 28th March 2012; revised: 16th April 2012; accepted: 18th April 2012

Introduction

Children and adolescents with multiple sclerosis (MS) constitute approximately 5% of the overall MS population.[1] Similarities to but also differences from adult MS have been reported regarding the development of clinical symptoms, magnetic resonance imaging (MRI) abnormalities as well as psychosocial aspects such as cognition, fatigue and mood.[1–3] Cognitive impairment in domains well known to be affected in adult MS was previously reported in 41% of patients with paediatric MS.[3] In addition, some 30% of those patients were diagnosed with a psychiatric disorder.[2,4] These psychosocial abnormalities are of high clinical relevance in a population where the brain is still developing, when myelination has not yet completed and personality is consolidating. Cognitive functioning is one major prerequisite for normal intellectual development and success in school. We here report the case of a 16-year-old boy with relapsing–remitting multiple sclerosis (RRMS) in whom a structured neuropsychological assessment indicated a relapse which may have been missed otherwise. We will discuss the clinical implications of such neuropsychological findings.

Case report

A 16-year-old MS patient was assessed at our clinic to clarify whether MS-related fatigue contributed to his school problems and an extreme form of exhaustion. First symptoms indicating a demyelinating disorder of the central nervous system (CNS) occurred at the age of 11 when he experienced an extreme form of physical and mental exhaustion accompanied by severe headache for three weeks. During this time he was unable to attend school and stayed in bed most of the time. After a severe relapse at the age of 15, the boy experienced weakness in his right leg leading to a fall at school. Further, he reported weakness of his right hand and paraesthesia in his right extremities. Again, an extreme form of physical and mental exhaustion accompanied the symptoms, which lasted for three months. Brain MRI showed multiple as well as contrast-enhancing lesions indicating an active demyelinating

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Table 1. Description of the applied neuropsychological examination.

Function	Applied test	
Questionnaires		
Wellbeing/quality of life	Berner Fragebogen zum Wohlbefinden Jugendlicher (BFW/J)	[A]
Depressive symptoms	Depressions-Inventar für Kinder und Jugendliche (DIKJ)	[B]
Fatigue	Fatigue Scale for Motor and Cognitive Functions (FSMC — adapted for kids)	[C]
Memory		
Verbal learning	Verbal Learning and Memory Test (VLMT)	[D]
Verbal short-term memory	DigitSpan forward	[E]
Verbal working memory	DigitSpan backward	
Visual memory	10/36 spatial recall test	[F]
Visual short-term memory	CorsiBlock forward	[E]
Visual working memory	CorsiBlock backward	
Attention		
Tonic and phasic alertness	Testbatterie zur Aufmerksamkeitsprüfung (TAP)	[G]
Mental speed/executive functions		
Mental speed	Symbol Digit Modalities Test (SDMT)	[H]
Executive functions	Regensburger verbal fluency test (RWT s-words)	[I]
	Regensburger verbal fluency test (RWT animals)	

[A] Grob A, Lüthi R, Kaiser FG, et al. *Diagnostica* 1991; 37: 66–75. [B] Stuebsneuer-Pelster J, Schürmann M, Duda K. Depressions-Inventar für Kinder und Jugendliche (DIKJ). Göttingen: Hogrefe, 1989. [C] Penner IK, Raselli C, Stoecklin M, et al. *Mult Scler* 2009; 15: 1509–1517. [D] Helmstaedter C, Lendt M, Lux S. Verbaler Lern- und Merkfähigkeitstest (VLMT). Göttingen: Beltz Test, 2001. [E] Härting C, Markowitsch HJ, Neufeld H, et al. Bern: Hans Huber, 2000. [F] Rao SM, Cognitive Function Study Group. Milwaukee: Medical College of Wisconsin, 1990. [G] Zimmermann P, Fimm B. Herzogenrath: Vera Fimm, Psychologische Testsysteme, 2009. [H] Smith A, Los Angeles: Western Psychological Services, 1973. [I] Aschenbrenner S, Tucha O, Lange KW. Göttingen: Hogrefe, 2000.

CNS disorder. At this time a treatment with Interferon-Beta-1a was started. During six months of treatment, he experienced three new relapses accompanied by gait ataxia, dysarthria and exhaustion. Brain MRI showed a significant increase in lesion load and new contrast-enhancing lesions left parietal. Multiple new lesions were also found in the spinal cord but were at the time of MRI examination not contrast enhancing. At this time his Expanded Disability Status Scale (EDSS) score was 4.0. Due to the persistent disease activity, relapses and disease progression in terms of his EDSS score, he was switched to Natalizumab. After one year, the clinical situation had stabilized, he had experienced no further relapses and his EDSS score was 3.0.

Since severe exhaustion was remaining and actually affecting school performance, he was referred to our clinic to test whether he suffered from MS-related fatigue. A neuropsychological examination was performed including quality-of-life instruments, depression and fatigue scales as well as several tests for cognitive functioning and intelligence. A detailed description of the applied test-battery is provided in Table 1.

No pathological findings were detectable in the assessed cognitive domains memory, attention, information processing speed, executive functioning and mental flexibility. Intelligence was high with a score at the 77th percentile. Self-reported quality of life was below the normal range and fatigue was considerably increased, indicating clinically relevant results. The depression score was high but below the usual cut-off indicating clinically relevant results.[5]

Due to the high depression and fatigue scores, the boy was re-examined two weeks later. At this follow-up visit, he self-reported not feeling well and having minor balance problems.

The neuropsychological profile of the follow-up visit (parallel versions were applied if available) revealed a non-significant performance decrease in verbal short-term memory, but a clinically meaningful decline in the performance of the alertness test, a measure for basic attention and information processing speed. Here, a decrease in performance was found, indicating severe slowing (see Figure 1). In addition, fatigue and depression symptoms worsened compared to baseline.

The striking cognitive slowing together with the self-report of not feeling well and being extremely exhausted prompted a neurological referral. The neurological examination showed a stable EDSS of 3.0. Due to the cognitive abnormality, an MRI was performed showing three new T2 hyperintense lesions as compared to the previous MRI four months earlier, but no contrast-enhancing lesions.

Due to the acute change in alertness performance, the obvious subjective feeling of not being well and minor balance problems, we decided to consider the new symptoms as a clinically meaningful relapse and treated the patient with a three-day course of intravenous methylprednisolone. Three weeks later, the EDSS proved to be stable and the patient reported a subjective improvement of his physical

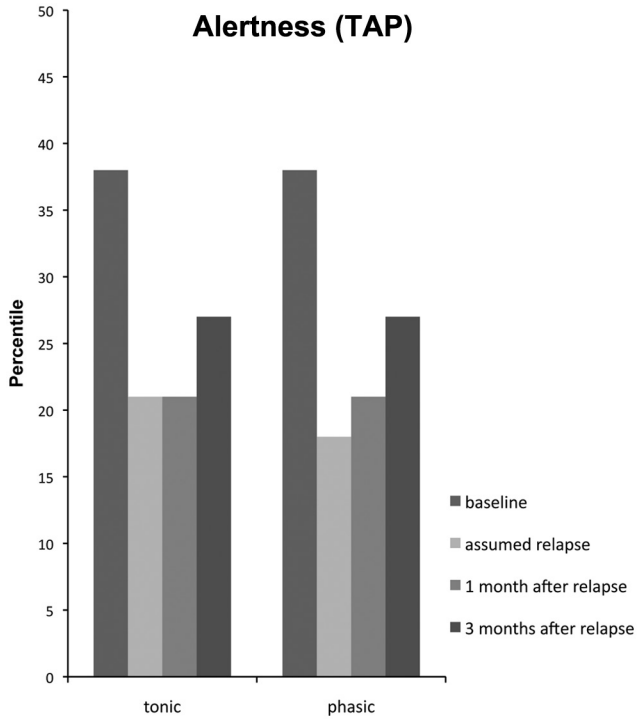

Figure 1. Performance of the 16-year-old patient on "tonic" and "phasic" alertness at baseline, two weeks later (assumed relapse), one month after relapse and three months after relapse. Performance is indicated as percentile rank.
TAP: Testbatterie zur Aufmerksamkeitsprüfung.

and mental condition. This was confirmed by disappearance of balance problems and by stabilisation of his cognitive profile. However, alertness performance remained deficient and depression as well as fatigue symptoms did not improve. The boy was followed up neuropsychologically after three months. While all cognitive domains were back to normal, a total recovery of alertness performance was not reached after three months.

Discussion

The initial neuropsychological examination of the boy revealed normal intelligence, normal cognitive performance, but clinically relevant fatigue and depression. Re-examination two weeks later revealed that almost all cognitive parameters remained stable except the performance in the alertness task. This task consists of a "tonic" and "phasic" part. The tonic aspect measures sustained attention and speed of response (button press when target cue appears). The phasic aspect measures the ability to profit from a cue before the target appears to facilitate a faster reaction. Both conditions focus on response speed. When we re-examined the patient, he showed a relevant increase in reaction times when performing this basic attention test. We considered this result together with the balance problems as an indication of an acute relapse. The MRI performed the same day, however, did not show contrast-enhancing active lesions. However, the fact that three new lesions had developed within a follow-up period of only four months indicated disease activity. The patient reported physical and cognitive improvement after corticosteroid pulse therapy, which was reflected by a stabilisation of his cognitive performance.

In accordance with the literature on adult MS,[6,7] processing speed seems to be one of the most vulnerable and sensitive cognitive domains in paediatric MS as well. Of importance to mention is that performance on the Symbol Digit Modalities Test (SDMT) was not pathological, pointing to the necessity of choosing a test measuring pure information processing speed without aspects of working memory. Of clinical interest and relevance is the time frame of recovery in this cognitive domain. The boy was not yet back to normal after three months, indicating that recovery on the cognitive speed component may take longer.

In conclusion, this case report demonstrates the utility of neuropsychological testing in children and adolescents with MS even in the context of guiding treatment decisions.

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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ORIGINAL RESEARCH ARTICLE
published: 08 April 2015
doi: 10.3389/fneur.2015.00078

Case-based fMRI analysis after cognitive rehabilitation in MS: a novel approach

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Background: Cognitive decline in multiple sclerosis (MS) negatively impacts patients' everyday functioning and quality of life. Since symptomatic pharmacological treatment is not yet available alternative treatment strategies such as cognitive rehabilitation are of particular interest.

Objectives: To analyse the ways in which MS patients respond to cognitive training, by combining behavioral and fMRI data in a case-based triangulation approach.

Methods: Ten relapsing-remitting (RR) MS patients aged between 39 and 58 years and between 1 and 8 years post MS diagnosis were included. EDSS ranged from 1 to 3.5. Participants had normal to high intelligence levels. Six patients were assigned to the training group (TG) and four to the control group (CG) without intervention. The TG received a 4-week computerized working memory (WM) training, consisting of 16 training sessions of 45 min duration each. Before and after the training a neuropsychological examination and fMRI investigation by using an *N*-back task of different complexity was applied.

Results: Patients in the TG responded differently to cognitive training. Four participants did not meet the triangulation criteria for being treatment responders. The two responders showed two distinct changes regarding activation patterns after training: (I) *decreased* brain activation associated with increased processing speed and (II) *increased* brain activation associated with higher processing speed and WM performance.

Conclusion: The occurrence of different and opposed response patterns after the same training indicates a risk in applying classical group statistics. Different and especially opposed patterns within the same sample may distort results of classical statistical comparisons. Thus, underlying processes may not be discovered and lead to misinterpretation of results.

Keywords: working memory, cognitive training, rehabilitation, plasticity, multiple sclerosis, fMRI

INTRODUCTION

For decades, it has been known that patients with multiple sclerosis (MS) suffer from cognitive deficits. However, their importance for both the patients' daily life and the overall health economy has been neglected for a long time. Meanwhile, they are regarded as a major element of the disease. Since symptomatic pharmacotherapy is not available, non-pharmacological approaches might further improve patients' situation. In this context, cognitive rehabilitation has been studied with respect to its effectiveness. Several heterogeneous rehabilitation studies have been conducted, targeting either specific cognitive functions such as attention (1–4) or memory (5, 6) or applying a non-specific neuropsychological treatment. Primarily due to methodological heterogeneities, meta-analyses report negative results (7) or found only low evidence (8) for the effectiveness of cognitive rehabilitation approaches. Rosti-Otajarvi and Hämäläinen (9) report low but nevertheless positive evidence for cognitive training effects on working memory (WM) and other memory functions. However, clear evidence is missing, so far.

Studies using fMRI to monitor the effectiveness of cognitive treatment assume that behavioral improvement after cognitive training may be based on "adaptive" processes in the brain. Most studies report increased and more widespread activation in patients with MS after cognitive rehabilitation (1, 3, 10, 11). While patients receiving cognitive training show overall increased activation, untreated patients often show a decrease over time (12). However, a small trial, including only four participants with MS receiving cognitive training, reported increased activation in posterior regions but decreased activation in frontal areas of the brain (13) highlighting that brain adaptation is not only reflected by increased but also by decreased activation of task relevant areas.

In MS patients, aspects such as disease course, disease activity, cognitive status, fatigue, and depression can impact the responsiveness to cognitive interventions. This heterogeneity may result

in different patterns of response to the same cognitive treatment. In trials with large samples, these influencing factors can statistically be controlled for, however, most rehabilitation studies only refer to small sample sizes. To address this problem, we propose a case-based approach to assess different patterns of response to cognitive training in heterogeneous and small samples. To underline the necessity of studying single patients more carefully, we present a case-series including six patients with early relapsing-remitting MS (RRMS) who received specific WM training during 4 weeks, and four control participants without intervention. The primary aim was to clarify whether (A) MS patients may show different brain activation responses to cognitive training and (B) how these changes in brain activation are finally related to individual cognitive performance. To answer these questions, a triangulation approach was applied.

MATERIALS AND METHODS

PARTICIPANTS

Sixteen patients with CIS and early RRMS under interferon-beta-1b (Betaferon) therapy were recruited. Inclusion criteria were as follows: time since diagnosis <10 years, EDSS below 6.0, no relapses 3 months prior to the baseline visit. Participants were randomly assigned to the treatment group (TG; $N = 9$), or the control group (CG; $N = 7$), respectively. In the TG, two patients were excluded because they did not match the inclusion criteria and one was excluded because of an acute relapse during the intervention. From the CG, one patient quit the study because of personal reasons and two more participants were excluded because of relapses during the study.

The remaining 10 participants (TG = 6; CG = 4) were aged between 39 and 58 years and were between 1 and 8 years post MS diagnosis. Time since last relapse was shorter in the TG (0.25–4.4 years) than in the CG (2.7–6.4 years). EDSS ranged from 1 to 3.5. T2 lesion volume was between 0.24 and 8.53 ml. Participants had normal or high intelligence level. Baseline characteristics of participants are displayed in **Table 1**. The participants gave written informed consent to participate in the study, which was approved by the local Ethics Committee (Basel).

STUDY DESIGN

All participants underwent two baseline neuropsychological assessments within 2 weeks to assure a stable cognitive baseline status. During the second assessment, a baseline brain imaging (structural MRI and fMRI) was performed. All participants in the TG started their computerized cognitive training (BrainStim) within 1 week after the second baseline testing. They trained for 4 weeks, four times a week, for 45 min. Participants trained at home and were supervised once a week by a trained psychologist. Computerized training sessions were logged to monitor adherence to training. Participants in the CG received no intervention. Within 1 week after completion of the training, participants were retested for cognitive performance and a second MRI/fMRI was conducted.

To analyse the case series, a triangulation approach was applied as it is used in qualitative research (14). This methodological procedure combines quantitative and qualitative aspects (15). In order to measure a response to the treatment, detectable changes in more than one outcome parameter are taken into account. By applying this method to our case-series, response to treatment was defined by a combined change in brain activation on the one hand and cognitive functions (WM and/or processing speed) on the other. To overcome the problem of different scaling and to allow for direct comparisons between fMRI and cognitive outcomes, we intentionally avoided pre-defined cut-off values but focused on a qualitative description of changes by visual inspection.

THE COGNITIVE TRAINING TOOL BrainStim

BrainStim (16) is a computerized training tool based on the WM model of Baddeley (17). It consists of three different modules targeting both, verbal and visual–spatial aspects of WM (18, 19). The first module trains spatial orientation. Participants have to memorize either a visually or verbally described route. This route has to be retraced on a virtual map afterwards. The number of crossings increases with higher levels of difficulty. A second module trains visual memory as well as the updating function of the central executive component. Participants have to remember the location of cards that have been turned over and back again. The task is to find

Table 1 | Baseline characteristics and possible factors for treatment response.

Case	Gender	Age	Disease duration (years)	Number of relapses	Last relapse prior to study	EDSS	T2 lesion volume (ml)	General intelligence	Depressive symptoms	Cognitive fatigue	Motor fatigue
TGI	Male	47	2	6	9 months	3.5	0.27	96 PR	No	Severe	Severe
TG2	Female	44	1	2	3 months	1.0	5.93	50 PR	No	No	Moderate
TG3	Female	42	2	4	7 months	3.5	0.31	50 PR	No	Moderate	Severe
TG4	Male	42	5	2	4 years 5 months	2.0	0.24	99 PR	Mild	Moderate	Severe
TG5	Female	52	3	2	8 months	2.5	8.53	93 PR	No	Mild	Severe
TG6	Female	58	2	2	6 months	2.0	2.05	93 PR	No	Mild	Moderate
CGI	Male	46	8	4	6 years 5 months	1.0	1.43	99 PR	No	No	No
CG2	Female	42	3	3	3 years 2 months	2.5	1.38	73 PR	Moderate	Severe	Severe
CG3	Male	39	3	1	2 years 8 months	1.0	2.67	96 PR	No	No	No
CG4	Male	52	2	1	3 years 6 months	2.0	4.61	79 PR	No	Severe	Severe

PR, percentile rank.

pairs of cards with corresponding figures. With increasing levels of difficulty, the number of cards in one set is increases. During the third module, participants have to remember digits, presented in a limited period of time, and recall them after having performed an arithmetic distraction task. With each increase of the level of difficulty, more digits have to be recalled.

BrainStim is designed to ensure training not only based on repetition and practice but also on the development and consolidation of strategies. Therefore, the stimuli of the modules are presented randomly, where the order of the modules is changing in each session. The level of difficulty adapts automatically to the participants performance. After a pre-defined number of correct responses, the level of difficulty increases. Whenever the participant fails to solve a certain amount of tasks, the level of difficulty is decreases again.

COGNITIVE ASSESSMENT

At the first baseline visit, we collected demographical data and assessed premorbid intelligence [MWT (20)], fatigue [fatigue scale for motor and cognitive functions: FSMC (21)], and depressive symptoms [BDI-fast screen (22)]. Based on previous work (18) where BrainStim has proven its specific effect on WM and processing speed, we defined these functions as primary cognitive outcome measures. The *Corsi Block backwards* task was used for visual WM and the *Digit Span backwards* test for verbal WM [Wechsler memory scale-revised (23)]. The *symbol digit modalities* test (SDMT) was used to measure WM performance and processing speed (24). To receive a measure for processing speed that is not confounded with WM, we used the *alertness* tasks (tonic and phasic) from of the *test battery for attention performance* [TAP (25)]. Age corrected normative data was available for all cognitive tests. For WM (Corsi Block bw and Digit Span bw) as well as for alertness (tonic and phasic) percentile ranks <16 were regarded as a clinically meaningful cognitive deficit. SDMT scores were z-transformed according to Scherer et al. (26) and z-scores less than -1.68 were rated as clinically significant.

fMRI PARADIGM

During fMRI, participants solved a N-back task with different WM loads [adapted from the TAP (25)]. Series of pseudo-randomized digits were continuously presented on a screen. Participants were asked to press a button as fast as possible whenever the target appeared. A target was a digit that was identical to the immediately preceding digit (1-back), the second to the last digit (2-back), or the third to the last digit (3-back). A block design was used for semi-randomized presentation of the N-back conditions and rest condition (fixation cross). One active block with a duration of 30 s consisted of 10 stimuli with 2 stimuli being targets. Each condition was presented four times during each session. Participants performed the paradigm two times with a break between the two sessions. In sum, each condition was presented during eight blocks. Reaction times for N-back tasks were logged, but due to technical problems this files were not available for all participants and time points and therefore excluded from further analysis. Immediately prior to the MRI, participants were familiarized with the N-back task outside the scanner to ensure comprehension.

MRI DATA ACQUISITION

The MR measurements were performed on a 3.0-T scanner (Magnetom VERIO, Siemens Healthcare, Erlangen, Germany) with a standard head coil. An anatomical image for registration purposes was acquired [sagittal T1-weighted 3D high resolution magnetization-prepared rapid gradient echo (MPRAGE) sequence: TR/TE/TI = 2000/3.37/1000 ms, 256 × 256 matrix, field of view (FoV) = 256 mm, providing an isotropic spatial resolution of 1 mm^3]. For lesion masking, a T2-weighted fluid attenuated inversion recovery (T2-FLAIR) sequence was obtained (TR/TE/TI = 8000/77/2370 ms, 40 slices with slice thickness of 3 mm and FoV = 220 mm).

Echo-planar imaging (EPI) sequences were used for functional imaging (TR/TE = 2000/23 ms, 34 slices with a slice thickness of 3 mm, FoV = 256 mm, voxel size = 4 mm × 4 mm × 3 mm). Slices were positioned parallel the AC–PC line. For both runs with the paradigm, 262 volumes with a total scan time of 8.5 min were recorded. After excluding the 5 five dummy scans per run, 514 volumes remained for further analysis.

MRI DATA MANAGEMENT AND ANALYSIS

Data were analysed using Statistical Parametric Mapping software package, SPM8 (http://www.fil.ion.ucl.ac.uk/spm). We identified T2 hyperintense white matter lesions with the lesion segmentation toolbox [LST (27)]. To choose the optimal initial threshold κ, lesion segmentation was run with different thresholds. Afterwards, two independent evaluators compared manually the resulting lesion maps with the original raw images. By this approach, an initial threshold of $\kappa = 0.2$ was chosen. Lesion masks were used for automatic lesion filling with intensities similar to the normal white matter voxels in T1-weighted images. We used these "lesion-free" T1-images for later registration steps. Further, the lesion-filled T1-images were segmented into gray matter, white matter, and CSF ("new segment"). Gray matter and white matter were fed to DARTEL to create a study-specific template (28).

fMRI data were realigned, unwarped, and co-registered with the T1-images. fMRI images were then normalized to MNI space with the corresponding DARTEL flow fields and a 8 mm Gaussian smoothing.

Since we were interested in changes between the two time points, all smoothed images were subject to a first-level analysis to define the model design and contrasts of interest. Movement parameters extracted from the realignment step were included as additional covariates in order to remove residual variance. Contrasts for changes between baseline MRI and the post-training MRI in each subject [$p < 0.001$, threshold: 10 voxels per cluster (29)] for all performance conditions (1-back, 2-back, and 3-back) were specified to identify activation increase and decrease between the times of measurement.

RESULTS

fMRI ASSESSMENT

For fMRI outcomes, contrasts between baseline and post-training for 1-back, 2-back, and 3-back conditions for each participant were built individually. Patterns of response were comparable for the three conditions. Therefore, only contrasts from the 2-back condition are displayed in **Figure 1** for clarity reasons ($p < 0.001$

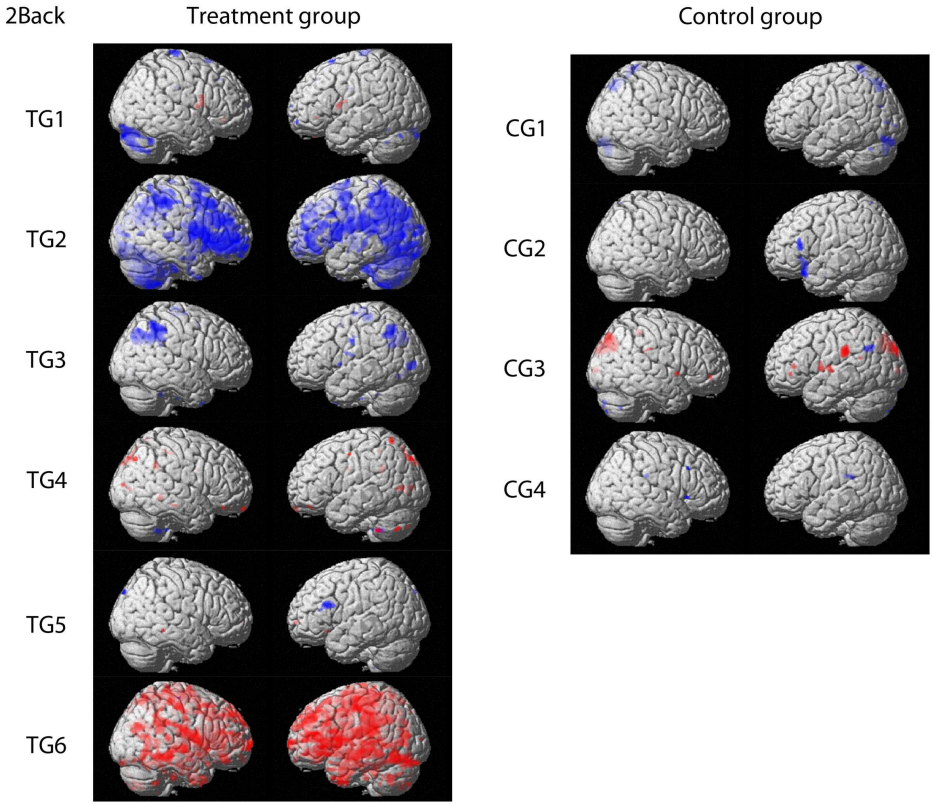

FIGURE 1 | Contrasts comparing baseline and post-training fMRI results for the treatment group and the control group, respectively. Activation increase is marked in red whereas decreased activation over time is highlighted in blue ($p < 0.001$ uncorrected; threshold: 10 voxels per cluster). Figures are shown in radiological convention.

uncorrected, threshold: 10 voxels per cluster). Four participants (TG1, TG3, TG4, TG5) receiving the training showed only minor changes in brain activation, which were comparable to changes observed in participants without training.

Two participants (TG2, TG6) showed changes in brain activation that exceeded changes observed in patients without training. One participant (TG2) showed decreased activation in primarily frontal and parietal regions. In TG6, the opposite pattern was observed. This participant showed increased brain activation spread across the whole brain except for the occipital lobe.

NEUROPSYCHOLOGICAL ASSESSMENT

At baseline, no participants were impaired regarding tonic alertness and SDMT. Three participants (TG2, TG5, CG2) had reduced phasic alertness of whom one participant (CG2) showed reduced visual WM span (corsi block backward) in addition. One participant (TG1) showed reduced verbal WM performance (digit span backward). On a group level, by applying Mann–Whitney-*U* test performance on the digit span backward in the CG was higher than in the TG whereas no other baseline differences were detectable. (Note: Although this work is focused on qualitative single subject analyses the authors included this information revealed by group analyses on explicit request by one reviewer.)

For longitudinal comparisons, we used raw scores as displayed in **Table 2**. When comparing baseline and post-training results, none of the participants showed a consistent increase in all cognitive domains. One TG participant (TG3) showed solely an increase in the visual WM task. Participant TG1 performed faster during both alertness tasks. Two participants (TG2, TG4) showed faster reaction times in the alertness tasks and increased scores in the SDMT. TG5 had increased WM functions but no speed increase. TG6 performed better after the training in four of the five outcome measures. In the CG, two participants (CG1, CG3) showed increased verbal WM scores, one participant (CG2) had faster reaction times during the alertness task and higher visual WM scores. CG4 showed faster reaction times during the phasic alertness task. Three participants of the CG (CG1, CG3, CG4) had decreased reaction times during tonic alertness after 4 weeks. No participant of the CG showed changes in the SDMT task. On group level, there were no differences between the TG and the CG after the training. (Note: Although this work is focused on qualitative single subject analyses the authors included this information revealed by group analyses on explicit request by one reviewer.)

DISCUSSION

To identify possible effects of WM training on brain functionality and cognitive status, we presented six cases with RRMS

Table 2 | Raw scores of primary cognitive outcome measures for all participants at baseline and after the training.

	Processing speed measures				Processing speed and WM (SDMT)		WM measures			
	Tonic alertness (TAP alertness A)		Phasic alertness (TAP alertness B)				Visual WM (corsi blocks bw)		Verbal WM (digit span bw)	
Case	**Baseline**	**Post-training**	**Baseline**	**Post-training**	**Baseline**	**Post-training**	**Baseline**	**Post-training**	**Baseline**	**Post-training**
TG1	266.5	242.0	251.5	217.0	50.5	54.0	9.5	10.0	5.0[a]	5.0
TG2	285.5	260.0	280.5[a]	264.0	65.0	75.0	9.0	9.0	6.0	5.0
TG3	293.0	293.0	247.5	248.0	56.5	59.0	7.5	9.0	6.0	7.0
TG4	242.0	227.0	233.5	204.0	45.5	61.0	10.0	10.0	7.0	8.0
TG5	276.5	271.0	312.0[a]	307.0	57.5	66.0	8.5	10.0	5.0	8.0
TG6	255.0	246.0	258.0	242.0	63.0	72.0	8.5	10.0	5.0	6.0
CG1	214.0	223.0	220.5	223.0	56.5	55.0	9.0	10.0	9.5	11.0
CG2	272.0	243.0	301.5[a]	235.0	56.5	59.0	7.0[a]	9.0	7.0	7.0
CG3	235.5	249.0	228.0	232.0	65.5	67.0	10.0	11.0	8.0	11.0
CG4	235.0	268.0	259.5	243.0	47.5	43.0	7.0	8.0	6.0	5.0

Improvements from baseline to post-training are highlighted in gray.

Alertness (TAP) scores represent reaction times.

bw, backward; WM, working memory; TG, training group; CG, control group.

[a] *Clinically meaningful baseline values (PR < 16 for alertness and WM tasks; z < −1.68 for the SDMT).*

receiving WM training during 4 weeks and four control cases without intervention. At a purely descriptive level, the key differentiators between TG and CG were SDMT and tonic alertness. Four out of six cases in the TG were able to increase their performance on the SDMT, whereas no participant in the control condition did so. Regarding tonic alertness, four of six participants in the TG showed higher performance after the training whereas three out of four participants in the CG showed even a performance decrease.

Regarding functional brain activation, four TG participants showed only minor changes in brain activation, which were comparable to changes observed in the CT. We therefore conclude that these minimal changes reflect a normal range of variation during a 4 weeks period and not a response to training.

Two TG participants met our triangulation criteria for being responders: both changes in brain activation and changes in WM or processing speed measures were observed. One participant showed a *decrease* in activation during the training period in frontal and parietal regions. The other responder showed an *increase* in brain activation in frontal and parietal regions as well as an additional increase in temporal regions.

The opposed response to treatment measured by fMRI might be reducible to different brain processes. Plasticity processes related to practice have been studied intensively in healthy individuals. Group analyses regarding short-term WM training (duration of training: 30–120 min in total) in healthy adults revealed decreased brain activation in frontal (dorsolateral, prefrontal, inferior frontal, precentral sulcus) and parietal regions (30–33), whereas more intense training led to mixed patterns of increases and decreases (34–37). In their review article, Kelly et al. (38) described four different patterns of change in brain activation due to practice: decrease, increase, redistribution, and reorganization. In a subsequent meta-analysis, Buschkuehl et al. (39) described the same patterns of response to WM training:

(1) Decrease in extent or strength of activation within one network that is associated with higher performance has often been reported after short-term training, mainly based on practice (30, 32). It is thought to be associated with a certain sharpening of response within the network where less neurons are firing in response to a task. This change might reflect more efficient information processing in the brain. The decrease of brain activation within the WM network in one of our responders might be related to this process. This change in activation was accompanied by an increase in processing speed on the behavioral level (Alertness and SDMT; for summary see **Table 3**). Thus, this increased processing speed can be regarded as the behavioral expression of more efficient information processing within the brain.
(2) A second pattern is referred to increased activation within one network (40). Here, increased intensity of activation is thought to be associated with a strengthening in response to a specific task, whereas increase in extent of the activated network reflects additional recruitment of cortical units. None of our participants showed a comparable change in brain activation.
(3) Combined increase and decrease within a network might occur in response to cognitive training (34, 41). This is referred to as redistribution of activation. The same cognitive process is used to solve the task, but due to practice and learning less attention control is needed and task specific processes are

Table 3 | Summary table of changes from baseline to post-treatment for all participants.

Case	Change in activation	Processing speed measures		Processing speed and WM (SDMT)	WM measures	
		Tonic alertness (TAP alertness A)	Phasic alertness (TAP alertness B)		Visual WM (corsi blocks bw)	Verbal WM (digit span bw)
TG1		↑	↑			
TG2	↓	↑	↑	↑		
TG3					↑	
TG4		↑	↑	↑		
TG5				↑	↑	↑
TG6	↑	↑	↑	↑	↑	
CG1		↓				↑
CG2		↑	↑		↑	
CG3		↓				↑
CG4		↓	↑			

empty spaces, no change; ↑, increase; ↓, decrease; bw, backward; TG, training group; CG, control group; WM, working memory.

more involved. None of our participants showed a similar pattern of change in brain activation.

(4) The fourth pattern of response can primarily be seen in clinical populations (38). In contrast to redistribution processes, where involved anatomical structures remain the same, reorganization processes include decreased activation in some areas and additional recruitment of new cortical regions. This shift of activation is thought to reflect a process shift: due to training, other cognitive processes become involved in solving the task. Additional recruitment of temporal regions outside the usual WM network in our second responder might reflect such a reorganization process. At the behavioral level, this participant showed higher processing speed (Alertness and SDMT) and visual WM performance potentially resulting from a reorganization process. The increase of activation was more apparent in the left hemisphere. We assume that the individual has developed a verbal coping strategy, which triggered the observed change in activation after training.

It should be noted, that non-responding participants and participants of the CG also showed changes regarding cognitive performance. Changes in the CG might reflect normal variations in performance, since improvement was isolated on single tests and never consistent across all tests within a single cognitive domain. Changes in non-responding participants of the TG in contrast were more systematic. One of these participants showed increased processing speed (Alertness and SDMT), whereas another participant performed better in all WM measures (SDMT and visual and verbal WM). However, these behavioral changes were not accompanied by changes in brain activation and thus triangulation criteria were not fulfilled.

We are aware that this case-series has several limitations. A first limitation is certainly the small sample size. Second, we did not predefine cut-off values for behavioral and fMRI changes. Third, observed changes in brain activation and cognitive performance might be the result of factors not assessed in the study. To exclude at least variations resulting from the circadian cycle, cognitive and fMRI assessment were always performed at the same daytime. Fourth, changes in fMRI might be caused by variability in the method itself (42). That is why these well-known intersession differences were partly controlled by the applied triangulation approach. Fifth, we used a passive CT instead of implementing a shamed training group (TG). Therefore, it cannot be excluded that changes in the two participants in the TG result from multiple factors such as motivation, social interaction, and emotional support. Sixth, only few participants showed significant cognitive deficits when compared to normative data. Thus, higher baseline performance might reduce the potential to observe significant changes induced by cognitive training due to a simple ceiling effect. A last limitation of the present study is that performance data from the *n*-back task during fMRI was missing due to technical problems. Therefore, fMRI activation patterns could not be compared directly to WM and speed performance inside the scanner but only to the performance outside the scanner in terms of a transfer effect.

These limitations might have modified the outcome of our case-series. Still, we were able to identify two different types of changes after cognitive training in patients with early RRMS: (A) a decreased brain activation, which was associated with increased processing speed and (B) a reorganization process, associated with higher processing speed and WM. The occurrence of different or even opposed patterns of response after the same training indicates a problem with traditionally applied group statistics. Different and especially opposed patterns within the same sample will distort results of classical statistical comparisons. Underlying processes may therefore remain concealed.

ACKNOWLEDGMENTS

We thank Bayer Schering AG Switzerland for supporting this research. We further thank Julia Reinhardt for her advice and technical support regarding MRI assessment.

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Conflict of Interest Statement: This study was supported by a research grant from Bayer Schering AG Switzerland. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Ludwig Kappos's Institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee,

advisory board, and consultancy fees (Actelion, Addex, Bayer Health Care, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB, Xenoport); speaker fees (Bayer Health Care, Biogen, Merck, Novartis, Sanofi-Aventis, Teva); support of educational activities (Bayer Health Care, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, Teva); royalties (Neurostatus Systems GmbH); grants (Bayer Health Care, Biogen, Merck, Novartis, Roche, Swiss MS Society, the Swiss National Research Foundation, the European Union, Roche Research Foundations). Iris-Katharina Penner received honoraria, research, or travel support from Bayer Pharma AG, Bayer AG Switzerland, Biogen Idec, Genzyme, Merck Serono, Novartis, the Swiss Multiple Sclerosis Society, and Teva. Martina Hubacher, Katrin Weier, Markus Stöcklin and Klaus Opwis have nothing to disclose.

Received: 22 January 2015; accepted: 23 March 2015; published online: 08 April 2015.
Citation: Hubacher M, Kappos L, Weier K, Stöcklin M, Opwis K and Penner I-K (2015) Case-based fMRI analysis after cognitive rehabilitation in MS: a novel approach. Front. Neurol. ***6****:78. doi: 10.3389/fneur.2015.00078*
This article was submitted to Multiple Sclerosis and Neuroimmunology, a section of the journal Frontiers in Neurology.

Restorative Neurology and Neuroscience xx (20xx) x–xx
DOI 10.3233/RNN-150497
IOS Press

Cognitive rehabilitation of working memory in juvenile multiple sclerosis–effects on cognitive functioning, functional MRI and network related connectivity

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Abstract.
Purpose: To assess possible effects of working memory (WM) training on cognitive functionality, functional MRI and brain connectivity in patients with juvenile MS.
Methods: Cognitive status, fMRI and inter-network connectivity were assessed in 5 cases with juvenile MS aged between 12 and 18 years. Afterwards they received a computerized WM training for four weeks. Primary cognitive outcome measures were WM (visual and verbal) and alertness. Activation patterns related to WM were assessed during fMRI using an N-Back task with increasing difficulty. Inter-network connectivity analyses were focused on fronto-parietal (left and right), default-mode (dorsal and ventral) and the anterior salience network. Cognitive functioning, fMRI and inter-network connectivity were reassessed directly after the training and again nine months following training.
Results: Response to treatment was seen in two patients. These patients showed increased performance in WM and alertness after the training. These behavioural changes were accompanied by increased WM network activation and systematic changes in inter-network connectivity. The remaining participants were non-responders to treatment. Effects on cognitive performance were maintained up to nine months after training, whereas effects observed by fMRI disappeared.
Conclusions: Responders revealed training effects on all applied outcome measures. Disease activity and general intelligence may be factors associated with response to treatment.

Keywords: Connectivity, cognitive rehabilitation, working memory, juvenile multiple sclerosis

1. Introduction

Multiple Sclerosis (MS), with its neuroinflammatory and neurodegenerative features has for a long time been regarded as a chronic disease with an onset in early adulthood. More recently, this early onset phase

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ISSN 0922-6028/15/$35.00

has shifted towards adolescence and childhood. It is estimated that 5% of all MS cases are represented in children (Banwell et al., 2007). Besides the physical symptoms that generally accompany the disease, neurocognitive and neuropsychiatric symptoms are also present in juvenile MS. The prevalence of impaired cognition is about 31% whereas more subtle cognitive dysfunction is estimated at 53% (Amato et al., 2008). Although cognitive deficits have a significant impact on daily functioning, the situation in juvenile MS is special in many respects. First the brain of affected children and adolescents is still undergoing development and maturation, particularly in the frontal lobes, and myelination is incomplete. Second, children and adolescents are still in educative phases where information processing speed, learning, storing of new information and retrieving learned material from memory are key to intellectual, emotional and social development. Thus, to suffer from signs of cognitive decline in such a delicate phase of life can have lifelong consequences.

One key cognitive function supporting school success is working memory (WM; DeStefano & LeFevre, 2004; St Clair-Thompson & Gathercole, 2006). This essential component of cognition enables us to store information for a limited period of time, to manipulate this information by linking and thereby refreshing new incoming information with that in long-term memory. WM has been shown to be affected in adults (Amato et al., 2010) as well as in children with MS (MacAllister et al., 2005). Further, MS patients often show attentional deficits and reduced processing speed (Amato et al., 2010; Amato et al., 2008; Kujala et al., 1997). These two cognitive functions support and interact with WM (Leavitt et al., 2011). A basic component of attention is alertness (Posner & Boies, 1971). Alertness can be divided in a tonic and phasic process. Tonic alertness represents a general state of wakefulness and is a measure of pure processing speed without any relation to WM. Phasic alertness on the contrary describes the ability to temporarily increase response readiness after an external cue.

WM processes are supported by a highly integrated and interconnected network between primarily prefrontal and parietal brain regions (Owen et al., 2005). Recent brain network analyses have revealed that the functionality of this network is supported by the default-mode network (DMN), and that the switching between these two networks is mediated by the salience network (SN; Sridharan et al., 2008). The latter is described as a network with main nodes in the anterior insula and the anterior cingulate cortex. This network is often coactivated with the fronto-parietal networks during tasks of attention and WM and seems to correspond to personal salience and choosing the most relevant internal or external stimuli (Critchley et al., 2004; Menon & Uddin, 2010; Seeley et al., 2007).

Since pediatric MS may hamper expected age-related cognitive gains (Charvet et al., 2014), an effective therapeutic approach is needed to support normal brain maturation and development at this young age. Given recent work showing the promising effects of cognitive rehabilitation in adults with MS (Chiaravalloti et al., 2012, 2013; Penner et al., 2007; Sastre-Garriga et al., 2011) this methodological approach might also be beneficial in juvenile MS.

The present explorative study utilized a computerized WM training program (BrainStim) which has been shown to be effective in adults with MS (Vogt et al., 2009) to examine its effectiveness in juvenile MS. Based on the work of Vogt et al. (Vogt et al., 2008) we hypothesized that training would result in specific improvement in WM as well as improved attention functions. It was also hypothesized that training would result in increased brain activation of WM networks and be accompanied by increased connectivity among spatially independent but to WM functions related networks (right and left fronto-parietal networks; ventral and dorsal part of DMN; anterior SN). Lastly, we expect to see long-term effects on cognitive and neuroimaging measures as a consequence of cognitive training.

2. Methods

2.1. Participants

Participants were included if they fulfilled the following criteria: definite diagnosis of MS at age between 9 and 18, and no other neurological or psychiatric diseases. Five participants with clinically definite MS according to McDonald's criteria (Polman et al., 2011) were consecutively included in the study (two boys, three girls). Participants were aged between 12 and 18 years and were between one and four years post MS diagnosis (diagnosed between age 9 and 15 years). According to parents' and treating physicians' statement, two participants had a relapse three months prior to the study and one had new Gd-enhancing lesions

Table 1
Baseline characteristics and possible factors for treatment response

	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	male	Male	female	female	female
Age	16	14	17	16	12
disease onset	15 y (11 y)	11 y	13 y	14 y	9 y
Therapy	Natalizumab	(Vit D)	Natalizumab	INFB-1a	INFB-1a
relapses	3	1	4	3	1
last relapse prior to study	3 months	2,5 y	2 y	3 months	3 y (new Gd enhancing lesions 4 months)
Raven matrices	77 PR	93 PR	85 PR	36 PR	1 PR
cognitive fatigue	moderate	no	moderate	severe	no
motor fatigue	severe	no	moderate	severe	no
Depressive symptoms	no	no	no	no	no
T2 lesion volume (ml)	4.224	5.379	5.996	0.085	9.075

Note. PR: percentile rank.

in an MRI four months prior to the study without accompanying clinical signs. The other two participants had their last relapse two and two and a half years prior to the study, respectively. Two participants reached high scores for general intelligence (Raven Matrices), two participants medium scores and one a low score. Fatigue was observed in three of five participants, whereas no participants showed depressive symptoms at baseline. T2 lesion volume was between 0.085 ml and 9.075 ml. All participants complained about cognitive problems in terms of concentration and memory deficits in their daily life. The variability regarding clinical and cognitive aspects between the participants was relatively high and is therefore reflecting the usually observed heterogeneity between MS patients. Baseline characteristics of participants which might have impacted the treatment response are displayed in Table 1. The participants and their parents gave written informed consent to participate in the study, which was approved by the local Ethics Committee (Basel).

2.2. Procedure (study design)

The design of the study is displayed in Fig. 1. All participants underwent two baseline neuropsychological assessments within two weeks to allow for a stable performance baseline. At the second visit, baseline brain imaging (structural MRI, fMRI and resting-state fMRI) was performed (T1).

Not later than one week after the second baseline testing, all participants started with the computerized cognitive training (BrainStim). The training consisted of 16 sessions during four weeks, four times a week for 45 minutes. Participants trained at home and were supervised once a week by a trained psychologist.

Within one week after completing the training, participants were retested for cognitive performance and received a second MRI (T2). Nine months after training, the same cognitive and MRI measures were applied again (T3).

Due to the small number of cases, statistical analyses on group level were avoided. Thus, intrasubject variances will be presented in a descriptive manner. For this purpose, a triangulation approach was chosen as it is commonly used in qualitative research studies (Denzin, 1978). This procedure claims more than one method to verify that the variance in the outcome measure reflects a real training effect. In the present study, the effects of cognitive rehabilitation on WM were assessed with three different methodological approaches – cognitive testing to assess the behavioural level and fMRI, and resting-state network analysis to assess the underlying brain functionality. Further, this detailed description of our five cases allows inspection of possible factors that may modulate effects of training.

2.3. The cognitive training tool BrainStim

The computerized training tool BrainStim (Penner et al., 2006) is based on Baddeley's WM model (Baddeley, 2000). It consists of three different modules targeting both, verbal and visual-spatial aspects of WM (Vogt et al., 2008, 2009). The first module, called *City Map*, trains spatial orientation. Participants have to memorize either a visually or verbally presented route. Afterwards, the path has to be retraced on a virtual

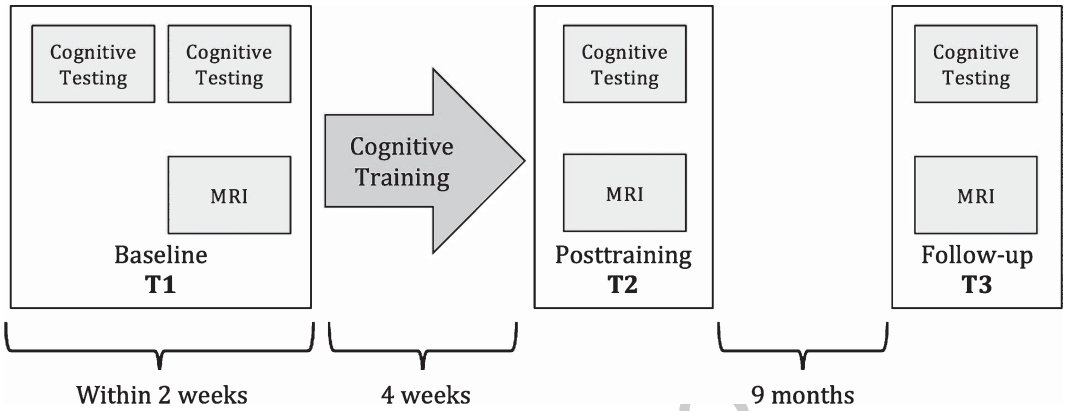

Fig. 1. Design of the pilot study: Baseline measures consist of two cognitive testings and an MRI within two weeks (T1). Directly after the second baseline testing participants receive a cognitive training over a period of 4 weeks. After the last training session posttraining measures are obtained (T2). Nine months later, participants are invited for a follow-up assessment (T3).

map. The visual instruction consists of arrows on the map. The verbal instruction contains inputs such as: "go north" or "turn right after the supermarket". The number of crossings increases with ascending level of difficulty. The second module, *Find Pairs* trains visual memory as well as the updating function of the central executive component. Participants have to remember the location of cards that have been turned over and back again and thereby find pairs of cards with the same subject on it. With each higher level of difficulty, the number of cards in one set increases. During the last module, *Memorize Numbers,* digits are presented on a screen for a limited period of time. After an arithmetic distraction task, the digits have to be recalled. The number of digits increases while the task becomes more difficult.

The order in which the modules were presented during one training session was changed during every session but was the same for all participants. The stimuli within each module were randomised to ensure that no task was presented twice. The software automatically adapts the level of difficulty of the various training modules to the user's personal performance. After several correctly solved tasks, the level of difficulty increases. If the participant fails to answer a specific amount of tasks, the level of difficulty descends again.

The randomised manner of presentation and the increased amount of information with ascending levels of difficulty ensures that the training is not only based on repetition and practice but on the development and consolidation of strategies.

2.4. Cognitive assessment

The primary outcome measures were restricted to WM functions and basic attention based on the previous work of Vogt et al. (Vogt et al. 2008). Visual and verbal WM were assessed with the *Corsi Blocks backwards* and the *Digit Span backwards* tests, respectively (Wechsler Memory Scale-Revised; Haerting et al., 2000) The *Symbol Digit Modalities* test (SDMT) was used to measure WM performance and processing speed (Smith, 1973). For measuring basic attention we used the *alertness* tasks (tonic and phasic) from the *Test Battery for Attention Performance* (TAP; Zimmermann & Fimm, 1992). The tests employed are commonly used in adults with MS. Therefore, normative data corrected for age was only available for visual and verbal WM measures.

Further, at the first baseline visit, general intelligence (Standard Progressive Matrices; Horn 2009) fatigue (Fatigue Scale for Motor and Cognitive Function: FSMC; Penner et al., 2009) and depressive symptoms (Depression Inventory for Children and Adolescents: DIKJ; Stuebsneuer-Pelster et al., 1989) were assessed.

2.5. fMRI paradigm

To study brain activation during WM processes we applied an N-back-task with different working memory loads (adapted from the TAP; Zimmermann & Fimm, 1992). Series of pseudo-randomised digits were presented continuously on a screen. Participants were

asked to press a button as fast as possible if they saw a target. A target was a digit that was identical with the immediately preceding digit (1-back), the second to the last digit (2-back) or the third to the last digit (3-back). A blocked-design was used for semi-randomised presentation of the N-back conditions and rest condition (fixation cross). One active block with a duration of 30 seconds consisted of 10 stimuli with two stimuli being targets. Each condition was presented four times during each session. Participants performed the paradigm two times with a break between the two sessions. In sum, each condition was presented during eight blocks. Reaction times for N-Back tasks were logged, but due to technical problems this files were not available for all participants and timepoints and therefore excluded from further analysis. Immediately prior to the MRI, children were familiarized with the N-Back task outside the scanner to ensure comprehension.

2.6. MRI data acquisition

Brain imaging data were collected using a 3.0-T MRI system (Magnetom VERIO, Siemens Healthcare, Erlangen, Germany) and a standard head coil. An anatomical image for registration purposes was acquired (sagittal T1-weighted 3D high resolution magnetization-prepared rapid gradient echo (MPRAGE) sequence: TR/TE/TI = 2000/3.37/1000 ms, 256×256 matrix, field of view (FoV) = 256 mm, providing an isotropic spatial resolution of 1 mm^3). Additionally, for lesion masking, a T2-weighted fluid attenuated inversion recovery (T2-FLAIR) sequence was obtained with the following parameters: TR/TE/TI = 8000/77/2370 ms, 40 slices with slice thickness of 3 mm and FoV = 220 mm.

For functional images, echo-planar imaging (EPI) sequences were applied (TR/TE = 2000/23 ms, 34 slices with a slice thickness of 3 mm, FoV = 256 mm, voxel size = $4 \times 4 \times 3$ mm^3). Slices were positioned parallel the AC-PC line. For both runs with the paradigm, 262 volumes with a total scan time of 8.5 min were recorded. After excluding the first five dummy scans, the remaining 257 scans were used for analysis. For resting-state fMRI, 200 volumes with a total scan time of 6.44 min were acquired. During the scans all participants were instructed not to move and for resting-state measures to close eyes and to not fall asleep.

2.7. Data management and analysis

Data were analysed using Statistical Parametric Mapping software package, SPM8 (http://www.fil.ion.ucl.ac.uk/spm). For detecting white matter lesions in our sample, the Lesion Segmentation Toolbox (LST; Schmidt et al., 2012) implemented in SPM8 was used. This toolbox automatically identifies and marks T2 hyperintense lesions on the basis of a three-dimensional T1-weighted and a FLAIR image. To choose the optimal initial threshold κ, segmentation was run with different thresholds and two independent evaluaters compared manually the resulting lesion maps with the original raw images. By this approach an initial threshold $\kappa = 0.2$ was chosen. Lesion masks were used for automatic lesion filling with intensities similar to the normal white matter voxels in T1-weighted images. These „lesion-free“ T1-images were used for later registration steps. Further, the lesion-filled T1-images were segmented into grey matter, white matter and CSF („new segment“). Grey matter and white matter of all three time points were fed to DARTEL to create a study-specific template (Ashburner, 2007).

fMRI data were realigned and unwarped and afterwards co-registered with the corresponding T1 images for each time point separately. FMRI images were then normalised to MNI space with the corresponding DARTEL flow fields and a 8 mm Gaussian smoothing.

Smoothed images of the two sessions with the WM paradigm were subjected to a first-level analysis to define the model design and contrasts of interest. To remove residual variance, movement parameters extracted from the realignment step were included as additional covariates. To identify WM related activation and deactivation patterns, the condition with the fixation cross of the fMRI paradigm was contrasted with the performance conditions (1-Back, 2-Back and 3-Back) in each subject (FWE corrected, $p = 0.05$).

After pre-processing, resting-state fMRI data of all time points were decomposed into spatially independent patterns and time-courses by a group-level spatial Independent Component Analysis (ICA) using the infomax algorithm implemented in the GIFT toolbox (http://mialab.mrn.org/software/gift/). To estimate the number of components we used the minimum description length (MDL) criterion (Calhoun et al., 2001). In our sample 43 components ($M = 42.93$, $SD = 5.34$) were estimated. Stability of the estimated components was assessed using the ICASSO toolbox, also implemented in GIFT. Therefore, the infomax algorithm

was run 10 times with bootstrapped datasets. Components representing artefacts were then excluded and only components corresponding to ventral- and dorsal DMN (template provided by GIFT), left and right fronto-parietal network and the anterior salience network were used for further analysis.

Temporal correlations between the selected components were assessed using the Functional Network Connectivity (FNC) toolbox (http://mialab.mrn.org/software/fnc/) as described by Jafri and colleagues (Jafri et al., 2008). Constrained maximal lagged correlation (±5 s) between networks was calculated and extracted per time point and subject separately. To evaluate meaningful changes of correlation coefficients we applied a Fisher's z-transformation and regarded z-value differences between baseline and after the training >|1.96| as significant.

3. Results

3.1. Behavioural

Although participants complained about some degree of cognitive impairment, none of the participants had WM deficits at baseline compared with normative data. All participants completed the training with at least 14 of the 16 training sessions. Performance during cognitive testing for all 5 participants are displayed in Table 2.

Four children showed higher performance on the SDMT (processing speed and WM) after the training relative to baseline. Case 2 reached the maximum score before the 90 seconds time limit after the training. Thus, his effective performance might be underestimated. Nine months after the training all participants showed stable or slightly decreased performance compared to their status directly after the training.

For tonic and phasic alertness (basic attention), two participants (Cases 2 and 3) showed faster reaction times after the training. One of them showed stable performance in the follow-up assessment, whereas the other child was slower in the tonic alertness task and showed stable performance in the phasic alertness task. Two participants (Cases 1 and 5) showed stable performance over time. One participant (Case 4) had slower reaction times after the training and decreased again in the follow-up testing.

Three participants increased their performance in verbal WM after the training (Cases 2, 3 and 4). Their

Table 2
Neuropsychological measures for all five cases at baseline (T1), directly after the training (T2) and 9 months after the training. To gain a better overview, performance increases from baseline to T2 are highlighted in grey

Cognitive domain	Neuropsychological test	Case 1			Case 2			Case 3			Case 4			Case 5		
		T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
WM and processing speed	SDMT	62	75	66	86	110	110	58	67	68	73	80	79	44	48	45
Tonic alertness	TAP Alertness A	245	247	248	235	222	226	238,5	220	254	251,5	276	237	275,5	277	269
Phasic alertness	TAP Alertness B	228,5	229	231	239,5	233	231	233,5	216	228	250	271	223	263,5	267	260
Visual WM	Corsi Blocks bw	10,5	10	12	10	12	12	9	12	11	9,5	11	12	6	6	8
Verbal WM	Digit Span bw	7	6	5	8.5	10	10	6.5	8	8	6	9	9	5	5	5

performance was stable 9 months after the training. The remaining two participants (Cases 1 and 5) were stable over time or even slightly decreased. For visual WM a similar effect was observed. The only difference was a small increase of performance in the follow-up assessment of the two participants showing no effect directly after the training.

3.2. Functional MRI

Several participants did not show significant activation during the 1-Back task. Therefore this contrast was excluded from further analysis. Activation patterns were similar between different levels of WM load (1-Back, 2-Back and 3-Back) except for an activation increase with increasing task difficulty. At baseline, all participants showed a diffuse activation pattern including mainly parietal and a few prefrontal regions, and deactivations mainly located in the occipital cortex. Directly after the training and during the MRI nine months after the training three participants showed similar patterns compared to baseline or activation even slightly decreased (Cases 1, 4 and 5). Two participants (Cases 2 and 3) activated more regions after the training in the parietal and frontal cortex and deactivated less. In the follow-up MRI, nine months after the training, these two participants showed activations below their baseline level. For illustration of the described changes, activation patterns of the 2-Back and 3-Back task are shown in Fig. 2.

3.3. Inter-network connectivity

The three networks of interest (mean across participants) are displayed in Fig. 3. Maximum lagged correlations for all possible combination of the selected networks are presented in Table 3. In two participants (Case 1 & 5), we observed several significant decreases as well as some increases in connectivity after training. Case 4 showed four increased connections after four weeks of training. Cases 2 and 3 revealed a comparable pattern: Both of them had higher connectivity between the right fronto-parietal network and the dorsal and the ventral part of the DMN after the training as well as between the two sub-networks of the DMN themselves. Especially this increased connection was not observed in Case 4. Further, they had increased correlation coefficients between the left fronto-parietal network and the dorsal or ventral part of the DMN respectively. For illustration purposes, significant changes comparing

Table 3
Correlation coefficients of inter-network connectivity for each patient at baseline (T1), after the training (T2) and nine months after the training (T3). Highlighted in dark grey are statistically significant increases in connectivity between T1 and T2, whereas decreases are marked in light grey

Connection		Case 1			Case 2			Case 3			Case 4			Case 5		
Between	and	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
right fronto-parietal network	left fronto-parietal network	−0.28	0.32	0.38	0.20	0.36	0.58	0.28	0.18	0.10	0.31	0.53	0.20	0.47	0.29	0.34
	dorsal DMN	−0.44	0.25	0.22	−0.14	0.40	0.41	−0.12	0.30	−0.19	0.23	0.27	0.42	0.29	0.35	−0.13
	ventral DMN	0.20	0.22	0.10	−0.17	0.42	0.37	−0.17	0.16	−0.45	0.43	0.38	0.37	0.56	0.36	0.28
	anterior SN	−0.15	−0.20	0.15	0.21	0.25	0.48	0.15	0.26	−0.13	−0.23	0.29	0.16	0.45	0.27	0.28
left fronto-parietal network	dorsal DMN	0.53	0.20	0.35	−0.18	0.53	0.56	0.34	0.38	0.48	0.38	0.32	0.29	0.29	0.31	−0.21
	ventral DMN	0.21	0.07	0.20	0.38	0.50	0.50	−0.24	0.38	0.41	0.43	0.65	-0.17	0.37	0.37	0.54
	anterior SN	0.51	0.26	0.53	0.43	0.57	0.62	0.35	0.40	0.60	0.42	0.59	0.28	0.45	0.46	0.42
dorsal DMN	ventral DMN	0.18	0.27	0.47	0.24	0.50	0.56	0.25	0.46	0.52	0.46	0.52	0.34	0.35	−0.28	−0.20
	anterior SN	0.44	0.23	0.33	0.14	0.55	0.58	0.33	0.44	0.59	0.44	0.42	0.31	0.35	0.37	0.39
ventral DMN	anterior SN	0.30	0.17	0.31	0.28	0.38	0.53	0.33	0.41	0.60	0.22	0.66	0.27	0.20	0.40	0.34

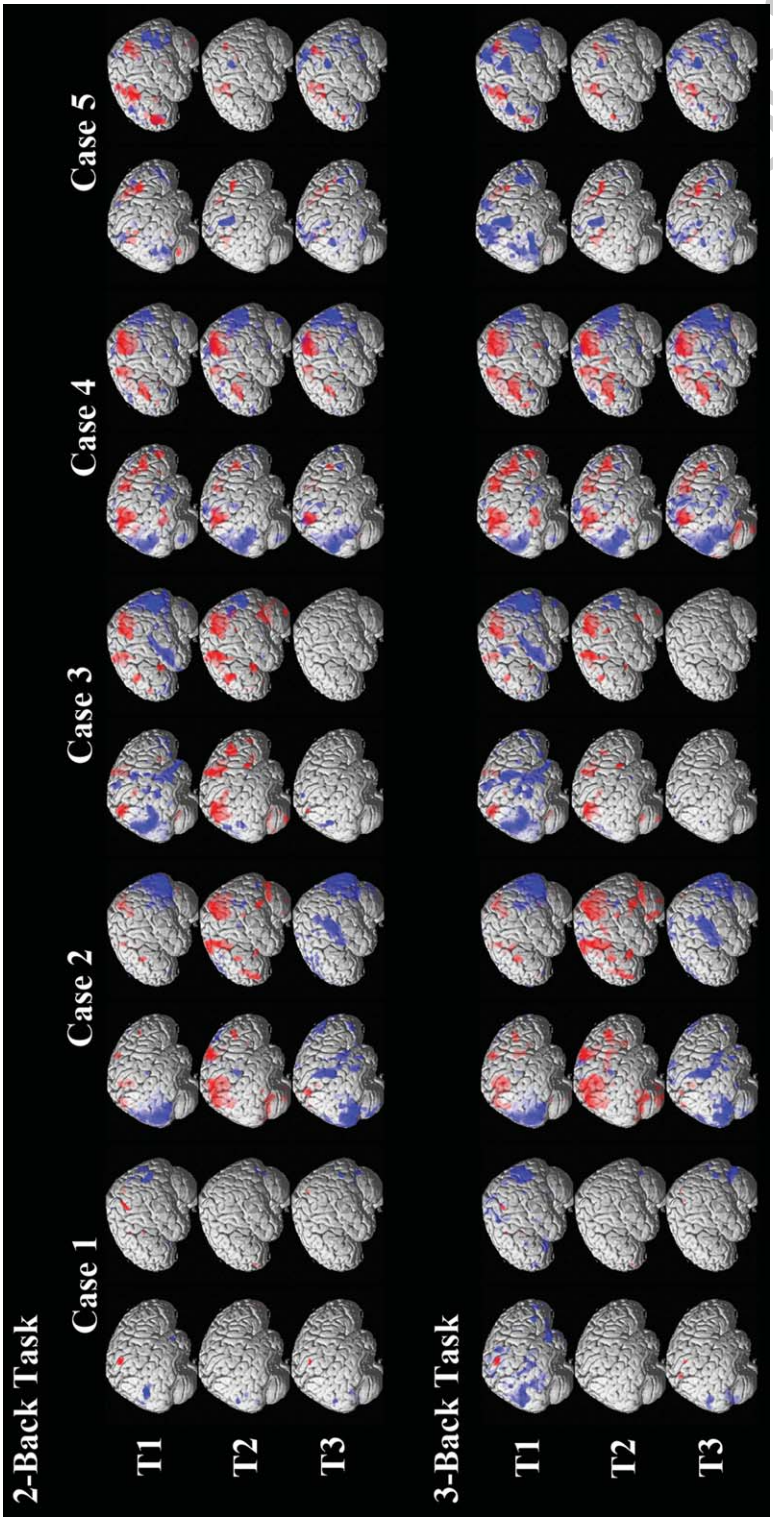

Fig. 2. Activation patterns during 2-Back and 3-Back conditions of the five participants at baseline (T1) directly after the training (T2) and nine months after the training (T3). Additional activation is displayed in red, whereas blue patterns represent deactivations.

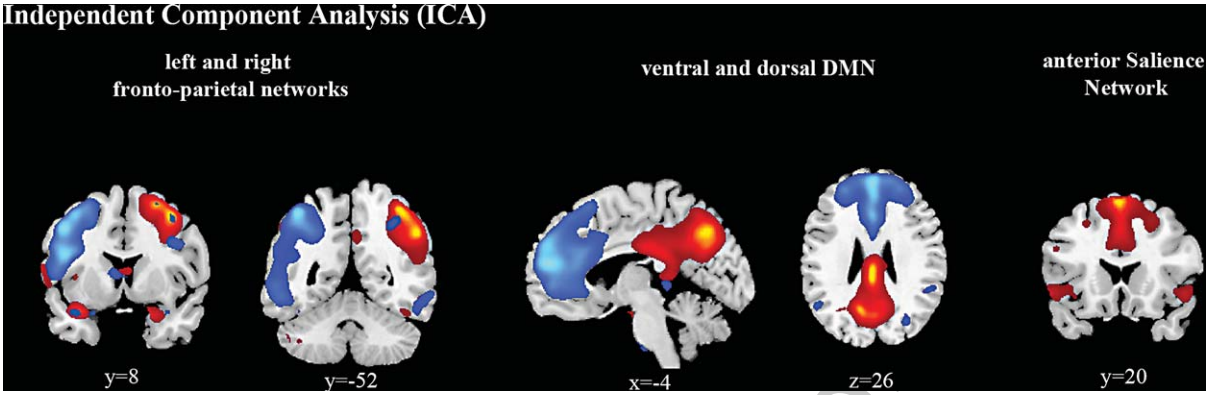

Fig. 3. Mean image of all patients and timepoints. The fronto-parietal networks (lateralised, left: blue, right: red) includes mainly the parietal lobule and the prefrontal cortex. The ventral DMN (red) includes the cingulate gyrus, the precuneus and the parietal lobe and had extensions to the temporal lobe. Core regions of the dorsal DMN (blue) were the superior frontal gyrus, medial frontal gyrus, middle frontal gyrus and the anterior cingulate cortex. The anterior salience network includes manly the superior and middel frontal gyrus and the insula.

Table 4
Overview of changes in neuropsychological and MRI measures directly after the WM training compared to baseline

	Behavioural effects					fMRI results	
	SDMT	Verbal WM	Visual WM	Tonic Alertness	Phasic Alertness	WM fMRI	Inter-network connectivity
m16	↑	0	0	0	0	0	unsystematic
m14	↑	↑	↑	↑	↑	↑	higher between sub-components of DMN
f17	↑	↑	↑	↑	↑	↑	higher between sub-components of DMN
f16	↑	↑	↑	↓	↓	0	unsystematic
f12	0	0	0	0	0	0	unsystematic

Note. (↑) increase; (↓) decrease; (0) stable performance.

baseline and post-training measures for all participants are visualised in Fig. 4.

In the follow-up MRI, some network-connections strengthened, whereas other correlations decreased. In the two responders connectivity between the ventral and dorsal DMN remained stable.

3.4. *Response to treatment - triangulation findings*

According to the triangulation technique, a statement about a positive training effect has to be based on more than one methodological approach. In this study, effects of cognitive training were examined by cognitive testing, fMRI with a WM task and resting-state fMRI.

To summarise the descriptive findings above, effects on cognitive and brain function observed after the training for each participant are displayed in Table 4.

Directly after the training two out of the five participants showed a higher performance in all cognitive tests (Cases 2 & 3) and especially differed from other participants by better alertness performance after training. This behavioural change was accompanied by increased brain activation and regarding internetwork connectivity, by increased connectivity between the sub-components of the DMN. On the other hand, participants with few or no positive effects on a behavioural level also showed no changes in brain activation and only unsystematic variations in internetwork connectivity.

4. Discussion

This is the first pilot study to examine the potential effects of computerized WM training on cognitive functioning, brain activation and network connectivity related to WM in juvenile MS. Directly after the training, behavioural and imaging effects were observed in two of five children. Cases 2 and 3 were, as expected, able to increase their performance in the WM and alertness tasks. In addition, they showed *increased* brain activation, a more *widespread* activation pattern and *less deactivated* regions during the WM fMRI task.

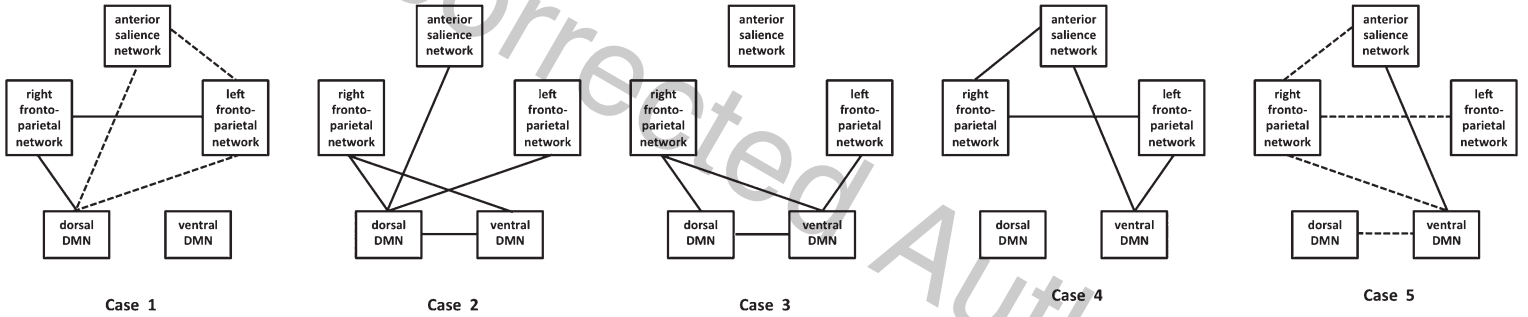

Fig. 4. Changes in inter-network connectivity after the training compared to baseline for all five cases. Significant correlation increases are marked with bold lines, whereas, significantly lower correlations are represented with dotted lines.

Furthermore, connectivity between the ventral and the dorsal DMN increased. Based on the work by Ros et al. (2013) it can be assumed that this increase in connectivity is directly related to performance increase in alertness.

Cases 1 and 5 showed no effects of the training on a behavioural level and no increase in activation during the WM fMRI task. Further, these two cases had no systematic increase of connectivity between the inspected resting-state networks, but instead showed several decreased connections. We therefore assume that these participants are non-responders. Case 4 increased her WM but not her alertness performance. In WM related fMRI no increase in brain activation was detectable. She had higher connectivity between some networks but no systematic variation could be observed.

By dividing our participants into "responding" and "non-responding" children, the question arises, which factors might be responsible for this finding. One baseline characteristic that was systematically different between the two responding children and the three others was the time to last relapse. Disease activity might therefore be a relevant factor affecting response to cognitive rehabilitation. Brain functionality seems to be still seriously affected three months after relapse (or after the occurrence of new Gd enhancing lesions). This is supported by literature in adult MS. Morrow, Jurgensen, Forrestal, Munchauer, and Benedict (2011) described reduced SDMT scores even three months after relapse. Further, Pardini and colleagues (2014) reported that patients with an isolated cognitive relapse had significantly lower SDMT scores six months and one year after the assumed relapse. Another possible factor for treatment success may be cognitive reserve (Sumowski et al., 2009). Since responders achieved higher scores in the test for general intelligence we suppose that the effectiveness of cognitive training is directly related to higher cognitive reserve. The concept of cognitive reserve assumes that patients with higher cognitive reserve are thought to better withstand brain damage because of the usage of other cognitive processes or compensatory mechanisms (Stern, 2009). Applying this to cognitive training, the higher premorbid intelligence level might help participants to profit more from cognitive training by more efficient learning of implicit strategies.

Our study provides first data on the potential effects of WM training on inter-network connectivity in children with MS. Rocca and colleagues (2014) described significant lower inter-network connectivity in children with MS compared to healthy controls between the DMN and the left WM network. If children with MS show lower connectivity between these networks, it is possible that the training applied in this study induced a "normalisation" of brain connectivity. However, given the small sample and other methodological limitations of this study, this can only be referred to as speculative at this time.

In this study, we also explored potential long-term effects of cognitive WM training after nine months. In "responders" behavioural effects were maintained over time whereas increased brain activation did not. One possible explanation for this observation might be the more efficient usage of the underlying neural network (Garavan, Kelley, Rosen, Rao, & Stein, 2000) over time, reflecting a shift from controlled to automatic task performance. Although this suggestion remains speculative there is evidence coming from a quantitative meta-analysis on functional brain changes due to training (Patel, Spreng, & Turner, 2013). "Non-responders" showed no change in most behavioural measures over time and fMRI WM patterns were comparable between all timepoints.

We are aware that our study has several limitations. First patients were not selected by a cognitive criterion but were included consecutively as they presented themselves in the neuropediatric department. Thus, it is possible that potential cognitive training effects were minimized by including those without objective cognitive impairment although all patients complained about cognitive changes. Second, our explorative study consisted of a very small convenience sample and did not include a control sample. As such, no significant conclusions can truly be made. However, given the total absence of cognitive rehabilitation trials that employ neuroimaging in juvenile MS and the need for even suggestive data on treatment effectiveness, the results of this small pilot study serves as a jumping-off point from which larger, hypothesis-driven studies can be conducted to examine effects and possible mediating factors of cognitive interventions.

Acknowledgments

This study was supported by a scientific grant of the Swiss MS Society. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation,

review, or approval of the manuscript; and decision to submit the manuscript for publication.

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