UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF

Kopf-Zentrum, Klinik und Poliklinik für Neurologie

Prof. Dr. med. C. Gerloff

Impairment and restrictions in possibly benign multiple sclerosis

Dissertation

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Laura Melanie Schäfer
aus Würzburg

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Content

1. Hypothesis

The main aim of this study was to describe a broad range of health dimensions of possibly benign multiple sclerosis (BMS) patients from the Hamburg university medical center (UMC) cohort. Physical and mental abilities as well as quality of life, leisure and daily life activities were cross-sectionally studied to estimate the true impact MS has on BMS patients' lives. Special attention was payed to neuropsychological impairment as well as to coping and daily functioning. We hypothised that despite of some limitations patients classified as BMS show a high level of adaptation to the disease.

In the light of the concept of BMS we have assessed the following questions:

- What is the prevalence of BMS regarding the Expanded Disability Status Scale disability (EDSS) and including cognitive impairment within the cohort of UCM Hamburg?
- What are the neuropsychological symptoms presented in the BMS cohort?
- How are coping, sense of coherence and support by the patient's social network represented in the cohort of BMS patients?
- What is the level of activity of BMS patients in their daily life and leisure time?

2. Introduction

2.1 Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Due to a broad variability in quality, severity and development the disease's course is unpredictable (Hauser et al. 2013, Degenhardt et al. 2009, Hawkins 2012). Not only physical disabilities as ambulation are relevant but also (neuro)psychiatric domains (Amato et al. 2006). Because of the early disease onset, the most productive period in people's life is affected.

There are mainly two MS phenotypes described. The relapsing-remitting MS (RRMS) and the progressive disease course. Whereas RRMS patients develop new symptoms in form of relapses with or without residues other patients present ongoing disability right at the beginning (primary progressive MS (PPMS)) or later on (secondary progressive MS (SPMS)) (Lublin 2014).

2.2 Benign multiple sclerosis (BMS)

2.2.1 Defining BMS

Since the end of the 19th century patients with a milder disease course have been described in literature. "It is not rare to encounter complete remission which is hoped to be definitive", Charcot pointed out in 1872 (Charcot 1872). Later, McAlpine described patients who "were without restriction for normal employment and domestic life but were not necessarily symptom-free" and renewed the discussion about existence and definition of benign multiple sclerosis (BMS) (McAlpine 1964). With the development of the Disability Status Scale (DSS) and later the Expanded DSS (EDSS) (Kurtzke 1983), BMS was increasingly characterized by low disability, assessed by EDSS related to disease duration (Ramsaransing and De Keyser 2006, Ton et al. 2017). In 1996, Lublin and Reingold presented the results of an international survey from the National Multiple Sclerosis Society (USA) coming to the agreement to define BMS as a "disease in which the patient remains fully functional in all neurologic systems 15 years after disease onset" (Lublin and Reingold, 1996). The term BMS was intended "to provide an indication of disease severity over time" and could be applied "to any MS phenotype" (Lublin et al. 2014).

2.2.2 BMS prevalence

There has been an ongoing discussion about cut-off scores defining BMS, leading to a broad variety in BMS prevalence (5% - 73%) (Ton et al. 2017, Skoog et al. 2012).

Most commonly, BMS was defined by EDSS ≤3 for a disease duration ≥10 years (Hawkins 2012). However, EDSS cut-off scores range from 0 to 4.0 after disease duration of 5 to 20 years in literature (Correale and Ysrraelit et al. 2012, Ramsaransing and De Keyser 2007).

Most of the studies, used Poser's diagnosis criteria to define MS for study inclusion (Poser et al. 1983, Ton et al. 2017). These MS criteria are quite restrictive, thus mild disease courses could have been neglected (Correale and Ysrraelit, et al. 2012).

Furthermore, referring to the first symptoms, disease duration is always a retrospective variable which contributes to inaccurate prevalence data (Hawkins 2012).

What is more, BMS studies vary considerably in their design. Only a couple of studies were really prospective and population based (Hawkins 2012, Skoog et al. 2012). Clinically based studies may tend to underestimate BMS prevalence due to a selection bias towards more severe cases in specialized institutions (Reynders et al. 2017, Sartori et al. 2017, Ramsaransing and De Keyser 2007). Hospital attendance could also vary due to national differences in health care systems in the study countries. This might also influence the implementation of disease modifying treatments (DMT) affecting the disease course.

In addition, the length of follow-up differed substantially (from 4 to 60 years) between BMS cohorts (Zivadinov et al. 2016, Skoog et al. 2012) and few studies took mortality into account (Ton et al. 2017, Glad et al. 2011).

The strongest approach defining BMS was proposed by Skoog et al. Their prospective and population based research found no MS associated disability at all at life end in 5% of the patients (Skoog et al. 2012). For more details see table1.

2.2.3 Restrictions of BMS Definition

The high prevalence of hidden MS symptoms not adequately assessed by EDSS has been used as a major argument that EDSS-based BMS may not really be benign. Amato and Portaccio criticized the definition of BMS being too focused on motor abilities neglecting neuropsychiatric symptoms, quality of life (QOL) and employment status (Amato & Portaccio 2012, Glad et al. 2010). If these parameters would be considered as well, only a small group of patients might "truly" be called benign (Amato et al. 2008, Correale and Peirano et al. 2012).

Amato found that 49% of a Florence BMS cohort, defined by EDSS ≤3.0 for ≥15 years (n=163) had relevant fatigue, 54% had depressive symptoms and 45% showed cognitive

impairment (CI). Main cognitive deficits were attention and information processing speed slowing (Amato et al. 2006).

Correale and Peirano et al. found 12.5% BMS patients in a cohort of 342 MS patients with EDSS ≤3 for more than10 years after disease onset. 81% of these BMS patients (n=43) had a "significant worsening of cognitive function, fatigue, pain or depression" influencing social activities as well as employment after a further 10-year follow-up (Correale and Peirano et al. 2012).

Sayao et al. found 59% BMS patients (EDSS ≤3 at 20 years after disease onset) who did not progress and stayed benign after 25-30 years of disease. These "long standing benign patients" had less fatigue, better physical quality of life (QOL) and employment outcomes and more infrequent cognitive impairment than patients not remaining benign after 25 years according to EDSS (Sayao et al. 2011). However, there was no difference concerning depression and mental QOL including "cognitive functioning, sexual satisfaction, energy and emotional wellbeing" (Bueno et al. 2015). Self-reported QOL correlated negatively with fatigue and depression (Bueno et al., 2015). In comparison, Hviid et al. found better patient reported outcome measurements (PROMs) concerning QOL, social support, depression and fatigue in BMS patients than in non BMS patients (Hviid et al. 2011).

As a result of this discussion, Tallantyre et al. estimated the prevalence of "truly BMS" patients in South Wales valley (UK) 2.9 % by taking EDSS <3.0 and the absence of fatigue, cognitive impairment, depression, employment restrictions and DMT into account. However, 69% of this cohort considered their BMS as benign.

2.2.4 Prediction parameters of BMS

Reliable prognostic factors to detect BMS in advance are still missing (Ton et al. 2017, Correale and Ysrraelit et al. 2012, Ramsaransing and De Keyser 2007). Some clinical prediction parameters such as number of attacks in the first 2 or 5 years, long time interval between the first and second relapse, relapsing-remitting disease course, young age at disease onset, female sex and relapses with afferent symptoms are controversly discussed (Correale and Ysrraelit et al. 2012, Reynders et al. 2017). Some authors discussed EDSS ≤2 at five or 10 years after onset as predictive for BMS (Sartori et al. 2017, Reynders et al. 2017).

Ramsaransing and De Keyser found a relapsing–remitting (RRMS) disease course at disease onset, small number of attacks in the first 5 years and low EDSS after 5 years as predictive for BMS (EDSS<3) after 10 years disease duration. Only the latter predicted a benign course at 20 years after disease onset (Ramsaransing and De Keyser, 2007).

2.2.5 The predictive value of BMS definition

However, other studies questioned the predictive value of a BMS definition based on a stable or low EDSS over 10 to 20 years as patients may no longer stay benign after further follow-up (Sayao et al. 2011, Costelloe et al. 2008, Skoog et al. 2012). Based on the Olmsted County cohort Pittock et al. concluded that patients with long duration of MS and low disability were more likely to remain stable (Pittock et al. 2004).

Portaccio et al. found cognitive preserved BMS patients to be more likely to remain benign after 5 years follow-up (90%) (Portaccio et al. 2009).

Finally, the consensus group advised 2014 to use the term BMS cautiously as even after years of seemingly benign course the disease may decompensate (Lublin 2014). Other groups suggested to add cognitive preservation as condition to the BMS definition (Amato and Portaccio 2012, Rovaris et al. 2008).

2.2.6 Magnet resonance imaging (MRI) in BMS research

Lacking objective genetic, laboratory and immunologic prognostic markers there is an ongoing research focusing on magnet resonance imaging (MRI)-based techniques to describe BMS more adequately (Ton et al. 2017, Correale and Ysrraelit et al. 2012). On the one hand, conventional MRI-scans showed similar lesion loads in BMS compared to other MS disease courses. On the other hand, "quantitative techniques have demonstrated a lower degree of tissue damage and/or higher reparatory and compensatory mechanisms in BMS as compared with other disease sub-types" (Correale and Ysrraelit et al. 2012). Furthermore, Rovaris et al. found in cognitive impaired BMS patients similar structural damage on MRI as in secondary progressive MS patients. The authors concluded that also in BMS "cognitive dysfunction is associated with severe structural damage which resembles that of patients with much more disabling course" (Rovaris et al. 2008).

2.2.7 The relevance of BMS classification

Due to the increasing trend for very early immunomodulatory treatment (Elovaara 2011) on one hand, while new diagnostic criteria (Thompson et al. 2017) have enabled a much earlier diagnosis on the other, it is highly important to clarify the true disease impact in possibly benign patients and provide accurate BMS prevalence rates. The possibility of having BMS needs to be included in the decision-making process for MS therapies.

Table. 1 BMS cohorts

authors, research group	cohort size (n), diagnostic criteria	cohort design	BMS definition	frequency =n(%)	follow-up[#] (years, n) SB= n, (%)	further included aspects
Skoog et al. 2012, Tendeholm et al. 2015, Gothenburg/ Sweden	n=255, Poser	population-based prospective	RRMS and EDSS <4 at life end	n= 202 =13/255(5)	26-50y, n=n.a. 47/255(8) 37-59y, n=43 SB=13/255(5)	prognosis DMT mortality
Glad et al. 2009a, 2010b, 2010c, Hordaland/ Norway	n=230, Poser/ re-classified in 2013 McDonald 2005	population-based retrospective-prospective	≥10y and EDSS <3.5 **	n=186 at -10-20y DD 70/186 (38) -17-29y DD 60/230(26)	8y; n=186 SB=38/70 (54)	cognition depression fatigue pain employ-ment prognosis
Sayao et al. 2007a, 2011b Bueno et al. 2015 BC/Canada	n=1094, Poser	population-based retrospective-prospective	at 10±1y EDSS <3.5 **	200/1094 (18)	10y, n=169 SB=88/169(52) 25-30y, n=61 SB=36/61(59)	prognosis mortality
Zivadinov et al. 2016, New York State/ US	n=6258, Poser	clinic-based cross-sectional retrospective and prospective	≥15y DD and EDSS <3.5 **	1237/6258 (20)	4y, n=788/1237 SB=511/788 (65)	prognosis DMT
Laray et al. 2012 Rennes/ France	n=2054, Poser RRMS	clinic-based retrospective-prospective	≥10y DD and EDSS <3.5 **	n=874 646/874(74)	≥20y DD 162/301(54) ≥30y DD 44/74(60)	prognosis
Pittock et al. 2004 Olmested County/ US	n=162, n.a.	Population-based retrospective-prospective	>10 y DD EDSS <4.5 EDSS <2.5	49/162(30) 28/162(17)	10y, n=47 SB=35/49(69) 20y, n=21 SB 9/21(43)	prognosis mortality
Ramsaransing et al. 2007, Groningen/ Netherlands	n=496, Poser	clinic-based retrospective-prospective	>10y DD and EDSS <3.5	151/496(30)	10y, n=49 SB=35/49(69) 20y, n=8 SB=7/8(88)	prognosis
Mastorodemos et al. 2015, Crete/Greece	n=587, McDonald 2005	population-based retrospective-prospective	≥10years and EDSS <3.5	n=268 102/268(38)	n.a.	prognosis
Sartori et al. 2017, Ottawa/ Canada	n=175, Poser	clinical-based retrospective-prospective	at 10years and EDSS <3.5 EDSS <2.5 EDSS <1.5	n.a.	20y, n=175 SB= 116/175(66) 92/128(72) 50/59(82)	prognosis
Hawkings et al. 1999 and McDonnell et al .1996 Northern Ireland	n=259, Poser	Population-based retrospective-prospective	≥10years and EDSS <3.5	n=181 1986: 33/181(18) 1995: 36/181(20)	10y, n=28/33 SB=20/28(71)	prognosis
Amato et al. 2006a and 2008b, Florence/Italy	n=163, Poser	clinic-based, cross-sectional	≥15y DD and EDSS < 3.5	n.a.	n.a.	cognition depression fatigue handicap

						MRI (n=47)
Portaccio et al. 2009, Florence/Italy	n=63, Poser	clinic-based, cross-sectional and prospective	≥15y DD and EDSS <3,5	n.a.	5y, n=61/63 *SB=45/63 (71)	cognition MRI
Hiviid et al 2011 Boston/US	n=115, McDonald 2005	clinic-based cross-sectional	≥15y DD and EDSS <3,5 EDSS<1.5	n.a.	n.a.	cognition QOL fatigue depression social support
Tallantyre et al. 2018, South Wales/ UK	n=3062, n.a.	population-based cross-sectional	>15y DD and EDSS <4 <3 and [§] self-report	n=1049 =200/1049 (19) =9/60[&] (15%) 33/69(69)		Cognition Fatigue Depression QOL Employ-ment
Gajofatto et a. 2015, Verona/ Italy	n=300, McDonald 2005	clinical-based retrospective-prospective	RRMS and >10y DD and EDSS <2.5	=228/300 =36/228(16)	5y, n=36 SB=36-32/36 (92-97)	cognition handicap MRI
Correale and Peirano et al. 2012, Buenos Aires/ Argentina	n=342, Poser and RRMS	clinical-based retrospective-prospective	RRMS, >10y DD and EDSS<3	n=342 =43/342(13)	n.a.	cognition fatigue depression handicap pain MRI

(Reynders *et al.*, 2017)(Ton *et al.*, 2017)

n.a.= not available, y=years, n(%)= frequency(percent), DD= Disease duration, FU= follow-up, SB= still benign, DMT= disease modifying treatment, MRI magnet resonance imaging, QOL= quality of life,
[#] if not other indicated
[§] no DMT, significant fatigue, cognitive impairment, depression or disrupted employment
[&] sample
* SB defined by EDSS <4 or SPMS
** further cut-off scores used

3. Material and methods

3.1 Study design

This study was designed as a cross-sectional study. MS patients fulfilling McDonald criteria (2005) who had presented themselves at least once at the MS outpatient clinic at the UMC in between January 1996 and June 2012 were considered. Patients fulfilling BMS criteria based on an illness duration ≥15 years and an EDSS score ≤3.5 at their last examination were included and recruited by letter. They gave their informed acceptance to the study and were invited for an assessment at the center. Questionnaires were sent to the patients in advance. In case patients were not able to take part in the assessment a telephone interview was performed. Patients who did not respond were contacted with a second letter including a feedback format for gathering information about their non-responsiveness and general clinical status (stable, improved, worsened). The standardized assessment took place between July 2012 and January 2013. Neuropsychological and physical impairment (neurological examination, assessment of walking and hand function, assessment of cognition, depression and fatigue), the impact on people's lives (quality of life, leisure activities, occupation) as well as coping and self-coherence were addressed.

3.2 Clinical tests

During the physical assessment a neurological examination as well as upper motor functions and walking tests were assessed.

3.2.1 Disability

Neurological impairment was assessed using Kurtzke's Expended Disability Status Scale (EDSS) (Kurtzke 1983). The EDSS is a common scale for measuring disease progression in MS studies (Cohen et al. 2012). Exact scoring rules standardize EDSS evaluation. Evaluation is based on neurological examination including the rating of eight systems: pyramidal tract, cerebellum, brain stem, sensibility, bladder and bowel, vision, cerebral and mental function. Impairment is quantified by giving 0 (normal) to 5 or 6 points (maximum impairment) for each system. The total score is a nonlinear scale and ranges between 0 (no impairment) to 10 (death due to MS). Especially scores higher than EDSS 4 are determined by ambulation and walking aids.

If patients could not take part in the assessment, EDSS was evaluated by phone. The telephone EDSS was found to be a comparable method to the examiner based score (Lechner-Scott et al. 2003). In patients only answering the feedback letter and stating stability since their last examination, we used their last EDSS. Some of the patients, who sent back their feedback letter, were examined in the outpatient clinic during the trial period (July 2012 till January 2013) independently from the study. Their EDSS was taken as well.

3.2.2 Mobility

Furthermore lower limb mobility was assessed in more detail by 3 tests including performance in walking speed, balance and walking endurance.

The timed 25-Foot Walk (T25FW) assesses minimum walking time in seconds required for a 7,62 meter /25 foot distance without running (Kieseier and Pozzilli 2012).

The TTW reflects not only motor abilities but also cerebellar function. Start and endpoint of three meters were marked. The patient was asked to set one foot, heel to tiptoe, to the other as fast as possible. The time taken for the three meters was stopped and noted (J P Stellmann et al. 2014).

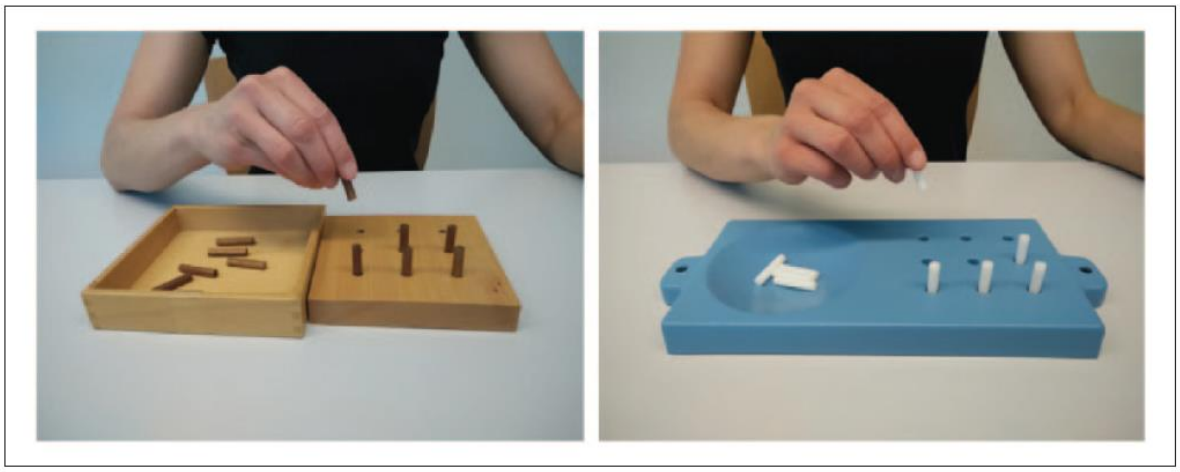
The six minute walking test (6MWT) measures the maximal walking distance a patient could reach in six minutes walking back and forth in a corridor, turning at each end (Goldman et al. 2008).

The walking tests were conducted at the end of the examination in the following order: TTW, T25FW, 6MWT. To avoid early fatigue each test was only taken once.

3.2.3 Hand function

Upper limb function was examined using the Nine Hole Peg Test (9HPT) (Goodkin et al. 1988). The test measures the time in seconds a patient takes for a upper limb coordination test, for each hand separately. The test consists of a plank with 9 holes and 9 sticks. The patient was asked to put the sticks into the holes one by one and as fast as possible. Then, without pausing, the patient should retrieve the sticks one by one. The time is stopped twice for each hand and the mean of the two times was taken (see picture 1). The test was conducted within the neuropsychological test battery. The 9HPT is widely used to assess upper limb function properly (Lamers et al. 2014). It is associated with activity of daily living, quality of life and a sensitive parameter for assessing longitudinal change in disability (van Munster et al. 2018, Feys et al. 2017).

Picture 1: Nine Hole Peg Test (9HPT)



The task is to put the sticks as fast as possible and one by one in the 9 holes and out.
(Peter Feys et al, Ise Lamers, Gordon Francis, Ralph Benedict, Glenn Phillips, Nicholas LaRocca, Lynn D Hudson, Richard Rudick and Multiple Sclerosis Outcome Assessments Consortium, 2017. Figure 1, in The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Multiple sclerosis Journal, 23(5): 711-720, page 3)

3.3 Neuropsychological assessment

A standardized battery addressing relevant cognitive functions in MS as verbal memory, working memory and information processing speed as well as attention, executive functions and verbal fluency was used taking about one hour.

3.3.1 Memory

The "Verbal Lerning and Memory Test" (VLMT) (Helmstaedter et al. 1999) describes different kinds of verbal memory categories: memory span, learning, short term memory and recognition. 15 different words were presented and had to be repeated by the patient regardless of the order they were called, describing the memory span (VLMTS1). The same words were presented four more times. The sum of words correctly repeated after all five runs reflect learning ability (VLMTS1-5). Short term memory was examined by asking the patients to recount the words freely after a disturbing round with new words (VLMT5-7). After 30 minutes different words were presented including some new and some words from the learned list. The task was to recognize the known words (VLMTW-F). All in all the VLMT presents five test scores. The scores were built by adding and subtracting the correct and wrong represented words. High scores indicate good verbal memory abilities.

For numeric verbal memory a repeating numbers test (ZN= "Zahlen Nachsprechen") was used (Oswald and Fleischmann 1997). The examiner presented an increasing amount of number sequences (starting with one up to five concatenated numbers) which had to be correctly repeated by the patient in the right order. One point was given for each correctly repeated

sequence. The test was split in two subtests. In the subtest ZN forward (ZNfw) numbers had to be repeated reflecting memory span for numbers. The subtest ZN backward (ZNbw) evaluated working memory by asking patients to repeat the numbers in the correct order but backwards. The more points the better the memory span or respectively the working memory.

The spoken "Symbol Digit Modality Test" (SDMT) evaluates visual processing speed for which attention as well as working memory is important (Schäffler et al. 2013). The task was to substitute geometric figures by a number, according to a key which defined pairs of numbers and figures. The key was explained and tested for the first ten signs at the beginning of the test. The number of correctly substituted figures in 90 sec produces a score. The higher the score, the better the test results.

3.3.2 Attention and speed of reaction

Attention was tested using the computerized "Test Battery of Attention" (TAP) (Zimmermann et al. 2012). Three subtests presenting different signals on a black background on the computer for a maximum of 2000 milliseconds (msec). The patient was asked to press an extern key as fast as possible when the signal appeared on the screen. The reaction time in msec was measured.

The subtest "Alertness" is a simple reaction time task lasting about four minutes and is subdivided in four runs. In each run 20 signals were presented. Every time an X appeared on the middle of the monitor, the patient was asked to press a key ("tonic alertness"). The subtest "phasic alertness" included a warning signal in advance. One tonic run was followed by two phasic runs and the test ended with a last tonic run.

Selective attention was evaluated by the subtest "GoNoGo". This test consists of one run, lasting two minutes and presenting 40 signs for 200 msec. The patient was asked to press a key only if an "x" was presented but to repress his answer if "+ "appeared on the monitor.

The last test reflects divided attention using specific visual and acoustic signals. The test took four minutes. Different configurations of 6 to 8 crosses are presented on a 4x4 matrix of 16 points changing every two seconds. The configuration was only a signal if four crosses appeared next to each other forming a little square. In total 100 configurations were presented including 17 signal configurations. At the same time 200 high and low tones were presented alternately. The second signal was the same tone played twice in succession. The patient was asked to press the key if one of the signals appeared or resounded. Thus the patient had to lay his attention to both signals and react appropriately and quickly to both of them producing two values.

The scores were built by the mean reaction time per test. Quick reaction represents a good state of attention. In conclusion the TAP offers five values describing different kinds of attention skills.

3.3.3 Executive functions and verbal fluency

The “Regensburger Wortflüssigkeitstest” (RWT) measures semantic and phonematic verbal fluency (Aschenbrenner et al. 2000). The task was to name as many different words as possible in one minute. Concerning phonematic verbal fluency animals had to be listed. For the semantic verbal fluency test the patient was asked to list words starting with letter “G” and “R” alternately.

Further executive functions were tested with the “Leistungsprüfsystem” (LPS, achievement testing) (Horn 1983). Subtest three (LPS3) evaluates logical reasoning by demonstrating sequences of signs. The signs were shown in a logical order. One sign per row did not fit in this sequence and had to be detected by the patient. The subtest seven (LPS7) reflects visual perception. Letters were shifted around their axis but one sign per row was mirror-inverted. This inverted sign had to be marked. For both tests a time limit was given. After this time all proper detected signs were added to a score.

All in all the whole neuropsychological examination consists of 16 test scores. Five scores representing memory and two scores reflecting working memory. Attention is evaluated by five scores and executive functions including verbal fluency, logical thinking and spatial perception by four tests.
Results were adjusted for gender, age and education and transferred to z-scores. We displayed our data in different groups, representing different cut-off scores (<-2SD, <-1SD, <-1.65SD) in a specific proportion of tests (10%, 20%, 30%, 50% of the tests). However, our main definition classified patients as cognitive impaired if they scored <-1.65 SD below the average of a normal population above 20% of the tests (Rao et al. 1991). Furthermore we built a composite score adding all mean z-scores for getting a global estimate of cognitive function.

3.4 Questionnaires

Patient-rated outcome measurements (PROMs) were assessed by questionnaires containing neuropsychological impairment as fatigue, cognition and depression as well as activities of daily living, hobbies and physical activity. In addition we had a look at the individual`s resources such as coping behavior and resilience.

In the end we measured health related QOL and asked for demographic information including education and work. All questionnaires are shown in the addendum (11.2.).

2.4.1 Health related quality of life and demography

To evaluate quality of life (QOL) the new version of "Hamburger Quality of Life in MS 10.0" Questionnaire (HAQUAMS) was used (Schäffler et al. 2013, Gold et al. 2003). This 44 item questionnaire was developed for MS patients and contains several disease specific categories composing 6 sub-scales: fatigue (four items), cognition (four items), lower extremity (four items), upper extremity (five items), communication (six items) and mood (five items). Further items contain remaining symptoms, disease progression and overall quality of life. Most of the questions are rated by the patient on a five point Likert scale. For calculation some items have to be inverted and the total score is created by adding the means of the six sub-scales. Sub-scores and total score ranges from 1 to 5. Low scores indicate a high QOL (Gold et al. 2010).

Furthermore we asked for demographic data including MS related information as well as social and occupational information.

3.4.1 Neuropsychological symptoms

3.4.1.1 Cognition

Patients were asked to rate cognitive impairment in 15 questions on a 0-4 point Likert scale using the "MS Neuropsychological Questionnaire" (MSNQ). The total score ranges between 0 to 60. The higher the score the higher the risk of neuropsychological impairment. Benedict proposed a cut-off score > 23 to detect cognitive affected or depressive patients (Benedict et al. 2004, Marrie et al. 2009)

3.4.1.2 Depression

Depression was assessed using the self-rated version of the 16 Item "Quick inventory of Depressive Symptomatology" (QIDS-SR16) (Rhush et al. 2003). Nine diagnostic symptoms of major depression according to the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-4) are inquired by the QIDS covering sleeping, sadness, appetite and weight, attention and decision making, death and suicide, interests, energy and psychomotoric symptoms. The score was created by adding the highest score from each symptom category, ranging from 0-27. The score classifies major depression as follows: 0-5= no, 6-10= mild, 11-15= moderate, 16-20= severe, 21-27= very severe depression.

3.4.1.3 Fatigue

Fatigue is described as a subjective lack of physical and/or mental energy and was measured using the "Fatigue Scale for Motor and Cognitive Functions" (FSMC) developed for MS patients (Penner et al. 2009). The 20-items long questionnaire differentiates between motor and cognitive fatigue. The sub-scores can be evaluated separately or build together a total score. The questionnaire classifies fatigue as followed:

FSMC Total Score (range=20-100): ≥43 mild fatigue, ≥53 moderate fatigue, ≥63 severe fatigue. FSMC Cognitive Score (range=10-50): ≥22 mild fatigue, ≥28 moderate fatigue, ≥34 severe fatigue. FSMC Physical Score (range=10-50): ≥22 mild fatigue, ≥27 moderate fatigue, ≥32 severe fatigue.

3.4.2 Individual resources

In order to also address patients social and psychological resources we asked for coping strategies and resilience.

3.4.2.1 Coping

The "Coping and Self-Efficacy Scale" (CSES) rates the extent of "one's confidence in performing coping behaviors when faced with life challenges" (Chesney et al. 2006). We used the 13-items short form of the questionnaire developed by Chesney et al in cooperation with Bandura (2003), to measure changing in coping behavior after performing Coping Effectiveness Training by patients with acquired immunodeficiency syndrome (AIDS) (Chesney et al. 2006). Three sub-scales discriminate between "problem-focused coping" (six items), "stop unpleasant emotions and thoughts" (four items) and to "get support from friends and family" (three items). Answers were scored from 0 ("cannot do at all") over 5 ("moderately certain can do") to 10 ("can certainly do") leading to a total-score ranged from 0-130. High scores reflect high confidences in performing coping behaviors.

3.4.2.2 Sense of Coherence

The "Sense of Coherence Scale of Antonovsky" (SOC) evaluates a "global orientation that expresses the extent to which one has a pervasive, enduring though, dynamic feeling of confidence that (1) the stimuli deriving from one's internal and external environments in the course of living are structured, predictable, and explicable; (2) the resources are available to one to meet the demands posed by the stimuli, and (3) these demands are challenges, worthy of investment and engagement". Antonovsky called these three components comprehensibility, manageability and meaningfulness and represented them in his scale as subcategories with 11,10 and eight items (Antonovxy 1993). The 26 item scale ranges from

29 - 203 and the answers are scored in a seven point Likert scale. High scores standing for high SOC.

3.4.3 Activities and participation

3.4.3.1 Activity of daily living

Activity of Daily Living (ADL) was measured by “Frenchay Activity Index” (FAI). Not only domestic chores but also leisure activities and work as well as outdoor activities are addressed by FAI (Halbrook and Skilbeck 1983).

The scale asked for the frequencies of 15 activities performed in the last three or six months: preparing main meals, washing up, washing clothes, light housework, heavy housework, local shopping, social outings (e.g. meeting friends, cinema), walking outside more than 15 minutes, actively pursuing hobby, driving a car/ going on bus, travel outings/ car rides, gardening, household/ car maintenance, reading books, gainful work.

Each activity was scored on a four point scale from 0-3 leading to a total score range from 0 to 45. The questionnaire can be separated in the three sub-scores domestic activities (question 0-5), leisure activities and work (question 7,9,11,13,15) and outdoor activities (question 6, 8,10, 12, 14). Each subscale ranges from 0-15. Due to the fact that in our study one question was missing (number 8: walk outside for more than 15 minutes) we used the individual's mean per question to create the total score.

3.4.3.2 Leisure Activities

Further activities were assessed according to the Stern measure of current hobbies and leisure activities (Scarmeas et al. 2001). The questionnaire lists 12 different leisure activities: visit lectures or concerts, theatre or movies, travel or go on tours, go for walks or rides, do arts and crafts or hobbies, sing or played a musical instrument, visit relatives, friends or neighbors, do sports, dancing or exercise, cook/prepare food as a hobby, participate as a member of a group or organization, participate in church or religious activities, do volunteer work (Schwartz et al. 2013). The patient was asked to estimate how often the activities had been performed during the last month (never=0, sometimes=1, often=2). We added some specifications to make the score more comparable between individuals. In question one to three “often” was specified as “more than once in a month”. In question four to 12 “often” meant “more than four times in the last month” and “sometimes” “once up to four times in the last month”. We produced a score ranging from 0-22.

3.4.3.3 Physical activity

Furthermore physical activity was assessed by Godin Leisure-Time Exercise Questionnaire (GLTQ) (Godin and Shephard 1985). GLTQ is a brief and validated self-reporting tool measuring physical activity in MS patients (Sikes et al. 2018). It consists of four items:

Patients were asked to fill in how many times per week strenous/ moderate or mild exercise was performed for more than 15 minutes (in the last seven days). A further question asked for the frequency the patient engaged in any regular activity long enough to work up sweat responding on a three point likert scale (1= often/ 2= sometimes/ 3= rarely or never). A total score for the first three questions was added by multiplying the exercise time by metabolic equivalents using the following formula:

(Frequency strenuous exercise x 9) + (Frequency moderate exercise x 5) + (Frequency light exercise x 3)= total leisure activity score.

3.4.3.4 Additional questions:

At the end of the assessment we asked the patients how much MS affects their leisure activities, social contacts and economic situation on a three point rated scale (not at all, little, highly). Concerning ADL the patient rated the impact of disease on a 10 point Likert scale (0= no impact to 10= very high impact on ADL). Additionally, patients described themselves as active or inactive persons and named the number of hobbies they regularly performed. The job performance was specified on a three point scale (patients rated their job accomplishment as: well, ok or exhausting). In the end we asked patients to estimate their disease as rather benign, neutral or rather malignant.

All in all we assessed ten questionnaires with a total of 210 to get an impression about the self-rated influence of MS on patients life.

3.5 Ethics

The Ethics Committee of the Hamburg Chamber of Physicians, Germany, approved of this study (Registration Number: PV4405).

3.6 Statistical analysis

For statistical analysis we used SPSS 19 (spss.com) and R (r-project.org). Depending on the nature of the data we report descriptive statistics as mean/SD (standard deviation), median/range or frequencies. We applied t-test and respectively a Person chi-square-test to compare study and dropout patients. To analyze the association between outcomes, we used linear models or Fisher's exact test. We extracted R-squared from significant models to quantify the strength of associations. For plotting, missing R-squared values from significant Fisher's exact tests were set to a fixed low value of 0.2. All p-values were corrected for multiple testing with the false discovery rate and were considered significant if still below 0.05. We analyzed the impact of different outcomes on QOL, the ability to work and the

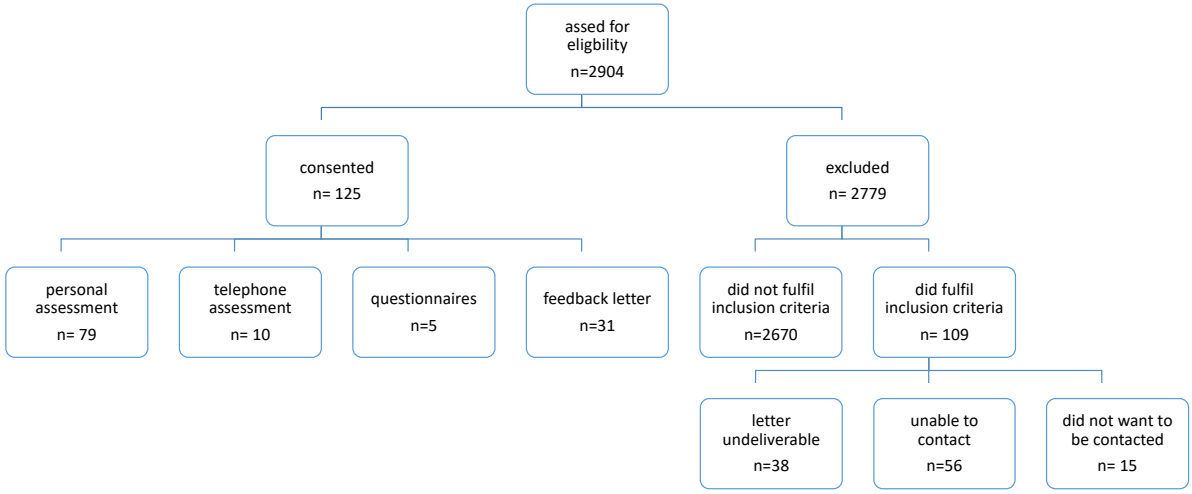
patient rated severity of their disease in multivariate models that underwent a stepwise selection of variables based on the Akaike Information Criterion (Akaike 2011).

4. Results

4.1 The Cohort

Out of 2904 patients from the database 879 (30%) had at least 15 years of disease duration, while 234 patients (8.1%) also fulfilled the inclusion criteria for possibly BMS with an EDSS ≤3.5. Mean EDSS was 2.5±0.9 with a disease duration of 23.4±6.2 years (mean±SD). 125 patients (53% of 234) could be contacted and built the actual studied cohort. 79 patients performed clinical assessment including neuropsychological examination, 10 patients were interviewed by phone and 5 patients just filled in questionnaires (see study flow-chart (fig1)). 31 patients just replied with a short feedback letter leading to n=125 with basic MS demographic data.

Figure 1. Composition of the cohort



n=879 MS database with EDSS <4, Cohort n=125, drop outs= 2779

There were no significant differences between the cohort and the dropouts based on the most recent EDSS score (p=0.58), disease duration (p=0.08), age (p=0.07) and gender (p=0.42). Only the time since the last EDSS examination was on average 1.2 years (p<0.01) shorter in the available cohort (see table 1).

Table 2: comparison of the cohort and the drop-outs

		cohort n=125	**drop-outs** n=109	**p-value**
gender (female: male)	(%) frequency	(74.4):(25.6) 93:32	(87.9):(21.1) 76:23	0.42
age (years)	mean (SD)	51.11 (8.87)	48.97 (9.30)	0.07
disease duration (years)	mean (SD)	24.04 (6.89)	22.65 (5.14)	0.08
last EDSS Score	mean (SD)	2.50 (0.87)	2.57 (1.00)	0.58
last EDSS examination (for mean (SD) years)	mean (SD)	2.67 (1.75)	3,89 (2.27)	0.00

Disease duration since first symptoms, EDSS= expanded disability severity scale, p-value= according to t-test or Person chi-square

4.2 Demography and physical disability

4.2.1 Demography

Included patients were on average 51 years old and had a female(f):male(m) ratio of 3:1. Mean disease duration was 24±8.87 years since the first symptoms. 58% of the patients fall ill for more than 20 years. Patients were mean 26.98±7.68 years old when the first symptoms began. Most patients (65%) had relapsing-remitting course (RRMS) and had never (42%), or less than 5 years (37%) been treated with DMT. 21% had been treated for more than 5 years including 2% with escalation therapy. At the time of assessment 35 (37%) had a DMT. Of these patients 7% has been treated with an escalation therapy.

Furthermore three patients took MS related medication such as Levodopa due to restless legs syndrome, Doxepin due to depression and Fampridin in order to improve walking distance. 46 patients reported to have further chronical mostly cardiovascular(n=18) and orthopedic(n=11) diseases. Other autoimmune or rheumatological diseases were named by 8 patients. 6 patients had a known depression. Further diseases as Hypothyroidism, dermatological diseases, asthma, benign prostate hyperplasia and cured malignant diseases were also specified.

All in all patients stated to have had a median of 6 relapses (range=2-96). 49% of the patients have had less than 5 relapses, 72% 10 or less and 89% 25 or less relapses. Of this median 2 relapses had occurred during the first two years (range 1-14). Looking more closely 72% had had two or less and 95% four times or less relapses in the first two years of disease.

4.2.2 Physical impairment and ambulation

Mean overall EDSS score was 2.8±0.99 (n=106, Median 2.5, range 0-6) including 15% patients with an EDSS >3.5. From these EDSS scores, 79 examinations took place due to the trial (median 2.5, range 0-6). Further nine patients were scored during a general visit in the MS outpatient clinic during the study period (median 2.5, range1-3.5). In addition, nine patients were scored by telephone-EDSS (median 3.0, range 2-4). Further nine patients stated to feel stable and we included their last EDSS (median 2.4, range 1-3.5).This results in 106 EDSS results including 18 EDSS scores above 3.5(18%). The EDSS progressed on average of 0.3 points since the last time of EDSS examination (for mean 2.7 years). 33% EDSS scores remained constant, 23 % scores decreased and 32 % increased to a maximum of one point. 10 % EDSS scores increased 1 to 2 points and 2% more than two points. The most affected functional systems were the pyramidal (mean 1.3±1.1), sensory (mean 1.39±0.94) and cerebral (mean 1.14± 0.93) system (n=92). 39% stated to have an unlimited walking distance.

Assuming the same EDSS distribution in drop-outs, the estimated rate of BMS defined by EDSS ≤ 3.5 in patients with disease durations > 15 years from our data base was 22.6% (199-out of 879, 95%, confidence interval (CI)=19.8 – 25.4%).

Mean 6MWT distance was 466 meter walked in mean 1.29 m/sec±0,34. 35 patients (45%) walked more than 500 meter in six minutes.

Patients needed mean 5 seconds for the T25FW (mean walking speed =1.57m/sec±0.37). 15 patients taking more than 6 seconds (18%), 8 patients needed more than eight sec for the 7.62 meter long walk (10%).

Furthermore patients took in mean 12 seconds for the 10 meter long tandem walk (TTW). This amounts a mean tandem walking speed of 1.02 m/s±0.44.

9HPT mean z-value -0.86±1.67 for the right and mean -0.76±1.93 for the left hand scored above -1.65 SD.

Table 3: MS demography, EDSS and ambulation

	n[1]	(%)[1]	n	
sex (female:male)	93:32	(74%: 26%)	125	
age, mean **(**SD**)**	51.11	(8.87)	125	
disease duration*, mean years (SD)	24.04	(6.89)	125	
disease courses			94	
RRMS	60	(65 %)		
SPMS[2]	23	(25 %)		
PPMS[3]	5	(5 %)		
Unknown	5	(5 %)		
medication			94	
never	39	(42 %)		
<5 years	35	(37 %)		
>5 years	20	(21 %)		
number of attacks, median (range)			94	missing ***
total	6	(6-96)		17
in the first 2 years	2	(1-14)		19
walking distance,			94	
unlimited	36	(39 %)		
>1000 m	29	(32 %)		
500 – 1000 m	23	(25 %)		
≤300 m	4	(4 %)		
pre-study EDSS score, mean **(**SD**)**	2.5	(0.87)	125	
last EDSS examination,			125	
Mean (SD) years ago	2.7	(1.75)		
actual EDSS, **			106	
total score, mean (SD)	2.8	(0.99)		
median (range)	2,5	(0-6)		
EDSS ≤2.0	36	(29 %)	125	
EDSS 2.5-3.5	69	(56 %)		
EDSS >3.5	19	(15 %)		
motor function			79	
9HPT right hand, mean sec (SD)	20.21	(0.43)		
9HPT left hand, mean sec (SD)	21.66	(0.57)		
T25FW, mean sec (SD)	5.22	(1.52)		
TTW mean sec (SD)	11.52	(5.68)		
6MWT mean meter (SD)	465.81	(122.91)		

[1]if not other indicated in frequency (%), [2] secondary progressive MS, [3] primary progressive MS, f=female, m=male, EDSS= expanded disability scale, 9HPT= nine-hole peg test, 25FWT= 25-Foot Walk, TTW= Timed Tandem Walk (TTW), 6MWT= 6 Minutes Walking Test.
* since first symptoms, ** total EDSS (n=106 median=2.7 range 0-6)= EDSS assessment (n=79, median=2.5, range 0-6)) + further assessment as described in methods (n=27 (Median 3; Range 1-4). ***= missing values.

4.2.3 Socioeconomic status

The majority had more than 10 years of education leading to higher education entrance qualification (59%), lived in a partnership (75%) and had children (59%). While 34% were fully or partly retired due to illness, further 6.5% had a reduced working time due to MS. Results are summarized in table 4.

Table 4: Socioeconomic status

	frequency[1]	**(%)[1]**	n=94
education			
>10y	55	(59%)	
≤10y	38	(41%)	
family status			
married	60	(65%)	
single	23	(25%)	
separated	7	(8%)	
widowed	2	(2%)	
partnership	70	(75%)	
no partnership	21	(25%)	
children			
>=1 child	55	(59%)	
mean (SD)	1.14	(1.17)	
employment			
pension	8	(8.5%)	
fulltime	33	(35.1%)	
halftime	9	(9.6%)	
half disability pension	10	(10.6%)	
disability pension	19	(20.2%)	
housewife	4	(4.3%)	
unemployed	5	(5.3%)	
education	1	(1.1%)	
other	4	(4.3%)	

[1]Frequencies and percent if not other indicated.

4.3 Neuropsychological assessment

In general z-scores of memory, working memory, attention and executive function tests were within the normal range. Most cognitive deficits were found in the domains of attention (5-18%), short term (9%) and working memory (8%) as well as word fluency (6-10%).

In summary 8% of the patients scored <-1.65 SD below average in more than 20% of the cognitive tests and were categorized as cognitively impaired. Using a cut-off score <-2 SD in more than 10% of the tests 14% of the patients were affected. 28% of the patients scored < -1 SD in more than 30% of the cognitive tests (table 5).

Sixteen patients with an EDSS below 4 were cognitively impaired resulting in 59.5% of BMS cases if BMS was defined by EDSS and cognition. Concerning the whole dataset, the corresponding rate of BMS corrected for cognitive impairment was 15.8% (139 out of 879, 95% CI=13.4 – 18.2%)

Table 5: Neuropsychological outcomes

category	test name	z mean(SD)	affected SD <-1.65	severely affected SD <-2	moderately affected SD <-1&≥-2	not affected SD ≥-1
			%	%	%	%
memory						
memory span	VLMTS1	0.24 (1.04)	3	0	8	92
	ZNfw	0.45 (1.23)	3	3	5	92
learning	VLMTS1-5	0.28 (0.92)	4	1	6	93
STM	VLMT5-7	-0.29 (0.95)	9	5	13	82
recognition	VLMTW-F	-0.10 (0.93)	5	4	11	85
working memory						
	SDMT	0.14 (1.02)	8	1	10	89
	ZNbw	0.04 (1.07)	4	4	20	76
attention						
alertness	tonic	-0.83(0.77)	11	3	34	63
	phasic	-0.89 (0.79)	9	2	46	52
selective attention	GoNoGo	-0.39 (0.93)	5	4	18	78
divided attention	visual	-0.25 (1.1)	11	8	15	77
	acoustic	-0.7 (0.99)	18	11	24	65
executive function						
verbal word fluency	semantic	0.69 (1.4)	6	4	4	92
	phonematic	-0.09 (1.23)	10	6	24	70
logical reasoning	LPS3	0.74 (0.50)	0	0	0	100
spatial perception	LPS7	0.60 (0.70)	0	0	1	99
score						
more than 50% tests abnormal			0	0	2.5	
more than 30% tests abnormal			5	1	28	
more than 20 % tests abnormal			8	3	35	
more than 10% tests abnormal			25	14	60	

n=79, fw=forward, bw=backward, VLMT = Verbal Learning and Memory Test", ZN= repeating numbers Test, SRM=short term memory, SDMT= "Symbol Digit Modality Test", LPS= Performing Assessment System

4.4 Questionnaires

Results from the patient rated outcome measurements (PROMs) are summarized in table 6 and 7. Based on MSNQ 27% of the patients rated themselves as cognitively affected. Mean QIDS score of 6.31±4.53 indicated mild depressive symptomatology. 30% of the patients had low grade depressive symptoms, 9% moderate and 7% severe depression. According to the FSMC 73% showed symptoms of fatigue including 43% patients with severe fatigue. Motor fatigue scored moderately and was slightly more present than cognitive fatigue (mild fatigue).
The HQUAMS evaluated MS related quality of life. The three reported main MS symptoms were walking difficulties (33%), fatigue (20%) and sensory symptoms (15%). Sub-scores rated upper extremity function and communication/social functioning “not” to “low affected”. Fatigue, cognition and lower extremity function were rated “low affected”. Asked for their overall QOL patients mean score on a single 5 point Likert scale item was 3.51 which means “quite satisfied”.
According to CSES overall coping (total score/question of 6.38±2.19) laid between “moderately certain”(5) and “certain can do”(10) it. The social support subcategory scored highest (7.2±2.31 mean/question). The SOC mean score of 5.1±0.84 scored high on a seven point Likert scale.

Table 6: Patient reported outcome measures

n= 94		mean (SD)	mean/question (SD)
MSNQ	total score	18.52 (9.25)	1.23 (0.62)
QIDS16	total score	6.31 (4.53)	0.70 (0.50)
FSMC	total score	57.43 (21.5)	2.87 (1.07)
	cognitive fatigue	27.34 (11.25)	2.73 (1.13)
	motor fatigue	30.1 (11.07)	3.01 (1.12)
CSES	total score (0-130)	82.87 (28.58)	6.38 (2.19)
	problem focused	39.32 (13.96)	6.55 (2.33)
	emotion focused	22.21 (11.06)	5.55 (2.77)
	with social support	21.34 (6.94)	7.12 (2.31)
SOC	total score	146.8 (24.45)	5.1 (0.84)
HAQUAMS	total score		2.06 (0.64)
	fatigue		2.29 (1.11)
	cognition		2.30 (1.08)
	lower Extremity		2.21 (0.86)
	upper Extremity		1.46 (0.60)
	communication		1.97 (0.88)

MSNQ= multiple sclerosis neuropsychological questionnaire (range total score=0-60, range mean/question 0-4), QIDS-16= quick inventory of depressive symptomatology (range total score=0-27, range mean/question 0-3), FSMC= fatigue scale for motor and cognitive functions (range total score=20-100, sub-scores range=10-50, range mean/question=1-5), CSES= Coping and Self-Efficacy (range total score= 0-130, range mean/question= 0-10) Scale, SOC= Sense Of Coherence Scale (range total score= 29-203, range mean/question= 1-7), HAQUAMS= Hamburg quality of live instruments in multiple sclerosis (range 1-5).

Daily activities which patients did not perform at all according to FAI were “gardening” (40%), “travel outing/car ride” (21%) and “heavy household work” (13%). Domestic activities (mean 11.81±2.98)) were performed most. In this category women showed higher scores (mean 12.84±1.99) then men (mean 8.96±3.45)). For more information see Addendum 9.4.1.

According to Stern Leisure activities 58% went for walks or rides, 43% cooked or prepared food as a hobby and 42% took part in sports, danced or exercised more than 4 times in the last month. With some limitation we contrasted the results with a US-MS Cohort from Schwarz et al. For more information see addendum 9.4.2).

The GLTQ indicated a physical activity level as following: in average patients did 0.66 times per week light, 1.74 times per week moderate and 1.75 times per week strenuous exercise. 24% stated to sweat often, 35% sometimes and 41% never or rarely during their exercise.

Table 7: Patient reported activity outcome measures

n=94		mean (SD)	median (Range)
FAI	total score (range 0-45)	31.19 (6.68)	32 (4-42)
	domestic activity (range 0-15)	11.81 (2.98)	12 (0-15)
	leisure activity /work (range 0-15)	10.73 (2.71)	11 (3-15)
	outdoor activities (range 0-15)	8.65 (2.25)	9 (0-12)
GLTQ	score	19.55 (20.55)	15 (0-119)
Stern	score	9.35 (4.51)	9 (0-22)

FAI= Frenchay activity index, GLTQ= Godin Leisure time questionnaire, Stern= Stern leisure activities.

Additional questions asked shortly about the disease impact on different areas of daily life. In 69% of the patients social contacts, 45% the economic situation and in 38% leisure activities are not at all affected by MS. ADL is rated as minorly affected (mean 3) on a 0 (not affected at all) to 10 (very affected) point likert scale. Asked for leisure activities 68% rated themselves as active persons, 57% are involved in at least one and 36.5 % even more than 3 activities. On the other hand 59% wished to be more active and 71 % felt their activity level restricted due to MS. More results are shown in table 8.

Table 8: Additional questions

n=88	not	a little bit -	very affected
leisure activities*	33 (37.5)	26 (29.5)	29 (33)
social contacts*	61 (69)	13 (15)	14 (16)
economic situation*	40 (45.5)	22 (25)	26 (29.5)
activity of daily living (ADL)			
mean (SD)	2.56 (2.32)		
range	0-8		
job accomplishment is affected * (n=64 working patients)	23 (36)	18 (28)	23 (36)

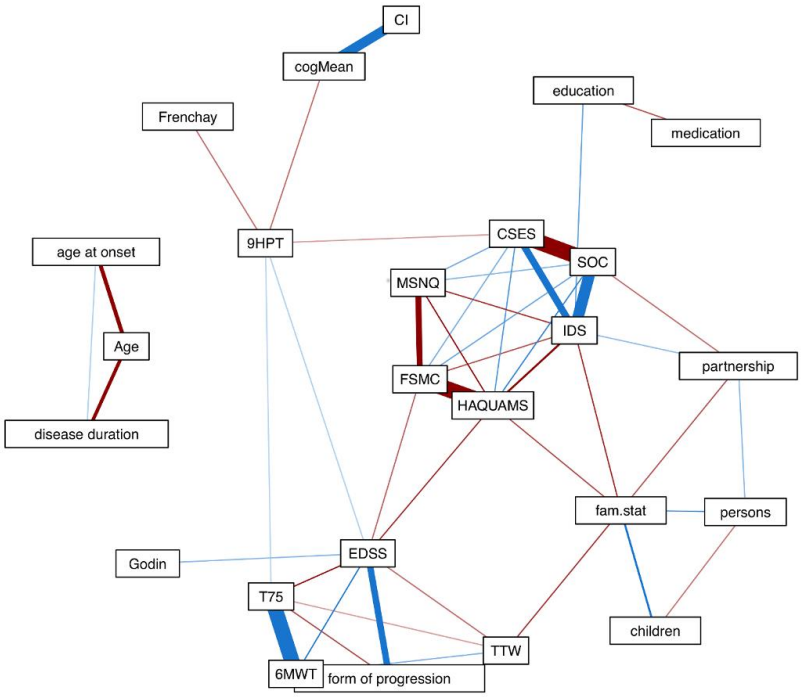
*frequency (%) if not other indicated

57 (76%) patients estimated their MS form as benign, 6 (8%) as malignant and 12 (16%) as neutral.

4.5 Associations

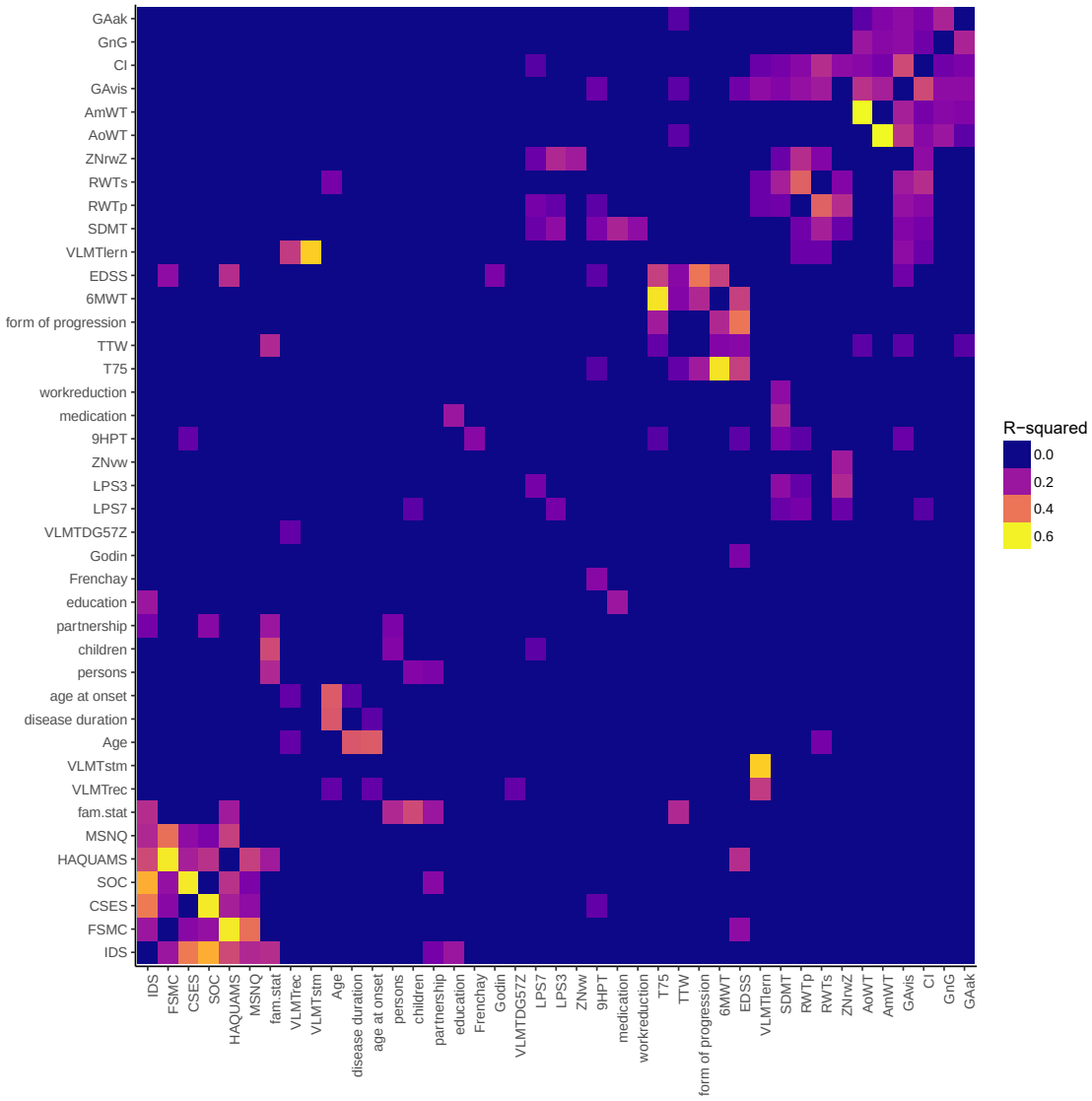
The associations and dependencies between outcomes are summarized in figure 2. We observed approximately four clusters: EDSS/mobility (TTW, T25FW, 6MWT, 9HPT), neuropsychology, family status and PROMs. However, there were only few links between the clusters that are more clearly visualized in Figure 3. QOL assessed with the HAQUAMS had a prominent position within the network of associations bridging between disability measures as EDSS or fatigue and family status, coping and mood.

Figure 2: Correlations between outcomes



Red color indicates negative, blue color positive correlation. Age at onset= age at disease onset, disease duration since first symptoms, fam stat= family status (not married, married, separated, widowed), persons= persons living at home, children= number of children, partnership= living in a partnership (yes or no), education= years of education, medication= medication>5 years, cogMean= composite score (mean sum of z-values of neuropsychological test battery), CI= cognitive impairment (yes/no), 9HPT=nine hole peg test, T75= T25FW= 25-Foot Walk, 6MWT= 6 Minutes Walking Test, TTW= timed tandem walk, MSNQ= multiple sclerosis neuropsychological questionnaire, IDS=QIDS-16= quick inventory of depressive symptomatology, FSMC= fatigue scale for motor and cognitive functions, CSES= Coping and Self-Efficacy Scale, SOC= Sense Of Coherence Scale, HQUAMS= Hamburg quality of live instruments in multiple sclerosis, FAI= Frenchay activity index, Godin= GLTQ= Godin Leisure time questionnaire,

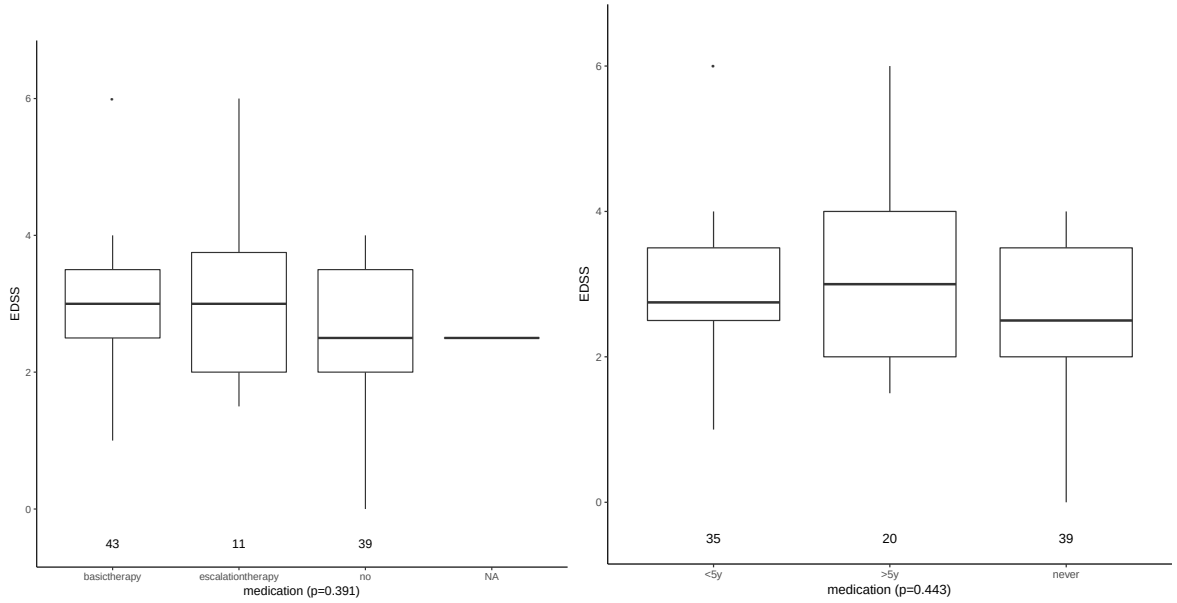
Figure 3: Association matrix of outcomes



Color scale indicates the strength of the association assessed with R^2. Zero values (blue) indicate non-significance after FDR correction. R2-values from significant Fisher's exact tests were set to 0.2 for plotting.
fam stat= family status, persons= persons living at home, ZNfw/ ZNrwZ= repeating numbers forward/ backward, RWTs/ RWTp= semantic/ phonematic word fluency, VLMTstm= memory span, VLMTSlern= lerning, VLMTDG5-7Z= remembering, VLMTrec= recognition, GAak/ GAvis= divided attention acustic/ visual, GnG= Selective attention, AmWT/ AoWT= tonic/ phasic alertness, CI= cognitive impairment (yes/no),
Age at onset= age at disease onset, disease duration = time from first symptoms? Oder ED?, fam stat= family status, persons= persons living at home, children= number of children, partnership= living in a partnership (yes or no), education= years of education, medication= medication>5 years, 9HPT= nine hole peg test, T75=25FWT= 25-Foot Walk, 6MWT= 6 Minutes Walking Test, TTW= timed tandem walk, MSNQ= multiple sclerosis neuropsychological questionnaire, IDS= QIDS-16= quick inventory of depressive symptomatology, FSMC= fatigue scale for motor and cognitive functions, CSES= Coping and Self-Efficacy Scale, SOC= Sense Of Coherence Scale, HQUAMS= Hamburg quality of live instruments in multiple sclerosis, FAI= Frenchay activity index, Godin= GLTQ= Godin Leisure time questionnaire.

Interestingly, cognitive impairment and immunotherapies were rather independent from other outcomes. Age and disease duration were not related to any other measurement. Especially, there was no correlation between EDSS and actual DMT, or a treatment over 5 years or the kind of therapy (see figure 3). Furthermore there was no correlation between the actual Immunotherapy and SDMT or Fatigue (FSMC). For further illustration see figure 4.

Figure 4: Association between EDSS and DMT



Boxplot picturing the association between EDSS and kind of taken immunotherapies (escalation therapy and basis therapy) for different times (no DMT at all, DMT >5 years and <5 years). NA= not available.

4.6 Multivariate models

To elucidate, what determines QOL, we investigated the impact of disease duration, coping, EDSS, cognition, fatigue, medication, ability to work and depression. After a stepwise selection of variables, the HAQUAMS score was substantially explained (R^2=0.68) by EDSS (p=0.001), FSMC (p<0.001), IDS (p<0.001) and occupational situation (p=0.038). In this context, we also analyzed the difference in QOL comparing differently defined BMS groups and observed a significant better QOL in BMS patients defined by EDSS alone (p=0.014) while BMS groups defined by cognitive impairment and EDSS did not differ in QOL (p=0.15). The ability to work was weakly explained by the HAQUAMS score alone (R^2=0.11, p=0.010), while disease duration, coping, EDSS, 6MWT, NHPT, cognition, depression or fatigue did not contribute. Patients rating of severity of their MS depended (p=0.007) on

coping and cognition. Lower coping scores were associated with a rating of MS as a severe condition. QOL, disease duration, EDSS, 6MWT, 9HPT, Fatigue, medication and depression did not contribute to the rating. Patients with a cognitive impairment avoided to rate their disease as benign or malignant and favored the neutral response. See figure 2 and 3.

5. Discussion

Studying a cohort of presumably benign MS we found a low prevalence of cognitive deficits but restrictions in motor function, fatigue and depression. These impairments however, had only moderate influence on QOL. Furthermore, most of the patients rated their MS as benign.

5.1 Neuropsychological impairment

5.1.1 Cognitive impairment

In general, cognitive impairment is common in MS (43-70%). Most affected are long-term memory and learning, working memory and information processing speed as well as attention, executive functions, visual perception and fluency. As a result activities, QOL and occupation can be substantially affected (Chiaravalloti and DeLuca 2008, Korakas and Tsolaki 2016). Furthermore, some authors considered, cognitive deficits might indicate a higher risk for later disability progression in BMS (Rao et al. 1991, Cristina et al. 2017, Correale and Ysrraelit et al. 2012, Sayao et al. 2007, Portaccio et al. 2009).

The few studies addressing cognitive impairment in BMS show a large variability from 17 to 47% (Amato et al. 2006, Ton et al. 2017, Correale and Ysrraelit et al. 2012, Gajofatto et al. 2015).

Our test battery broadly addressed MS relevant cognitive domains and used established tasks which have already been used in other MS studies (Briken et al. 2014, Heesen et al. 2010).

Interestingly, we found less substantial cognitive deficits than other authors. Comparable to other studies, we found cognitive impairment independently from other disability dimensions. However, in contrast to these studies we did not observe a relevant association between cognitive performance and QOL or ADL (Rao et al. 1991).

Qualitatively and quantitatively different neuropsychological batteries and cut-offs to define cognitive impairment, restricts the comparability of studies (Ton et al. 2017, Fischer et al. 2014, Schretlen et al. 2008). While most studies define two to three tests scores below -2 SD of a normal population as cognitive impairment, the practical implication of this definition for restrictions in daily life remains a matter of discussion (Gajofatto et al., 2015).

Regarding the MSNQ, patients rated their cognition as more affected than the test battery showed. This is consistent with previous studies where high correlations to depressive symptoms and other PROMs as fatigue but low sensitivity had already been described

(Benedict et al. 2004, Marrie et al. 2009, Kinsinger et al. 2010). In this study PROMs as cognition, fatigue and depression were closely associated.

5.1.2 Fatigue and depression

Fatigue is present in the general population (7-45%) but even more in the majority of MS patients (33-75%) often with impact on daily life and retirement (Berger et al. 2013, Bol et al. 2010, Patejdl et al. 2016). In our study we detected a substantial amount of fatigue. Compared to other BMS cohorts reporting a fatigue prevalence of 33 to 54% we found more affected patients (Amato et al. 2006, Correale and Peirano et al. 2012, Sayao et al. 2011).

Furthermore, symptoms of depression as well as anxiety are often present in MS patients (Marrie et al. 2009). The QIDS has proved to be a good inventory for depression screening, measuring severity and change of symptoms also in MS (Rush et al. 2003, Barry et al. 2018). In our cohort, we found frequent, but mainly mild depression comparable to other BMS cohorts (21-54%) (Amato et al. 2006, Correale and Peirano et al. 2012, Sayao et al. 2011).

5.2 Restrictions on patients life

5.2.1 Quality of Life (QOL) and activities

Nowadays, especially in chronic diseases, patient rated wellbeing as QOL has become more and more relevant in research (Weldring and Smith 2013).

In MS, lower QOL scores than in patients without chronic diseases are likely (Pfaffenberger *et* al. 2006). In general, QOL was negatively associated with disability severity, fatigue and depression. At disease onset, QOL was found to be more affected than later on. However, concerning progredient or relapsing-remitting disease courses, no difference in self-rated QOL has been found (Hviid et al. 2011).

In our study, HAQUAMS mean scores were 0.15 to 0.42 points lower than in other MS cohorts meaning a better QOL. Given a minimal important difference of 0.2 points, our results indicate a preserved high QOL (Schäffler et al. 2013, Gold et al. 2010). Thus, even a high prevalence of self-rated fatigue did not have a severe impact on the QOL of our patients.

In comparison to the few existing BMS cohorts addressing QOL, better scores than in general MS have already been described (Bueno et al. 2015, Sayao et al. 2011, Hviid et al. 2011). However, Bueno et al. found only physical QOL was associated with EDSS. We found QOL substantially associated with EDSS, fatigue, depression and employment which is consistent with the other two cohorts (Sayao et al. 2011, Hviid et al. 2011). Furthermore supporting background, effective coping strategies as well as good sense of coherence contributed to QOL.

Similar, daily and leisure activities as assessed by FAI and Stern leisure activities showed high functionality.

Originally, the FAI was developed to evaluate pre-morbid lifestyle and changes according to stroke (Halbrook and Skilbeck 1983). Later, the FAI was used to asses ADL in other chronic diseases such as in MS (Einarsson et al. 2006). The questionnaire showed comparable results to a healthy UK cohort (Turnbull et al. 2000) and higher activity scores than a Swedish population based MS cohort (Einarsson et al. 2006). Especially, looking at leisure activity FAI sub-score almost all of our patients scored above the first quartile of the healthy UK cohort (Turnbull et al. 2000). As a limitation, one question was missing in our questionnaire.

High activity levels are also reflected by a couple of hobbies which were performed in the last month according to the Stern activity index and additional questions. This includes a frequent prevalence of social events. Domestic leisure activities showed a gender difference towards higher activity levels in women similar to other cohorts (Turnbull et al. 2000). Nevertheless, more than half wished to be more active and felt restricted by MS.

Disease impact on activities in BMS have rarely been examined. Some studies measured handicap in social activities and employment with the Environmental Status Scale (ESS) (Amato et al. 2008, Gajofatto et al. 2015). These studies found that ESS score was associated with cognitive impairment. Furthermore, Gajafatto et al. described lower handicap in BMS patients compared to non-BMS patients. In our cohort, ADL was only slightly associated with hand function measured with the 9HPT.

5.2.2 Employment

In contrast to QOL and activity outcomes, the impact on employment in our cohort was substantial. However, other authors described even lower employment rates in BMS (unemployment due to MS=16%) (Glad et al. 2009). Furthermore, also in longstanding (33%) and EDSS <2 classified BMS cohorts (31%) employment was still affected (Sayao et al. 2011, Tallantyre et al. 2018). Although, in comparison to patients not staying benign at follow up, QOL and employment rates in long-term BMS patients were higher (Sayao et al. 2011). Alone Skoog et al. could not detect any restriction on employment in their longstanding BMS cohort (Skoog et al. 2012).

In this study, we identified QOL as an exclusive but very weak predictor for employment status. Other studies found a correlation between employment and depression (Glad et al. 2009).

5.3 Possible resources and the model of salutogenesis

5.3.1 Social support and coping

In chronic diseases like MS, coping strategies are very important (Pöttgen et al. 2015). In our study, most patients reported a high level of coping self-efficacy. Social support was the strongest contributive factor. In comparison, Mikula et al. found comparable coping abilities in a general MS cohort using the long CSES26 version but coping by "stopping unpleasant thoughts" was prominent. Furthermore, they found associations between coping and mental QOL in MS patients (Mikula et al. 2014). Here, especially patients' impression of a benign disease course was associated with better coping abilities.

In addition, most of our patients lived in a partnership and had children which is in contrast to previous observations in the general MS population reporting higher divorce rates (Pfleger and Koch-Henriksen 2010) and lower pregnancy rates (Alwan et al. 2015). Our findings indicate a high level of social integration and support in our cohort.

5.3.2 Sense of coherence

Antonovski`s model of salutogenesis focuses on a holistic health perception leading to the question how to get more healthy and less ill on a "health ease/ dis-ease" continuum (Bengel et al. 2001). He developed his model of salutogenesis based on the observation that some people stayed healthy despite life-threatening conditions. He assumed, that besides external factors and resources (e.g. economic situation, social contacts, education), the individuals SOC contributes to the health-disease continuum (Bengel et al. 2001). Thus, a high SOC influences the use of suitable resources, the perception of stressors and the confidence in one`s coping abilities during challenging life events. However, Antonovsky assumed very high SOC values were less likely associated with better health, but with a missing sense of reality (Bengel et al. 2001).

The three SOC components, comprehensibility, manageability and meaningfulness are represented in the questionnaire. Nevertheless, factor analysis could not differentiate between these categories, thus only the total score has been used in most of the studies (Schumacher et al. 2000). The SOC Scale showed good validity, reability and applicability and is widely used in different languages (Flensborg-Madsen et al. 2005) but rarely in MS (Gottberg et al. 2015).

In our study, SOC scores were overall high and comparable to a healthy German population based cohort (n=2005, mean SOC/question=5.02± 0.84) (Schumacher et al., 2000). Only 8% scored -1.65 SD below the average scores of this cohort. Thus, our MS patients resembled healthy individuals in their perception of meaningfulness of life.

While previous studies found associations of SOC with mental health, correlation with physical health is less distinctive (Flensborg-Madsen et al. 2005). Furthermore, very high negative correlations have been found with fear and depression. This arouses the question whether SOC is an independent factor or only the opposite of fear and depression (Bengel et al. 2001). Similarly, in our study correlation with other PROMs especially coping and depression but also fatigue and QOL were detected. Latter is consistent with a Swedish study which detected an influence of SOC on QOL (Eriksson and Lindström 2007). Nevertheless, SOC in MS has been mainly evaluated on a cross-sectional design. Thus, a causal relation between SOC and better health cannot be assumed.

Finally, while Antonovsky suspected SOC to be relatively stable after an age of 30 years, some studies showed higher SOC scores at older age (>50years) (Eriksson and Lindström 2005). As a limitation, higher age in our cohort might have influenced SOC positively. However, SOC values of the German cohort of Schumacher et al. with a similar age distribution (age 41-60 years) were comparable (n=700, mean SOC/question=5.04± 23.30) (Schumacher et al. 2000).

5.3.3 Education

Furthermore, the education level was nearly twice as high than in a general German population at the same time (27% higher education >10years) (Statistisches Bundesamt 2017). Interestingly there was an association between low education level and a neutral point of view when asked to rate their disease course as benign, malignant or neutral.

5.4 Physical impairment and walking

At the time of examination, some patients were no longer BMS according to EDSS (15%) and ambulation. Correspondingly, other motor-focused objective assessments as T23FW, 6MWT and TTW showed some restrictions.

The T25FW is one of the best evaluated objective tests assessing gait impairment in a wide range in MS (Kieseier and Pozzilli 2012). Furthermore, associations with occupational changes (T25FW> six seconds), activities of daily living (ADL), family status and government health care assistance (T25FW > eight seconds) have been found (Goldman et al., 2013). Less affected T25FW showed a quicker walk compared to an US-MS Cohort (n=400, mean=8.5±11.6 sec). Nevertheless, some patients scored over the proposed cut-offs of six and even over eight sec, implicating restrictions on people's lives (Goldman et al. 2013).

The TTW, described as a more sensitive test to detect disability especially in mildly affected patients, showed minor impairment in our cohort (J P Stellmann et al. 2014). Stellmann et al.

found a TTW >9 sec predictive for impairment in the motor or cerebellar system and a TTW>10 sec associated with EDSS 3-4 in 18-50 year old patients. In our cohort, patients scored slightly above a supposed cut-off score of 9 and 10 sec.

The 6MWT was originally developed for assessing physical performance in cardiac and respiratory diseases. In MS, the 6MWT has become a good test for assessing walking fatigability and walking distance especially of mildly affected patients (Kieseier and Pozzilli 2012). In our cohort, TTW also showed restrictions. Compared to moderately affected MS patients (EDSS 3-4) of a small US-cohort, our patients walked slightly less in 6 minutes (US-cohort: n=40, mean 507m±103) (Goldman et al. 2008).

However, due to higher age of patients within our cohort compared to other studies, walking distance cannot easily be compared.

Among all objective outcomes, mobility restrictions contributed highest to the QOL underlining previous reports about the importance of ambulation for MS patients (Heesen et al. 2017).

Self-reported physical activity showed restrictions as well. Patient's GLTQ was only half of a younger population from Toronto (n=306, mean 31 years old, GLTQ mean 45.8) (Godin and Shephard 1985) but similar to MS cohorts with comparable age and gender distribution (n=1142, mean19.12±21.12) (Schwartz et al. 2013), (n=196, mean 23.6±22) (Motl et al. 2006).

5.5 MS demography

5.5.1 Therapy

Since 1995 more and more DMTs are available for MS and thus have to be considered when describing MS disease course. However, due to BMS definition criteria (>10 to >20 years disease duration) many patients of existing BMS cohorts have already been ill for some time when DMT had been introduced. Thus, assuming the trend to treat patients rather early than late, the effect of DMT on the disease curse might be of less extent (Sartori et al. 2017).

In our cohort, the minority has been treated for a relevant time with DMT although a few of them received escalation therapies. However, having or having had DMT did not seem to influence any of our outcomes including QOL, EDSS, SDMT and fatigue.

In comparison, some studies found BMS patients to be less frequently treated with DMT than not or no longer BMS patients (Ramsaransing and De Keyser 2007, Sartori et al. 2017, Mastorodemos et al. 2010, Sayao et al. 2007). This observation might be explained by the assumption that clinicians tend to avoid to treat mildly affected patients with DMT (Sartori et

al. 2017). However, the report over DMT is very heterogenous in BMS cohorts. Some BMS studies miss to name treated patients in general (Hviid et al. 2011, Hawkins and McDonnell 1999) while other authors report DMT in a variable number (0-74%) (Skoog et al. 2012, Correale and Peirano et al. 2012, Reynders et al. 2017). DMTs are often retrospectively analyzed (Reynders et al., 2017) and only few studies differentiated the treatment concerning length and type (Sartori et al. 2017, Ramsaransing and De Keyser 2007, Zivadinov et al. 2016).

In comparison to our study, some studies did not describe a difference in outcomes including cognition between treated and untreated patients (Gajofatto et al. 2015). In addition, further studies did not find a correlation between DMT and BMS status (Leray et al. 2013, Sartori et al. 2017). Zivadinov et al. however, found the use of DMT "significantly associated with maintaining benign disease state" in a New York State MS Consortium cohort (Zivadinov et al. 2016).

Other disease specific Immunotherapies were of very low prevalence in our cohort.

5.5.2 Possible demographic BMS prediction parameters

Previously reported BMS prediction parameters are discussed controversial. In our cohort, only some of the proposed variables were present. Due to the cross-sectional design, causality conclusions cannot be made.

First of all, a couple of patients had a progressive disease course. While a consensus group defined BMS independently of the disease course phenotype (Lublin et al. 2014), other authors proposed the absence of progression as a condition to define BMS (Skoog et al. 2014, Correale and Peirano et al. 2012, Gajofatto et al. 2015). However, even primary-progressive MS patients presumed to have a worse prognosis show a heterogeneous disease evolution (Stellmann et al. 2014). Therefore, we decided against a paradigmatic exclusion of a possibly benign progressive disease course. Here, we observed only a moderate association between the disease course and disability while QOL or FAI were independent from the disease course.

Secondly, the female:male ratio in this study was comparable with general MS-populations (Scalfari et al. 2010). However, few studies found female sex associated with a more benign course (Hawkins and McDonnell 1999).

Thirdly, some authors described higher age at disease onset (e.g. above 40 years) associated with more disability (Hawkins and McDonnell 1999). Similarly, in this study mean age at onset was slightly lower than in general MS populations (31 years) (Degenhardt et al. 2009).

Finally, our mean (overall) relapse rate resembles the 13 Gothenburg patients with longstanding BMS (median 4, range 2–12) (Skoog et al., 2012). According to Scalfari et al., most of our patients had a low to intermediate relapse rate in the first 2 years after disease onset. However, mean relapse rate was similar to this geographical based general MS cohort (Scalfari et al. 2010). This observation is limited due to a high relapse range from 2 to 92 in our cohort.

Other studies, found having one relapse in the first 5 years was predictive for BMS (Reynders et al. 2017) whereas three or more relapses in the first five years were associated with disease progression (Degenhardt et al. 2009).

5.6 Prevalence and Definition of BMS

In our cohort, the estimated BMS prevalence was in the lower middle when compared to other cohorts (5-73%) (Ton et al. 2017). We also considered cognitive impairment which led to a slightly lower BMS prevalence and used McDonald criteria 2005 for study inclusion. Nevertheless, the clinical based design might have led to an underestimation of BMS prevalence.

Comparable to the amount of still benign patients according to EDSS was the number of patients rating their MS as benign at time of examination. However, no association between EDSS and the patient`s own rating could be found.

Similar results have been observed in an UK cohort (Tallantyre et al. 2018). Tallantyre et al. considered disability in a broad range including cognition, fatigue and depression as well as occupation in their study leading to a very low estimate of BMS prevalence (3%). On the first view, this observation stayed in contrast to the finding that 69% of patients of this UK cohort (last EDSS<4 for >15 years) rated their MS as benign.

However, looking more closely the proportion of EDSS based BMS patients resembled the self-rated BMS patients (76% (EDSS <4):69% (patient-rated benignity)) comparable to our study.

The discrepancy between substantial fatigue, cognitive impairment, affected employment and subjective disease course rating might be explained by a more resources orientated model.

In this regard, our study found high scores in SOC, social support and coping. Latter was especially associated with the patients disease course rating.

As a result, despite of spending more effort in accurate disability measurements, research should focus on patient-rated impact of the disease on patients life like QOL and activities.

5.7 Limitations

As a limitation nearly half of the patients could not be contacted and only a third could be assessed clinically. But baseline demographic data of these compared to the analyzed cohort gave no indication of a selection bias. In addition, we hypothesized that especially the less impaired MS patients might not seek medical attention at a tertiary clinic. Thus, a negative selection bias might rather lead to an overestimation of impairment in the clinically investigated cohort.

Even though the EDSS of the majority of patients was clinically assessed, we also used retrospective data in some cases, which is a further limitation.

As already discussed before, DMT could have influenced the disease course. However, prevalence of DMT was low and without relevant correlations to other parameters.

Furthermore, this study included no healthy control cohort but referred to normative data from the literature which weakens the validity of findings to some extent.

5.8 Conclusion

In conclusion, existence and prevalence of BMS is a heavily disputed scientific topic and our data adds to the complexity of the picture. Presumably benign patients seem to have some impairment, especially walking restriction and fatigue, but most patients live their lives as they want to. The majority of the patients rated their MS as benign, reflected in high SOC and QOL scores.

Thus, we propose that BMS needs to be defined at least partially by educated patients themselves, based on their estimates how far MS impacts their life goals and impairs their ability to adapt to life`s challenges. This view might help to stress resources and resilience rather than clinical deficits. Highly sensitive disability measures as for example neuropsychological batteries have a questionable value for a patient and might not be the best approach to define “benign” in a patient centered way.

6. Summery

The aim of the study was to describe a broad range of health dimensions in possibly benign multiple sclerosis, hypothesizing that in spite of some limitations, there is a high adaptation to the disease. In order to that all patients from the UCM outpatient clinic registry with an Expanded Disability Status Scale (EDSS) ≤3.5 and disease duration ≥15 years were addressed in a cross-sectional study. Physical impairment, neuropsychological functioning, but also influence on activities and patient reported outcome measures, including coping and sense of coherence were studied. 125 patients were included (mean EDSS: 2.8; mean disease duration: 24 years).

Cognitive impairment was minor (8%) but fatigue (73%) was substantial and ambulation showed some restrictions. 15% of the patients were no longer benign due to an EDSS ≥3.5. Nevertheless, QOL and daily activities compared to patients with MS not classified as benign seemed to be less affected. High social support, coping abilities and sense of coherence, which was predictive for self-perceived benign course. Based on EDSS alone, we estimated the rate of benign MS after 15 years of MS as high as 23% decreasing to 16% if cognition was included in the definition. However, cognitive performance was not relevantly associated with other outcomes. As a conclusion, common benign MS definitions seem to simplify the picture of a complex disease in which different impairments and personal resources lead to more or less impact on people's lives.

Zusammenfassung:

Ziel der Studie war es, einen allumfassenden Überblick gesundheitsrelevanter Dimensionen bei vermutlich benignen MS Patienten (BMS) darzustellen. Wir stellten die Hypothese auf, dass die Patienten, trotz relevanter Beeinträchtigungen eine hohe Anpassungsfähigkeit an die Erkrankung aufweisen. Für diese Querschnitts-Studie wurden alle Patienten mit einem EDSS ≤3.5 und einer Krankheitsdauer ≥15 Jahre aus der Datenbank der MS-Ambulanz des Universitäts Klinikums Hamburg-Eppendorf berücksichtigt. Neben physischen wurden auch neuropsychologische Beeinträchtigungen untersucht. Außerdem wurden der Einfluss der Erkrankung auf die Alltags- und Freizeitaktivitäten der Patienten sowie Coping und Kohärenzgefühl untersucht. 125 Patienten wurden in die Studie eingeschlossen (mittlerer EDSS: 2,8, mittlere Erkrankungsdauer: 24 Jahre). Es zeigten sich wenig kognitive Beeinträchtigungen (8%), jedoch substantielle Einschränkungen im Bereich Fatigue (73%)

und Depression (46%). Dennoch waren die Auswirkungen auf die Lebensqualität und Aktivität der Patienten gering. Die Patienten waren sozial gut eingebunden, wiesen gute Coping-Strategien und ein schützendes Kohärenzgefühl auf. Diese Parameter zeigten sich prädiktiv für die Wahrnehmung des Patienten eine benigne MS zu haben. Die BMS Prävalenz wurde, basierend auf dem EDSS allein auf 23% und in Kombination mit erhaltener Kognition auf 16% geschätzt. Kognition war jedoch mit keinem anderen Parameter assoziiert. Wir schlussfolgerten, dass bisherige BMS Definitionen dem komplexen Bild des benignen Krankheitsverlaufes nicht gerecht werden. Hierbei, scheinen nicht nur Beeinträchtigungen sondern auch persönliche Ressourcen eine wichtige Rolle zu spielen.

7. Abbreviations

ADL: Activities of daily life

AIDS: acquired immunodeficiency syndrome

BMS: Benign Multiple Sclerosis

CI: Confidence interval

CSES: Coping and Self-Efficacy Scale

DD: disease duration

DMT: Disease modifying treatment

DSS: Disability Status Scale

EDSS: Expanded Disability Status Scale

f: female

FSMC: Fatigue Scale for Motor and Cognitive Functions

FU: follow-up

GLTQ: Godin Leisure-Time Exercise Questionnaire

GoNoGo: Selective attention

HQUAMS: Hamburger Quality of Life in MS

9HPT: Nine Hole Peg Test

LPS: " Leistungsprüfsystem", achievement testing system

LPS3: evaluates logical reasoning

LPS7: reflects visual perception

m: meter

MRI: magnet resonance imaging

MS: Multiple Sclerosis

msec: milliseconds

MSNQ: Multiple Sclerosis Neuropsychological Questionnaire

n.a: not available

6MWT: 6 Minutes Walking Test

QIDS-SR16: Quick inventory of Depressive Symptomatology- Self-rated 16 items

QOL: quality of life

RRMS: relapsing-remitting Multiple Sclerosis

PPMS: primary progressive Multiple Sclerosis

PROMs: patient rated outcome measurements

RWT: “Regensburger Wordflüssigkeitstest”, Verbal Fluency Test

SB: still benign

sec: seconds

SD: Standard deviation

SDMT: Symbol Digit Modality Test

SOC: Sense of coherence scale

SPMS: secondary progressive Multiple Sclerosis

TAP: Test Battery of Attention

T25FW: Timed 25-Foot Walk

TTW: 3-meter Timed Tandem Walk

UCM: University Medical Center (Hamburg)

VLMT: Verbal Lerning and Memory Test

VLMTS1: memory span

VLMTS1-5: learning

VLMT5-7: short term memory

VLMTW-F: recognition

y: years

ZN: “ Zahlen nachsprechen”, repeating numbers

ZNfw: ZN forward, short term memory

ZNbw: ZN backward, working memory

8. Literature

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9. Addendum

9.1 Expanded disability status scale (EDSS)

To ensure unbiased EDSS assessment in controlled clinical trials, the EDSS rater should not inquire about the patients' condition except as necessary to perform the EDSS assessment.

Patients must be observed to walk the required distance.

NEUROSTATUS (NS)
In the Neurostatus «signs only» is noted when the examination reveals signs of which the patient is unaware.

FUNCTIONAL SYSTEMS (FS)
A score of 1 in the Functional Systems implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities (with the exceptions of optic, vegetative and cerebral functions).

EXPANDED DISABILITY STATUS SCALE (EDSS)
EDSS should not be lower than the highest score of the FS.
Symptoms which are not MS-related will not be taken into consideration for assessments, but should be noted.

In the definitions of EDSS grades 6.0 and 6.5 both a description of assistance required and of the walking range are included.
In general, the distinction of bilateral versus unilateral assistance required to walk overrules the walking range.
However, the following exceptions are suggested,
If a patient is able to walk considerably longer than 100 m with two sticks, crutches or braces he is in grade 6.0.
If a patient is able to walk more than 10 m and less than 100 m with two sticks, crutches or braces he is in grade 6.5.
If a patient needs assistance by another person (as opposed to one stick, crutch or brace) and/or is not able to walk more than 50 m with one stick, crutch or brace he is in grade 6.5.

VISUAL (OPTIC) FUNCTIONS

Definitions

Visual acuity

The visual acuity score is based upon the line on the Snellen chart at 20 feet (5 m) for which the patient makes no more than one error (use best available correction).
Alternatively best corrected near vision can be assessed but this should be noted and consistently done during follow up.

Fields

0 = normal
1 = signs only, deficits present only on formal testing
2 = moderate, patient aware of deficit, but incomplete hemianopsia on examination
3 = marked, complete homonymous hemianopsia or equivalent

Scotoma

0 = none
1 = small, detectable only on formal (confrontational) testing
2 = large, spontaneously reported by patient

Disc pallor

0 = not present
1 = present

OPTIC FUNCTIONS	OD	OS
Visual acuity (corrected)		
Visual fields		
Scotoma		
Disc pallor		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = disc pallor and/or mild scotoma and/or visual acuity of worse eye (corrected) less than 30/30 (1.0) but better than 20/30 (0.67)
	2 = worse eye with large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
	3 = worse eye with large scotoma or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.2)
	4 = worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.1–0.2); grade 3 plus maximal acuity of better eye of 20/60 (0.3) or less
	5 = worse eye with maximal visual acuity (corrected) less than 20/200 (0.1); grade 4 plus maximal acuity of better eye of 20/60 (0.3) or less
	6 = grade 5 plus maximal visual acuity of better eye of 20/60 (0.3) or less

BRAINSTEM FUNCTIONS

Definitions

Assessment of impairment/disability

0 = normal

1 = signs only: clinically detectable numbness, facial weakness, or cranial nerve deficit of which patient is not aware

2 = mild: clinically detectable numbness, facial weakness, dysarthria or cranial nerve deficits of which patient is aware

3 = moderate: diplopia with incomplete paralysis of any eye movement, impaired discrimination of sharp/dull in 1 or 2 trigeminal branches, trigeminal neuralgia (at least one attack in the last 24 hours), weakness of eye closure, cannot hear finger rub and/or misses several whispered numbers, obvious dysarthria during ordinary conversation impairing comprehensibility

4 = severe (marked): complete loss of movement of either eye in one direction, impaired discrimination of sharp/dull or complete loss of sensation in the entire distribution of one or both trigeminal nerves, unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids, sustained difficulty with swallowing, incomprehensible voice

Nystagmus

0 = normal

1 = signs only

2 = gaze evoked nystagmus below limits of "moderate" (usual equivalent is grade one in FS score)

3 = moderate, sustained nystagmus on 30° horizontal or vertical gaze, but not in primary position, patient may or may not realize disturbance (usual equivalent is grade 2 in FS score)

4 = severe, sustained nystagmus in primary position or coarse persistent nystagmus in any direction interfering with visual acuity, complete internuclear ophthalmoplegia with sustained nystagmus of abducting eye, oscillopsia

CRANIAL NERVE EXAMINATION	
EOM (extra ocular movements) impaired	
Nystagmus	
Trigeminal damage	
Facial weakness	
Hearing loss	
Dysarthria	
Dysphagia	
Other bulbar signs	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = signs only
	2a = moderate nystagmus or/and
	2b = other mild disability
	3a = severe nystagmus or/and
	3b = marked extraocular weakness or/and
	3c = moderate disability of other cranial nerves
	4a = marked dysarthria or/and
	4b = other marked disability
	5 = inability to swallow or speak

PYRAMIDAL FUNCTIONS

Definitions * = optional

REFLEXES

0 = absent, 1 = weak, 2 = normal, 3 = exaggerated, 4 = cloniform, 5 = inexhaustible (indicate difference between R & L by < or >)

Plantar response

0 = flexor, 1 = neutral, 2 = extensor

Cutaneous reflexes

0 = normal, 1 = weak, 2 = absent

***Palmomental reflex**

0 = absent, 1 = present

LIMB STRENGTH

The weakest muscle in each group defines the score for that group. Use of functional tests like jumping with one foot, walking on toes or heels are recommended in order to assess grades 3-5 BMRC.

BMRC Rating scale

0 = no activity, 1 = visible contraction without visible joint movement, 2 = visible movements with elimination of gravity, 3 = movements against gravity possible but impaired, 4 = movements against resistance possible but impaired, 5 = normal strength

FUNCTIONAL TESTS

*Position test UE (upper extremities)

Sinking, 0 = none, 1 = mild, 2 = evident

***Position test LE (lower extremities)**

Sinking, 0 = none, 1 = mild, 2 = evident

1 = only separate lifting possible (grades from horizontal position in hip joints...°)

2 = even separate lifting not possible

***Walking on heals/tiptoes**

0 = normal, 1 = impaired, 2 = not possible

***Monopedal hopping**

0 = normal, 1 = 6–10 times, 2 = 1–5 times, 3 = not possible

LIMB SPASTICITY

0 = normal, 1 = mild, barely increased muscular tone after rapid flexion of an extremity, 2 = moderate, 3 = severe, barely surmountable increased spastic tonus after rapid flexion of an extremity, 4 = contracted

Gait spasticity

0 = normal, 1 = barely perceptible, 2 = evident, minor interference with function, 3 = permanent shuffling, major interference with function

REFLEXES	R	><	L
Biceps			
Triceps			
Radial			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
*Palmomental reflex			

LIMB STRENGTH		
Shoulder		
Elbow flexors		
Elbow extensors		
Hand/finger flexors		
Hand/finger extensors		
Hip flexion		
Knee flexors		
Knee extensors		
Foot/toe flexors		
Foot/toe extensors		
*Position test UE, pronation		
*Position test UE, sinking		
*Position test LE, sinking		
only lifting of single leg possible	°	°
*Walking on heals		
*Walking on tiptoes		
*Hopping on one foot		

SPASTICITY		
Arm		
Leg		
Gait		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = abnormal signs without disability
	2 = minimal disability, patient complains about fatiguability in motor tasks and/or BMRC grade 4 in one or two muscle groups
	3a = mild to moderate paraparesis or hemiparesis (usually BMRC grade 4 in more than two muscle groups or BMRC grade 3 in one or two) movements against gravity are possible 3b = severe monoparesis, refers to BMRC grade 2 or less in one muscle group
	4a = marked paraparesis or hemiparesis (usually BMRC grade 2 in 2 limbs) 4b = moderate tetraparesis (refers to BMRC grade 3 in 3 or more limbs) 4c = monoplegia (BMRC grade 0 or 1 in one limb)
	5a = paraplegia, BMRC grade 0 or 1 in all muscle groups of the lower limbs 5b = hemiplegia 5c = marked tetraparesis (BMRC grade 2 or less in 3 or more limbs)
	6 = Tetraplegia (grade 0 or 1 in all muscle groups of upper and lower limbs)

CEREBELLAR FUNCTIONS

Definitions
UE = upper extremities
LE = lower extremities
EO = eyes open
EC = eyes closed

Head tremor, rebound
0 = normal
1 = mild abnormality
2 = moderate abnormality
3 = severe abnormality

Truncal ataxia
0 = none
1 = signs only
2 = mild, swaying with EC
3 = moderate, swaying with EO
4 = severe, unable to sit without assistance

Limb ataxia
0 = none
1 = signs only
2 = mild, tremor or clumsy movements seen easily, minor interference with function
3 = moderate, tremor or clumsy movements interfere with function in all spheres
4 = severe, most functions are very difficult

Gait ataxia
0 = none
1 = signs only
2 = mild, abnormal balance only on heel or toe walking, or walking along a line
3 = moderate, abnormal balance on ordinary walking or while seated
4 = severe, unable to walk more than a few steps or requires support by another person or walking aid because of ataxia

Romberg test
0 = normal
1 = mild, mild insecurity with EC
2 = moderate, not stable with EC
3 = severe, not stable with EO

Straight line walking
0 = without problems
1 = impaired
2 = not possible

Note
The presence of severe gait ataxia alone results in a grade of 3 in the cerebellar FS. If weakness interferes with the testing of ataxia, score the patient's actual performance, but also indicate the possible role of weakness by marking the box marked 'X'.

CEREBELLAR EXAMINATION	
Head tremor	
Truncal ataxia, EO	
Truncal ataxia, EC	

	R	L
Tremor/dysmetria UE		
Tremor/dysmetria LE		
Rapid alternate movements impaired UE		
Rapid alternate movements impaired LE		
Gait ataxia, EO		
Straight line walking, EO		
Other, e.g. rebound		
Romberg test		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = abnormal signs without disability
	2 = mild ataxia
	3a = moderate truncal ataxia 3b = moderate limb ataxia
	4 = severe ataxia in all limbs or trunk
	5 = unable to perform coordinated movements due to ataxia
	X = weakness (grade 3 or more on pyramidal) interferes with testing

SENSORY FUNCTIONS

Definitions * = optional
UE = upper extremities
LE = lower extremities

Superficial sensation – Touch/pain
0 = normal
1 = signs only, patient is not aware of deficit, but slightly reduced sensation of feeling (temperature, figure writing)
2 = mild, patient is aware of impaired light touch or pain, but able to discriminate sharp/dull
3 = moderate, impaired discrimination of sharp/dull
4 = severe, no discrimination of sharp/dull and/or unable to feel light touch
5 = complete loss, anaesthesia

Vibration sense
0 = normal
1 = mild, graded tuning fork 5–7 of 8 (alternatively) detects more than 10 sec. but less than examiner
2 = moderate, graded tuning fork 1–4 of 8 (alternatively) detects more than 2 sec. but less than 11 sec.
3 = marked, complete loss of vibration sense

Position sense
0 = normal
1 = mild, 1–2 incorrect responses on testing, only distal joints affected
2 = moderate, misses many movements of fingers or toes, proximal joints affected
3 = marked, no perception of movement/astasia

***Lhermitte**
0 = negative
1 = positive

***Paraesthesia (tingling)**
(do not influence FS-score)
0 = none
1 = present

SENSORY EXAMINATION	R	L
Superficial sensation (touch/pain) UE		
Superficial sensation trunk		
Superficial sensation LE		
Vibration sense UE		
Vibration sense LE		
Position sense UE		
Position sense LE		
*Lhermitte		
*Paraesthesiae UE		
*Paraesthesiae trunk		
*Paraesthesiae LE		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mild vibration or figure-writing decrease only in 1 or 2 limbs
	2a = mild decrease in touch or pain or position sense and/or moderate decrease in vibration in 1 or 2 limbs 2b = mild vibration or figure-writing decrease alone in 3 or 4 limbs
	3a = moderate decrease in touch or pain or position sense and/or essentially lost vibration in 1 or 2 limbs 3b = mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs
	4a = marked decrease in touch or pain or loss of proprioception, alone or combined in 1 or 2 limbs 4b = moderate decrease in touch or pain and/or severe proprioceptive decrease in more than 2 limbs
	5a = loss (essentially) of sensation in 1 or 2 limbs 5b = moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
	6 = sensation essentially lost below the head

BOWEL/BLADDER FUNCTIONS

Definitions * = optional

BLADDER

Hesitancy/retention

0 = none
1 = mild, no major impact on lifestyle
2 = moderate, urine retention, frequent UTI
3 = severe, requires catheterisation
4 = loss of function, overflow incontinence

Urgency/incontinence

0 = none
1 = mild, no major impact on lifestyle
2 = moderate, rare incontinence, no more than once a week, must wear pads
3 = severe, frequent incontinence, several times a week up to once daily, must wear urinal
4 = loss of function, loss of bladder control

Catheterisation

0 = none
1 = intermittent self catheterisation
2 = constant

Bowel

0 = none
1 = mild, no incontinence, no major impact on lifestyle, constipation
2 = moderate, must wear pads or alter lifestyle to be near lavatory
3 = severe, in need of intermittent enemata
4 = complete loss of function

***Sexual dysfunction**

0 = none
1 = mild
2 = moderate
3 = severe
4 = loss

BLADDER AND BOWEL FUNCTIONS	
Hesitancy/retention	
Urgency/incontinence	
Catheterisation	
Bowel dysfunction	
*Sexual dysfunction	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mild urinary hesitancy, urgency and/or constipation
	2 = moderate urinary hesitancy and/or urgency and/or rare incontinence and/or severe constipation
	3 = frequent urinary incontinence or intermittent self catheterisation, needs constantly enemata or manual measures to evacuate bowel
	4 = in need of almost constant catheterisation
	5 = loss of bladder or bowel function, external or indwelling catheter
	6 = loss of bowel and bladder function

CEREBRAL FUNCTIONS

Definitions
The presence of depression and/or euphoria alone results in a score of 1 on the cerebral FS, but does not affect the EDSS score.

Depression/euphoria
0 = none
1 = present
Patient complains of depression or is considered depressed or euphoric by the investigator or «significant other».

Decrease in mentation
0 = none
1 = signs only, not apparent to patient and/or «significant other»
2 = mild, difficulties apparent to patient and/or «significant other» such as impaired ability to follow a rapid course of association and of surveying complex matters, impaired judgement in certain demanding situations, able to handle the daily routine, but no tolerance for additional stressors, intermittently symptomatic to even normal levels of stress, reduced performance, tendency toward negligence due to obliviousness or fatigue. However, not apparent while taking the history or performing the routine neurological examination.
3 = moderate, definite abnormalities on formal mental status testing, but still oriented to time, place and person
4 = marked, not oriented in 1 or 2 spheres of time, place or person, marked effect on lifestyle
5 = dementia, confusion and/or complete disorientation

Fatigue
0 = none
1 = mild, not interfering with daily activities
2 = moderate, interfering but not limiting daily activities for more than 50 %
3 = severe, significantly limiting daily activities (> 50% reduction)

MENTAL STATUS EXAMINATION	
Depression	
Euphoria	
Decrease in mentation	
Fatigue	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mood alteration only (does not affect EDSS score)/mild fatigue
	2 = mild decrease in mentation/ moderate or severe fatigue
	3 = moderate decrease in mentation
	4 = marked decrease in mentation
	5 = dementia

AMBULATION

Definitions
Actual walking distance without assistance obligatory up to 500 m (if possible). Actual walking distance with assistance obligatory up to 150 m (if possible).

In the definitions of EDSS grades 6.0 and 6.5 both a description of assistance required and of the walking range are included. In general, the distinction of bilateral versus unilateral assistance required to walk overrules the walking range.
However, the following exceptions are suggested,
If a patient is able to walk considerably longer than 100 m (> 120) with two sticks, crutches or braces he is in grade 6.0.
If a patient is able to walk more than 10 m and less than 100 m with two sticks, crutches or braces he is in grade 6.5.
If a patient needs assistance by another person (as opposed to one stick, crutch or brace) and/or is not able to walk more than 50 m with one stick, crutch or brace he is in grade 6.5.

AMBULATION

Walking range as reported (without help or sticks)

meters

in min

Able to walk without rest or assistance

- ≥ 100 meters, but < 200 meters
- ≥ 200 meters, but < 300 meters
- ≥ 300 meters, but < 500 meters
- ≥ 500 meters but not unrestricted
- Unrestricted

Actual distance (obligatory up to 500 m if possible)

meters

Unable to walk 100 m without constant assistance

Unilateral assistance meters

- Cane/crutch
- Other

Bilateral assistance meters

- Canes/crutches
- Other

Other person

SYNOPSIS OF FS SCORES

- Visual [1,3]
- Brainstem
- Pyramidal
- Cerebellar
- Sensory
- Bladder/Bowel [2,3]
- Mental

[1] For calculation of the EDSS the score of the visual FS is to be converted as follows, 6 = 4; 5 = 3; 4 = 3; 3 = 2; 2 = 2; 1 = 1.

[2] Scores of the bowel/bladder FS are converted as follows: 6=5, 5=4, 4=3, 3=3, 2=2, 1=1.

[3] Please enter both the actual and the converted score.

KURTZKE EXPANDED DISABILITY SCALE (EDSS)

EDSS steps below 4 refer to patients who are fully ambulatory, and the precise step is defined by the functional systems (FS) score(s). EDSS steps between 4.0 and 5.0 are defined by both FS-scores and walking range. In general, the worst of both should determine the score. Steps 5.5-8.0 are exclusively defined by ability to ambulate or use wheelchair.

EDSS should not change by 1.0 step unless there is a change in same direction of at least one step in at least one FS.
EDSS should not be lower than each of FS (excepted visual and bowel/bladder FS).

0	normal neurological exam (all grade 0 in FS)
1.0	no disability, minimal signs in one FS1 (i.e. grade 1)
1.5	no disability, minimal signs in more than one FS1 (more than one grade 1)
2.0	minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	ambulatory without aid or rest for > 500 m; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps
4.5	ambulatory without aid or rest for > 300 m; up and about much of the day; characterised by relatively severe disability usually consisting of one FS grade 4 or combinations of lesser grades exceeding limits of previous steps
5.0	ambulatory without aid or rest for > 200 m (usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5	ambulatory without aid or rest > 100 m
6.0	unilateral assistance (cane or crutch) required to walk at least 100 m with or without resting
6.5	constant bilateral assistance (canes or crutches) required to walk at least 20 m without resting
7.0	unable to walk 20 m even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 h a day
7.5	unable to take more than a few steps; restricted to wheelchair; may need some help in transfer and in wheeling self
8.0	essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5	essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0	helpless bed patient; can communicate and eat
9.5	totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	death due to MS

Actual EDSS

Signature

[1] Mental function's grade 1 does not contribute to EDSS-step definitions

9.2 Written neuropsychological tests

9.2.1 Verbal Lerning and Memory test (VLMT)

Protokollbogen A VLMT (Version: 11.11.03)

Liste A	Abruf Liste A (*vor Abruf jeweils neu präsentieren*)					Liste B	Abruf Liste B	Liste A (*nicht präsentieren*)		
Liste A	**1**	**2**	**3**	**4**	**5**	**Liste B**		**Liste A**	**6**	**7**
Trommel						Tisch		Trommel		
Vorhang						Förster		Vorhang		
Glocke						Vogel		Glocke		
Kaffee						Schuh		Kaffee		
Schule						Ofen		Schule		
Eltern						Berg		Eltern		
Mond						Handtuch		Mond		
Garten						Brille		Garten		
Hut						Wolke		Hut		
Bauer						Boot		Bauer		
Nase						Lamm		Nase		
Truthahn						Gewehr		Truthahn		
Farbe						Bleistift		Farbe		
Haus						Kirsche		Haus		
Fluss						Arm		Fluss		

Richtige										
Perseverationen (P)										
Falsch Positiv (FP)										
						Interferenz				

Scores ΣDG1-5 ☐ DG5-7 ☐ W-F ☐ ΣFP ☐

ΣP ☐ ΣIn ☐

Wiedererkennen A

Bei "Ja"-Antwort jeweiliges Zeichen umkringeln

	Richtige	Liste B	Intrusion
Vorhang	A		
Sonne			SA
Boot		B	
Vase			PA
Farbe	A		
Glocke	A		
Ofen		B	
Lehrer			SA
Kuh			PB
Hut	A		
Schuh		B	
Schule	A		
Fenster			SA
Förster		B	
Mond	A		
Tisch		B	
Fisch			PB

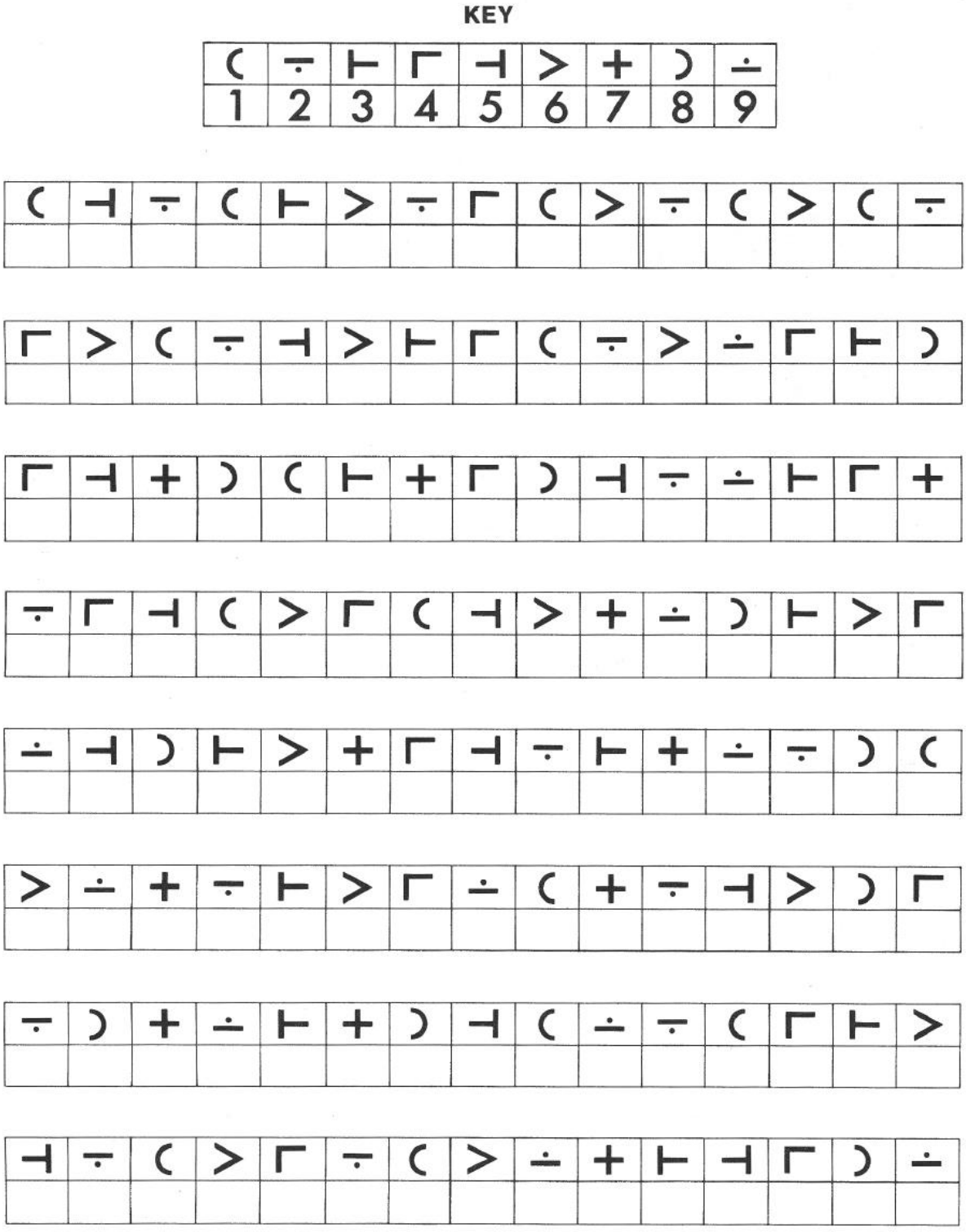
	Richtige	Liste B	Intrusion
Kuchen			SA
Lamm		B	
Nase	A		
Garbe			PA
Bleistift		B	
Maus			PA
Wolke		B	
Kaffee	A		
Locke			PA
Jäger			SB
Fluss	A		
Gewehr		B	
Stille			PB
See			SA
Haus	A		
Handtuch		B	
Mut			PA

	Richtige	Liste B	Intrusion
Mauer			PA
Truthahn	A		
Vogel		B	
Bein			SB
Brille		B	
Schaf			SB
Garten	A		
warten			PA
Eltern	A		
Pauke			SA
Berg		B	
Trommel	A		
Kinder			SA
Bauer	A		
Arm		B	
Kirsche		B	

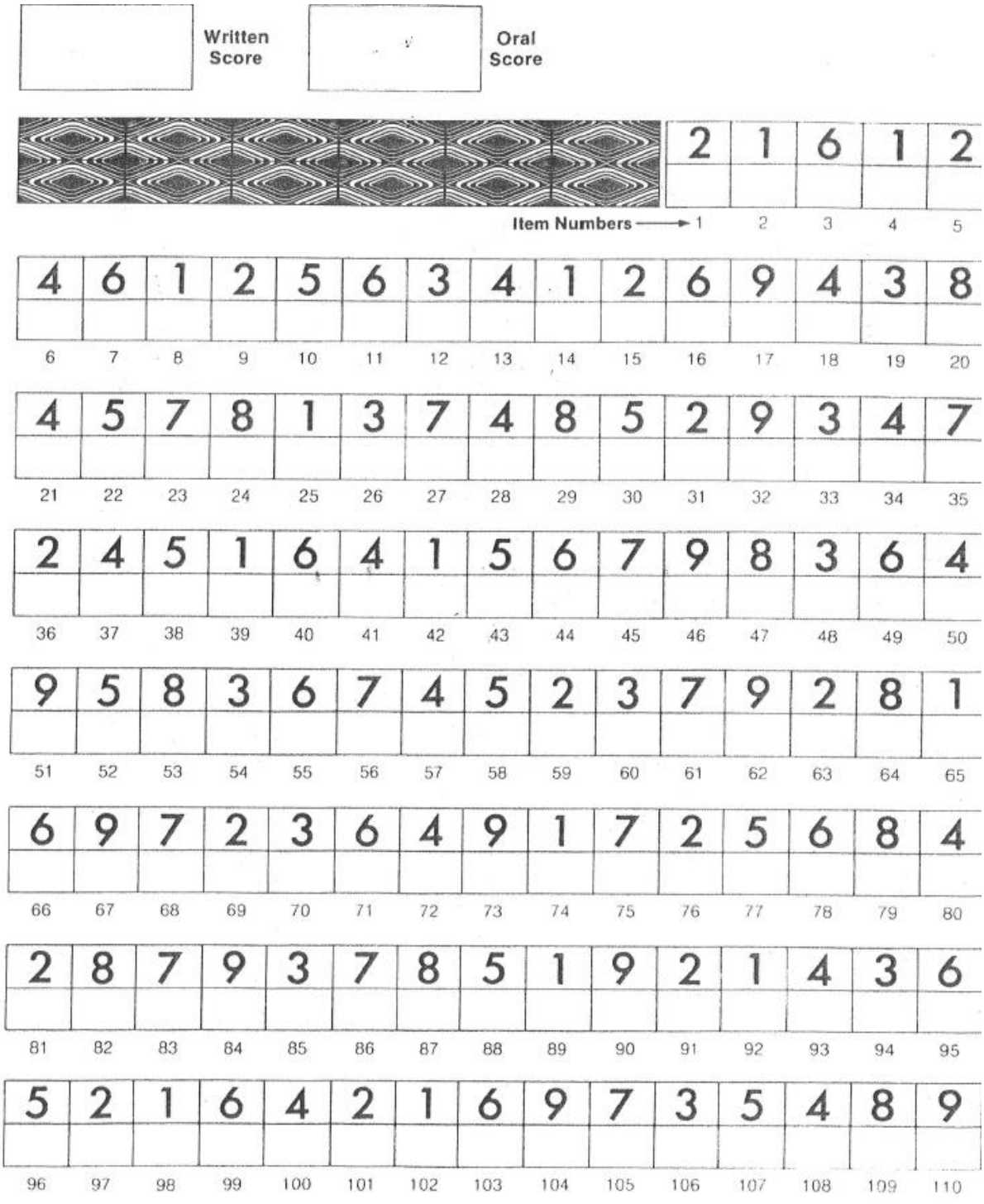
Scores A ☐ SA&SB ☐ PA&PB ☐

9.2.2 Symbol Digit Modality Test (SDMT)

Patient Sheet



Control Sheet:



9.2.3 Repeating numbers (Zahlen nachsprechen (ZN))

ZAHLENSPANNE Brechen Sie ab, wenn beide Versuche misslingen. Führen Sie immer beide Versuche durch, auch wenn der erste gelang.					
ZAHLENSPANNE VORWÄRTS					2, 1 oder 0 Punkte
Aufgabe	1. Versuch	1 od. 0	2. Versuch	1 od. 0	
1	6-2-9		3-7-5		
2	5-4-1-7		8-3-9-6		
3	3-6-9-2-5		6-9-4-7-1		
4	9-1-8-4-2-7		6-3-5-4-8.2		
5	1-2-8-5-3-4-6		2-8-1-4-9-7-5		
6	3-8-2-9-5-1-7-4		5-9-1-8-2-6-4-7		
Max. = 12 Gesamt vorwärts					
ZAHLENSPANNE RÜCKWÄRTS Bitte auch durchführen, wenn zuvor 0 Punkte					2, 1 oder 0 Punkte
Aufgabe	1. Versuch	1 od. 0	2. Versuch	1 od. 0	
1	5-1		3-8		
2	4-9-3		5-2-6		
3	3-8-1-4		1-7-9-5		
4	6-2-9-7-2		4-8-5-2-7		
5	7-1-5-2-8-6		8-3-1-9-6-4		
6	4-7-3-9-1-2-8		8-1-2-9-3-6-5		
Max. = 12 Gesamt rückwärts					
Max Gesamt = 24					

BLOCKSPANNE Brechen Sie ab, wenn beide Versuche misslingen. Führen Sie immer beide Versuche durch, auch wenn der erste gelang.					
BLOCKSPANNE VORWÄRTS					2, 1 oder 0 Punkte
Aufgabe	1. Versuch	1 od. 0	2. Versuch	1 od. 0	
1	2-6		8-4		
2	2-7-5		8-1-6		
3	3-2-8-4		2-6-1-5		
4	5-3-4-6-1		3-5-1-7-2		
5	1-7-2-8-5-4		7-3-6-1-4-8		
6	8-2-5-3-4-1-6		4-2-6-8-3-7-5		
7	7-5-6-3-8-7-4-2		1-6-7-4-2-8-5-3		
Max. = 14 Gesamt vorwärts					
BLOCKSPANNE RÜCKWÄRTS					2, 1 oder 0 Punkte
Aufgabe	1. Versuch	1 od. 0	2. Versuch	1 od. 0	
1	3-6		7-4		
2	6-8-5		3-1-8		
3	8-4-1-6		5-2-4-1		
4	4-6-8-5-2		8-1-6-3-7		
5	7-1-8-3-6-2		3-8-1-7-5-4		
6	1-5-2-7-4-3-8		6-7-4-3-1-5-2		
Max. = 12 Gesamt rückwärts					
Max Gesamt = 26					

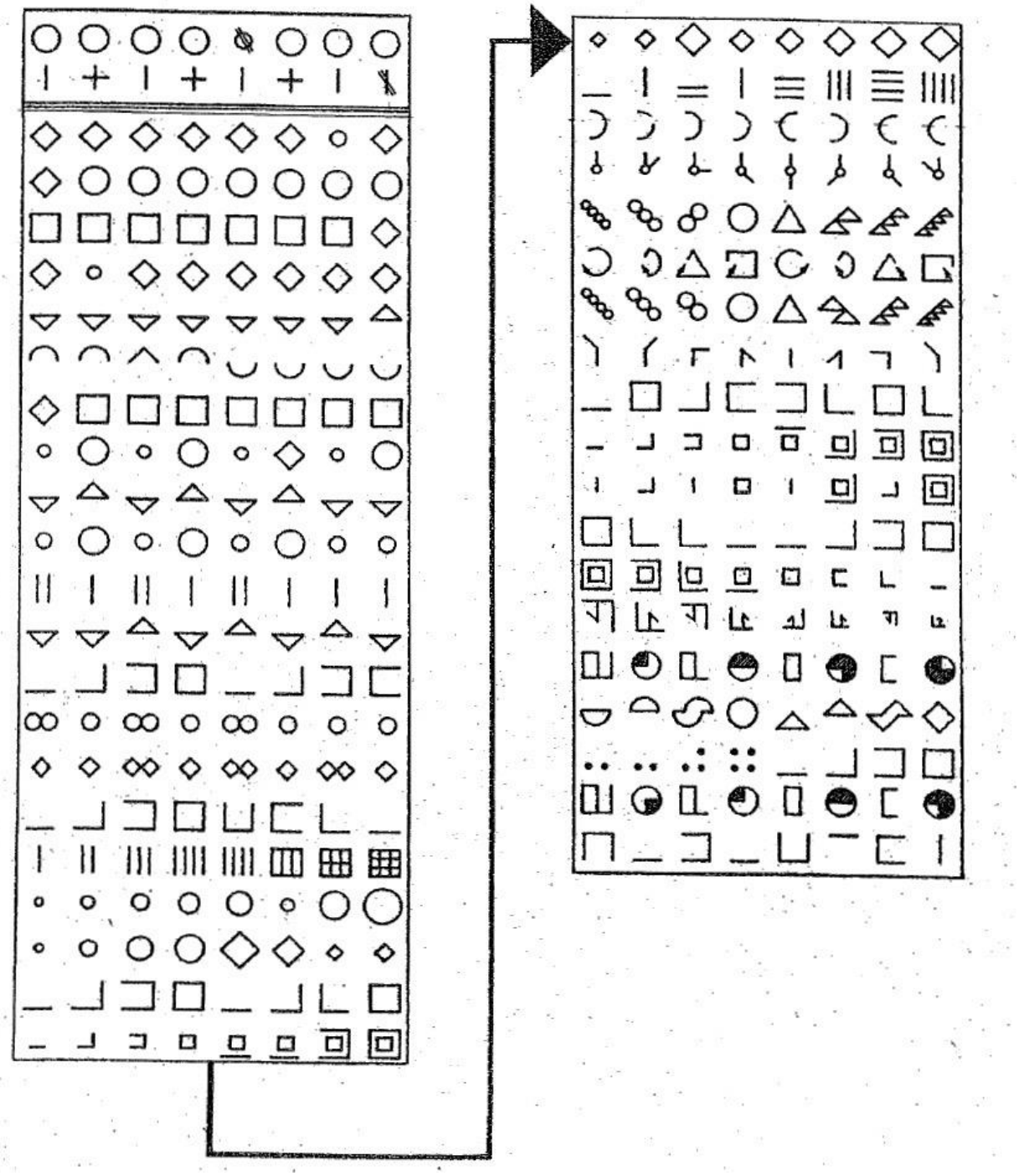
9.2.4 Verbal Fluency Test (Regensburger Wortflüssigkeitstest (RWT))

RWT

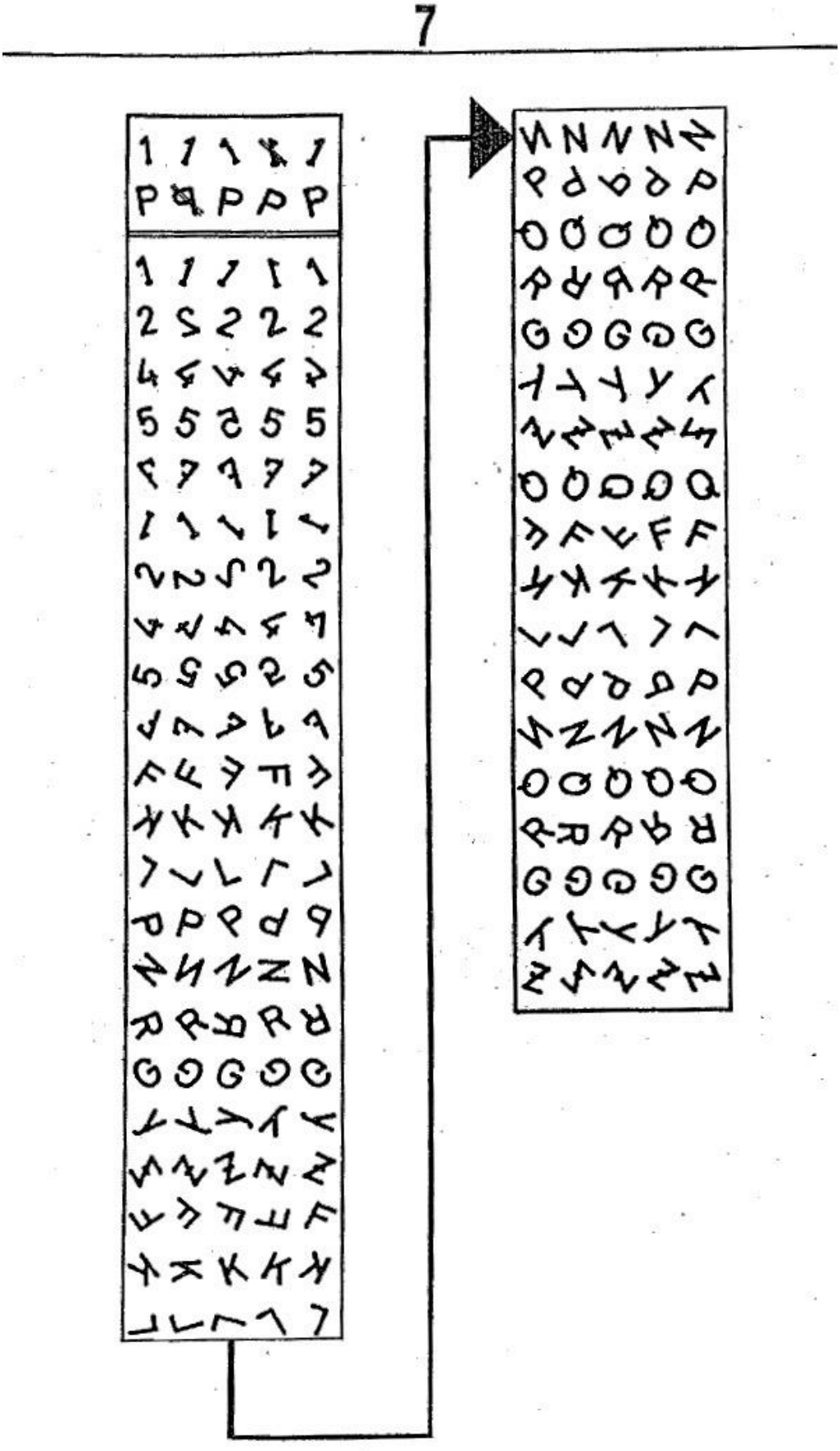
Hinweis: Für Monitoring-Pat und post12 immer Buchstabe B und Kategorienwechsel H➔ T
Hinweis: Für Kinder von 8 – 15 Jahre nur Buchstabe S, kein Kategorienwechsel

Semantisch-kategorielle Flüssigkeit				**Semantischer Kategorienwechsel**			
Anweisung: „Bitte nennen Sie möglichst schnell viele verschiedene Wörter aus der Kategorie *Tiere* (*Berufe*) innerhalb von 2 Minuten. Bitte keine Wörter mehrfach nennen! **Als letzten Hinweis:** Bitte möglichst schnell möglichst viele verschiedene Wörter nennen!“				Anweisung: „Bitte nennen Sie möglichst schnell viele verschiedene Wörter, die abwechselnd mit den Buchstaben *G und R* (*H und T*) beginnen innerhalb von 2 Minuten. Bitte mit *G* (*H*) beginnen. Bitte keine Wörter mehrfach nennen! **Als letzten Hinweis:** Bitte möglichst schnell möglichst viele verschiedene Wörter nennen! Wichtig ist, die Buchstaben abwechselnd zu benutzen!“			
Untertest: Tiere ◘ Berufe ◘				**Untertest:** **H ➔ T** ◘ **G ➔ R** ◘			
1. Minute			**2. Minute**			**1. Minute**			**2. Minute**	
	Wörter	√	**Wörter**	√		**Wörter**	√	**Wörter**	√
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
21									
22									
23									
24									
25									
26									
∑		∑		∑		∑			
	gesamt	∑				**gesamt**	∑		

9.2.5 Logical reasoning (Leistungsprüfsystem (LPS 3))



9.2.6 Visual perception (Leistungsprüfsystem (LPS 7))



9.3 Questionnaires

9.3.1 Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), self-rated (SR)

MSNQ Patient

Anweisungen:
Die folgenden Fragen beziehen sich auf Probleme, dir Sie betreffen könnten. Bitte geben Sie die Häufigkeit **UND** die Schwere der Probleme an. Legen Sie Ihren Einstufungen Ihr Befinden in den **letzten drei Monaten** zugrunde.

Bitte kreuzen Sie das entsprechende Eingabefeld an.

	Sehr oft, sehr störend	Ziemlich oft, beeinträchtigt Lebensstil	Gelegentlich, selten problematisch	Sehr selten, unproblematisch	Nie, kommt nicht vor
	4	3	2	1	0
1.lassen Sie sich leicht ablenken					
2.Verlieren Sie Ihre Gedanken, wenn Sie jemanden zuhören					
3. Sind Sie langsam beim lösen von Problemen					
4.Vergessen Sie Termine?					
5.Vergessen Sie was Sie gelesen haben					
6. Fällt es Ihnen schwer, Sendungen, Programme zu beschreiben, die Sie kürzlich gesehen haben?					
7. Müssen Anweisungen für Sie wiederholt werden					
8. Müssen Sie daran erinnert werden, Aufgaben zu erledigen?					
9. Vergessen Sie Besorgungen, die geplant waren?					
10. Fällt es Ihnen schwer, Fragen zu beantworten?					
11.Fällt es Ihnen schwer, zwei Dinge auf einmal zu behandeln?					
12. Fällt es Ihnen schwer, das Wesentliche zu begreifen, dass jemand mitzuteilen versucht					
13. Fällt es Ihnen schwer, sich unter Kontrolle zu haben?					
14. Lachen oder Weinen Sie nahezu grundlos?					
15. Sprechen Sie übertrieben viel und konzentrieren sich übermäßig auf Ihre eigenen Interessen?					

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9.3.2 Quick inventory of Depressive Symptomatology, self-rated, 16 items (QIDS-SR16)

QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELF-REPORT)

KREUZEN SIE BITTE JEWEILS DIE ANTWORT AN, DIE FÜR DIE LETZTEN 7 TAGE AM BESTEN AUF SIE ZUTRIFFT.

1. Einschlafen:

⌜0 Ich habe nie länger als ½Stunde gebraucht, um einzuschlafen.

⌜1 Ich habe an höchstens 3 Tagen ½ Stunde oder länger gebraucht, um einzuschlafen.

⌜2 Ich habe an 4 oder mehr Tagen ½ Stunde oder länger gebraucht, um einzuschlafen.

⌜3 Ich habe an 4 oder mehr Tagen länger als eine Stunde gebraucht, um einzuschlafen.

2. Nachtschlaf:

⌜0 Ich bin nachts nicht aufgewacht.

⌜1 Ich hatte einen unruhigen, leichten Schlaf und bin jede Nacht ein paar Mal kurz aufgewacht.

⌜2 Ich bin nachts mindestens einmal aufgewacht, aber schnell wieder eingeschlafen.

⌜3 Ich bin an 4 oder mehr Tagen mehr als einmal nachts aufgewacht und 20 Minuten oder länger wachgeblieben.

3. Zu frühes Aufwachen:

⌜0 Ich bin meistens nicht mehr als ½ Stunde früher aufgewacht, als ich aufstehen musste.

⌜1 Ich bin an 4 oder mehr Tagen mehr als ½ Stunde früher aufgewacht, als ich aufstehen musste.

⌜2 Ich bin fast immer mindestens eine Stunde früher aufgewacht, als ich aufstehen musste, aber nach einiger Zeit wieder eingeschlafen.

⌜3 Ich bin immer mindestens eine Stunde früher aufgewacht, als ich aufstehen musste und konnte nicht wieder einschlafen.

4. Zu viel Schlaf:

⌜0 Ich habe nicht mehr als 7-8 Stunden jede Nacht geschlafen und tagsüber kein Nickerchen gemacht.

⌜1 Ich habe in einem Zeitraum von 24 Stunden nicht mehr als 10 Stunden geschlafen, Nickerchen eingeschlossen.

⌜2 Ich habe in einem Zeitraum von 24 Stunden nicht mehr als 12 Stunden geschlafen, Nickerchen eingeschlossen.

⌜3 Ich habe in einem Zeitraum von 24 Stunden mehr als 12 Stunden geschlafen, Nickerchen eingeschlossen.

5. Traurigkeit:

⌜0 Ich war nicht traurig.

⌜1 Ich war weniger als die Hälfte der Zeit traurig.

⌜2 Ich war mehr als die Hälfte der Zeit traurig.

⌜3 Ich war fast immer traurig.

QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELF-REPORT)

KREUZEN SIE BITTE JEWEILS DIE ANTWORT AN, DIE FÜR DIE LETZTEN 7 TAGE AM BESTEN AUF SIE ZUTRIFFT.

Bitte entweder Frage 6 oder 7 beantworten (nicht beide)

6. Verminderter Appetit:

Γ0 Mein Appetit war nicht vermindert.

Γ1 Ich habe seltener oder weniger gegessen als sonst.

Γ2 Ich habe viel weniger gegessen als sonst und nur, wenn ich mich dazu gezwungen habe.

Γ3 Ich habe in einem Zeitraum von 24 Stunden kaum gegessen und nur, wenn ich mich sehr dazu gezwungen habe oder andere mich dazu überredet haben.

7. Gesteigerter Appetit:

Γ0 Mein Appetit war nicht gesteigert.

Γ1 Ich hatte das Bedürfnis, öfter zu essen als sonst.

Γ2 Ich habe öfter und/oder größere Mengen als sonst gegessen.

Γ3 Ich habe den Drang verspürt, sowohl zu den Mahlzeiten als auch zwischen den Mahlzeiten mehr als sonst zu essen

Bitte entweder Frage 8 oder 9 beantworten (nicht beide)

8. Gewichtsabnahme (in den letzten zwei Wochen):

Γ0 Ich habe nicht abgenommen.

Γ1 Ich habe das Gefühl, dass ich ein wenig abgenommen habe.

Γ2 Ich habe 1 kg oder mehr abgenommen.

Γ3 Ich habe mehr als 2 kg abgenommen

9. Gewichtszunahme (in den letzten zwei Wochen):

Γ0 Ich habe nicht zugenommen.

Γ1 Ich habe das Gefühl, dass ich ein wenig zugenommen habe.

Γ2 Ich habe 1 kg oder mehr zugenommen.

Γ3 Ich habe mehr als 2 kg zugenommen.

10. Konzentration/Entscheidungsfähigkeit:

Γ0 Meine Fähigkeit, mich zu konzentrieren oder Entscheidungen zu treffen war unverändert.

Γ1 Ich war manchmal unentschlossen oder habe festgestellt, dass meine Aufmerksamkeit abschweift.

Γ2 Ich musste mich meistens sehr anstrengen, um mich zu konzentrieren oder Entscheidungen zu treffen.

Γ3 Ich konnte mich nicht genug konzentrieren, um zu lesen oder konnte nicht einmal unwichtige Entscheidungen treffen.

11. Selbstbild:

Γ0 Ich habe mich selbst als genauso wertvoll betrachtet wie andere Menschen.

Γ1 Ich habe mir öfter als sonst Vorwürfe gemacht.

Γ2 Ich bin mir ziemlich sicher, dass ich anderen Menschen Probleme bereitet habe.

Γ3 Ich habe fast ständig über große und kleine Fehler nachgedacht, die ich habe.

12. Gedanken an den eigenen Tod oder an Selbstmord:

Γ0 Ich habe nicht an Selbstmord oder an meinen Tod gedacht.

Γ1 Ich hatte das Gefühl, das Leben ist leer und habe mich gefragt, ob es lebenswert ist.

Γ2 Ich habe mehrmals in der Woche für einige Minuten an Selbstmord und an meinen Tod gedacht.

Γ3 Ich habe mehrmals am Tag bis in Einzelheiten an Selbstmord oder an meinen Tod gedacht, oder genaue Selbstmordpläne gemacht, oder tatsächlich versucht, mir das Leben zu nehmen.

QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELF-REPORT)

KREUZEN SIE BITTE JEWEILS DIE ANTWORT AN, DIE FÜR DIE LETZTEN 7 TAGE AM BESTEN AUF SIE ZUTRIFFT.

13. Allgemeines Interesse:

Γ0 Mein Interesse an anderen Menschen oder an Tätigkeiten war unverändert.

Γ1Ich habe bemerkt, dass ich mich weniger für Menschen oder Tätigkeiten interessiere.

Γ2 Ich habe festgestellt, dass ich nur noch an einer oder zwei der Tätigkeiten Interesse habe, denen ich früher nachgegangen bin.

Γ3 Ich hatte nahezu kein Interesse mehr an Tätigkeiten, denen ich früher nachgegangen bin.

14. Energie:

Γ0 Meine Energie war unverändert.

Γ1Ich wurde schneller müde als sonst.

Γ2 Ich musste mich sehr dazu zwingen, mit meinen Alltagstätigkeiten zu beginnen oder sie zu erledigen (z.B. Einkaufen, Kochen, Ausbildung oder zur Arbeit gehen).

Γ3 Ich konnte die meisten meiner Alltagstätigkeiten nicht ausführen, weil mir einfach die Energie dazu
fehlte.

15. Gefühl der Verlangsamung:

Γ0 Ich habe so schnell gedacht, gesprochen und mich bewegt wie immer.

Γ1 Ich hatte das Gefühl, dass mein Denken verlangsamt ist oder dass meine Stimme monoton oder ausdruckslos klingt.

Γ2 Auf die meisten Fragen konnte ich erst nach mehreren Sekunden antworten und ich bin mir sicher, dass mein Denken verlangsamt war.

Γ3 Ich konnte auf Fragen oft nur mit größter Mühe antworten.

16. Unruhe:

Γ0 Ich war nicht unruhig.

Γ1 Ich war oft zappelig, habe meine Hände geknetet oder musste beim Sitzen hin und her rutschen.

Γ2 Ich hatte das plötzliche Bedürfnis mich zu bewegen und war ziemlich unruhig.

Γ3 Manchmal konnte ich nicht sitzen bleiben und musste herumlaufen.

Hiermit bestätige ich die Richtigkeit dieser Angaben	Initialen des Patienten/der Patientin	Datum:

QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SCORE SHEET)

_____ Enter the highest score on any 1 of the 4 sleep items (1-4)
_____ Item 5
_____ Enter the highest score on any 1 of the appetite/weight items (6-9)
_____ Item 10
_____ Item 11
_____ Item 12
_____ Item 13
_____ Item 14
_____ Enter the highest score on either of the 2 psychomotor items (15 and 16)
_____ Total Score (Range: 0-27)

Rush et al, Biol Psychiatry (2003) 54: 573-83.
EPI0905.QIDSSR
Germany (German)

NOTE: THIS SECTION IS TO BE COMPLETED BY THE STUDY PERSONNEL ONLY.

9.3.3 Fatigue Scale for Motor and Cognitive Gunctions (FSMC)

Fatigue Skala für Motorik und Kognition

Anleitung

Im folgenden Fragebogen geht es um alltägliche Probleme, die im direkten Zusammenhang mit einer extremen Form von Müdigkeit (Fatigue) stehen. Unter dieser extremen Form der Müdigkeit wird ein nicht zu beherrschender Zustand der Abgeschlagenheit, Erschöpfung und Energielosigkeit verstanden, der schlagartig eintritt, unabhängig von eindeutigen äusseren Urlachen. Gemeint sind damit nicht Einzelereignisse, wie sie jeder Mensch im Laufe des Tages, nach einer Anstrengung oder nach einer schlaflosen Nacht erlebt!

Bitte lesen Sie jede Aussage genau durch. Entscheiden sie dann, inwieweit die entsprechende Aussage auf Sie und Ihren Alltag zutrifft. Bitte treffen Sie Ihre Antwort möglichst unabhängig von Ihrem momentanen Befinden und versuchen Sie uns ein Bild von Ihrem Zustand zu geben, wie Sie ihn Tag für Tag erleben. Setzen Sie hierzu bitte ein Kreuz in den entsprechenden Kreis (pro Aussage bitte nur ein Kreuz!).

		Trifft gar nicht zu	Trifft wenig zu	Trifft teils-teils zu	Trifft ziemlich zu	Trifft völlig zu
1.	Wenn ich mich längere Zeit konzentrieren, erschöpfe ich schneller als andere Menschen	O	O	O	O	O
2.	Meine Bewegungen werden im Zustand der Erschöpfung deutlich ungeschickter und unkoordinierter.	O	O	O	O	O
3.	Wegen meiner Erschöpfungszustände brauche ich heute bei körperlichen Tätigkeiten häufigere und/oder auch längere Ruhepausen als früher.	O	O	O	O	O
4.	Im Zustand der Erschöpfung bin ich unfähig Entscheidungen zu treffen	O	O	O	O	O
5.	Ich fühle mich heute körperlich schneller erschöpft als früher, wenn ich stressigen Situationen ausgestzt bin.	O	O	O	O	O
6.	Wegen meiner Erschöpfungszustände habe ich wesentlich weniger soziale Kontakte als früher	O	O	O	O	O
7.	Wegen meiner Erschöpfungszustände fällt es mir heute schwerer, etwa Neues zu lernen als früher	O	O	O	O	O
8.	Berufliche Anforderungen lassen mich geistig schneller erschöpfen als früher.	O	O	O	O	O
9.	Erschöpfungszustände spüre ich besonders stark in meinen Muskeln.	O	O	O	O	O
10.	Bei körperlichen Anstrengungen über einen längeren Zeitraum habe ich mehr Mühe durchzuhalten als früher.	O	O	O	O	O

(Penner *et al.*, 2009)

9.3.4 Coping and Self-Efficacy Scale (CSES, short version)

Coping-Selbstwirkamkeits-Skala (Kurzform)

Liebe Patientin, lieber Patient,
wenn Sie Probleme haben und die Dinge nicht gut laufen für Sie, wie zuversichtlich sind Sie dann, dass Ihnen das Folgende gelingt?
Für alle der folgenden Fragen kreuzen Sie bitte eine der Zaheln 0-10 aus der folgenden Bespiel-Skala an.

Gelingt sicher nicht				gelingt vermutlich						gelingt sicher
0	1	2	3	4	5	6	7	8	9	10

Wenn Sie Probleme haben und die Dinge nicht gut laufen für Sie, wie zuversichtlich sind Sie.....

1. ...dass es Ihnen gelingt zu sortieren, was veränderbar und was nicht beeinflussbar ist?

0	1	2	3	4	5	6	7	8	9	10

2. ...dass Sie emotionale Unterstützung von Freunden und Familie bekommen?

0	1	2	3	4	5	6	7	8	9	10

3. ...dass es Ihnen gelingt, Lösungen für Ihre schwierigsten Probleme zu finden?

0	1	2	3	4	5	6	7	8	9	10

4. ...dass es Ihnen gelingt, ein belastendes Problem im kleine Teilprobleme zu unterteilen?

0	1	2	3	4	5	6	7	8	9	10

5. ...dass es Ihnen gelingt, sich verschiedene Handlungsmöglichkeiten offen zu halten, wenn sich Stress entwickelt?

0	1	2	3	4	5	6	7	8	9	10

6. ...dass es Ihnen gelingt, sich einen Handlungsplan zurechtzulegen und dem nachzugehen?

0	1	2	3	4	5	6	7	8	9	10

7. … dass es Ihnen gelingt, unangenehme Gedanken aus den Kopf zu kriegen?

0	1	2	3	4	5	6	7	8	9	10

8. … dass Sie nicht traurig werden?

0	1	2	3	4	5	6	7	8	9	10

9. ...dass es Ihnen gelingt, sich von unangenehmen Gedanken nicht so sehr mitnehmen zu lassen?

0	1	2	3	4	5	6	7	8	9	10

10. ...dass es Ihnen gelingt, neue Freundschaften zu schließen?

0	1	2	3	4	5	6	7	8	9	10

11. ...dass es Ihnen gelingt, Freunde zu bitten, Ihnen bei der Erledigung notwendiger Dinge zu helfen?

0	1	2	3	4	5	6	7	8	9	10

12. ...dass es Ihnen gelingt, unangenehme Gedanken zu verscheuchen?

0	1	2	3	4	5	6	7	8	9	10

13. ...dass es Ihnen gelingt, nur an ein Teil des Problems zu Zeit zu denken?

0	1	2	3	4	5	6	7	8	9	10

(Chesney et al.,2003)

9.3.5 Sens of Coherence (SOC)

Fragebogen zur Lebensorientierung (SOC-Skala)

Nach: Antonovsky, A. (1997): Salutogenese. Zur Entmystifizierung der Gesundheit. Dt. erweiterte Herausgabe von A. Franke. Tübingen:dgtv.
Mit freundlicher Genehmigung des Verlages.

Fragebogen zur Lebensorientierung
Die folgenden Fragen beziehen sich auf verschiedene Aspekt Ihres Lebens. Auf jede Frage gibt es 7 mögliche Antworten.Bitte kreuzen Sie jeweils die Zahl an, die Ihre Antwort ausdrückt. Geben Sie auf jede Frage Antwort.

1. Wenn Sie mit anderen Leuten sprechen, haben Sie das Gefühl, das diese Sie nicht verstehen?

Haben nie das Gefühl

habe nie dieses Gefühl	1	2	3	4	5	6	7	habe immer diese Gefühl

2. Wenn Sie in der Vergangenheit etwas machen mussten, dass von der Zusammenarbeit mit anderen abhing, hatten Sie das Gefühl, dass die Sache

keinesfalls erledigt werden würde	1	2	3	4	5	6	7	sicher erledigt werden würde

3. Abgesehen von denjenigen, denen Sie sich am nächsten fühlen- wie gut kennen Sie die meisten Menschen, mit denen Sie täglich zu tun haben?

Sie sind ihnen völlig fremd	1	2	3	4	5	6	7	Sie kennen sie sehr gut

4. Haben Sie das Gefühl, dass es Ihnen ziemlich gleichgültig ist, was um Sie herum passiert?

äußerst selten oder nie	1	2	3	4	5	6	7	sehr oft

5. Waren Sie schon überrascht vom Verhalten von Menschen, die Sie gut zu kennen glaubten?

das ist nie passiert	1	2	3	4	5	6	7	das kommt immer wieder vor

6. Haben Menschen, auf die Sie gezählt haben Sie enttäuscht?

das ist nie passiert	1	2	3	4	5	6	7	das kommt immer wieder vor

7. Das Leben ist

ausgesprochen interessant	1	2	3	4	5	6	7	reine Routine

8. Bis jetzt hatte Ihr Leben

überhaupt keine klaren Ziele oder Zweck	1	2	3	4	5	6	7	sehr klare Ziele und einen Zweck

9. Haben Sie das Gefühl, ungerecht behandelt zu werden

sehr oft	1	2	3	4	5	6	7	sehr selten oder nie

10. In den letzten zehn Jahren war Ihr Leben

voller Veränderungen, ohne dass Sie wussten was als nächstes passiert	1	2	3	4	5	6	7	ganz beständig und klar

11. Das meiste, was Sie in Zukunft tun werden, wir wahrscheinlich

völlig faszinierend sein	1	2	3	4	5	6	7	todlangweilig sein

12. Haben Sie das Gefühl, in einer ungewohnten Situation zu sein und nicht zu wissen, was Sie tun sollen?

sehr oft	1	2	3	4	5	6	7	sehr selten oder nie

13. Was beschreibt am besten, wie Sie das Leben sehen?

man kann für schmerzliche Dinge im Leben immer eine Lösung finden	1	2	3	4	5	6	7	es gibt keine Lösung für schmerzliche Dinge

14. Wenn Sie über Ihr Leben nachdenken, passiert es sehr häufig, dass Sie

fühlen, wie schön es ist zu leben	1	2	3	4	5	6	7	sich fragen, warum Sie überhaupt da sind

15. Wenn Sie vor einem schwierigen Problem stehen, ist die Wahl einer Lösung

immer verwirrend und schwierig	1	2	3	4	5	6	7	immer völlig klar

16. Das, was Sie täglich tun, ist für Sie eine Quelle

i

tiefer Freude und Zufriedenheit	1	2	3	4	5	6	7	von Schmerz und Langeweile

17. Ihr Leben wird in Zukunft wahrscheinlich

voller Veränderungen sein, ohne dass Sie wissen, was als nächstes passiert	1	2	3	4	5	6	7	ganz beständig und klar sein

18. Wenn in der Vergangenheit etwas Unangenehmes geschah, neigten Sie dazu,

sich daran verzehren	1	2	3	4	5	6	7	zu sagen: „Nun gut, sei's drum, ich muss damit leben“ und weitermachen

19. Wie oft sind Ihre Gefühle und Ideen ganz durcheinander?

sehr oft	1	2	3	4	5	6	7	selten oder nie

20. Wenn Sie etwas machen, dass Ihnen ein gutes Gefühl gibt,

werden Sie sich sicher auch weiterhin gut fühlen	1	2	3	4	5	6	7	wird sicher etwas geschehen, das das Gefühl verdirbt

21. Kommt es vor, dass Sie Gefühle haben, die Sie lieber nicht hätten?

sehr oft	1	2	3	4	5	6	7	selten oder nie

22. Sie nehmen an, dass Ihr zukünftiges Leben

ohne jeden Sinn und Zweck sein wird	1	2	3	4	5	6	7	voller Sinn und Zweck sein wird

23. Glauben Sie, dass es in Zukunft *immer* Personen geben wird, auf die Sie zählen können?

Sie sind sich dessen ganz sicher	1	2	3	4	5	6	7	Sie zweifeln daran

24. Kommt es vor, dass Sie das Gefühl haben, nicht genau zu wissen, was gerade passiert?

sehr oft	1	2	3	4	5	6	7	selten oder nie

25. Viele Menschen-auch solche mit starken Charakter- fühlen sich in bestimmten Situationen wie ein Pechvogel oder Unglücksrabe. Wie oft haben Sie sich in der Vergangenheit so gefühlt?

nie [1] [2] [3] [4] [5] [6] [7] sehr oft

26. Wenn etwas passiert, fanden Sie im allgemeinen, dass dessen Bedeutung

über- oder unterschätzten [1] [2] [3] [4] [5] [6] [7] richtig einschätzten

27. Wenn Sie an Schwierigkeiten denken, mit denen Sie in wichtigen Lebensbereichen wahrscheinlich konfrontiert werden, haben Sie das Gefühl, dass

es Ihnen immer gelingen wird, die Schwierigkeiten zu meistern [1] [2] [3] [4] [5] [6] [7] Sie die Schwierigkeiten nicht werden meistern können

28. Wie oft haben Sie das Gefühl, dass die Dinge, die Sie täglich tun, wenig Sinn haben?

sehr oft [1] [2] [3] [4] [5] [6] [7] selten oder nie

29. Wie oft haben sie Gefühle, bei denen Sie sich nicht sicher sind ob Sie sie kontrollieren können?

sehr oft [1] [2] [3] [4] [5] [6] [7] selten oder nie

9.3.6 Frenchay Activity Index (FAI)

Frenchay Activity Index

In den letzten 3 Monaten, wie häufig haben Sie folgende Tätigkeiten vollbracht:

		Nie	Seltener als einmal pro Woche	1-2 mal pro Woche	An den meisten Tagen
1	Zubereitung der Haupmahlzeiten	0	1	2	3
2	Abwaschen	0	1	2	3
		Nie	1-2 mal in 3 Monaten	3-12 mal in 3 Monaten	Mindestens einmal pro Woche
3	Wäsche waschen	0	1	2	4
4	Leichte Hausarbeit	0	1	2	4
5	Schwere Hausarbeit	0	1	2	4
6	Einkaufen in der Umgebung	0	1	2	4
7	Ausgehen (Freunde treffen, Kino..)	0	1	2	4
8	Spazieren gehen für mehr als 15 Minunten	0	1	2	4
9	Aktiv ein Hobby nachgehen	0	2	2	4
10	Auto fahren/ Bus benutzen	0	1	2	4

In den letzten 6 Monaten wie häufig haben Sie folgende Tätigkeiten vollbracht

		Nie	1-2 mal in 6 Monaten	3-6 mal in 6 Monaten	Mindestens alle 14 Tage
11	Urlaubsreise/ Längere Autofahrten	0	1	2	4
12	Gartenarbeit	0	1	2	3
13	Haushalt/ Auto..	0	1	2	3
		Nie	1 mal in 6 Monaten	Seltener als alle 14 Tage	Mehr als einmal in 14 Tagen
14	Ein Buch gelesen	0	1	2	3
		Nie	Bis zu 10 Stunden pro Woche	10-30 Stunden pro Woche	Mehr als 30 Stunden pro Woche
15	Erwerbsarbeit	0	1	2	3
	Total				

According to (Halbrook and Skilbeck, 1983)

9.3.7 Leisure Activities

Freizeitaktivitäten nach Stern

Wie oft sind Sie /haben Sie in dem letzten Monat.....	Oft (2)	Manchmal (1)	Nie (0)
	Mehr als 1x/Monat	Mindeste 1x in3 Monaten	weniger
• in Lesungen oder Konzerte gegangen			
• in das Theater oder Kino gegangen			
• Gereist oder haben Ausflüge unternommen			
	Mehr als 4x /Monat	1-3x/ Monat	weniger
• Spazieren gegangen oder Fahrrad gefahren			
• Gemalt /gezeichnet/ gebastelt oder ein anderes künstlerisches Handwerk ausgeübt			
• Gesungen oder ein Musikinstrument gespielt			
• Freunde oder Nachbarn eingeladen oder diese besucht			
• Sich sportlich betätigt oder getanzt			
• Als Freizeitbeschäftigung gekocht oder Essen zubereitet			
• Als Mitglied an einer Gruppe oder Organisation teilgenommen			
• In die Kirche gegangen oder haben Sie an anderen kirchlichen Aktivitäten teilgenommen			
• ehrenamtlich gearbeitet			

According to (Scarmeas et al, 2001 and Schwarz et al, 2013)

9.3.8 Godin Leisure- Time Exercise Questionnaire (GLTQ)

Godin Leisure-Time Exercise Questionnaire

1. Wie häufig machen sie durchschnittlich, in einem typischen **7-Tage Zeitraum** (eine Woche), eine der folgenden Übungen für **mehr als 15 Minuten** in Ihrer Freizeit?

a) anstrengende Übungen
{z.B. Rennen, Joggen, Fußball, Squash, Basketball, Skiwandern, Judo, Roller blade, energisches Schwimmen, energisches Radfahren über längere Strecken) _____ mal pro Woche

b) moderate Übungen
(z.B. schnelles Gehen, Walken, Tennis, lockeres Fahrradfahren, Volleyball, Badminton, lockeres Schwimmen, Skifahren, Tanzen) mal pro Woche _____ mal pro Woche

c) leichte Übungen
(z.B. Yoga, Bogenschießen, Fischen, Bowling, gölf, Spazieren) mal pro Woche _____ mal pro Woche

2. Wie häufig machen sie in Ihrer Freizeit, in einem typischen **7-Tage Zeitraum** (eine Woche), eine regelmäßige Aktivität **lang genug, um ins Schwitzen zu kommen** (Herz schlägt schnell)?

Oft	Manchmal	Selten oder Nie
1. ☐	2. ☐	3 ☐

According to (Godin and Shephard, 1985

9.3.9 Hamburg Quality of Life in MS (HAQUAMS)

Institut für Neuroimmunologie und
Klinische Multiple Sklerose Forschung

Im Folgenden finden Sie eine Liste mit Beschwerden, die bei MS-Patienten eine Rolle spielen können. Bitte markieren Sie mit einer Einkringelung wie zutreffend jede Aussage (in den letzten 7 Tagen) war. Fragen, die für sie nicht zutreffen bitte durchstreichen.

Mißempfindungen	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
4. Ich habe Schmerzen.	1	2	3	4	5
5. Kribbeln/Taubheitsgefühle beeinträchtigen mich.	1	2	3	4	5

Müdigkeit	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
6. Ich muß mich tagsüber ausruhen.	1	2	3	4	5
7. Ich habe Schwierigkeiten etwas anzufangen oder zu Ende zu führen weil ich müde bin.	1	2	3	4	5
8. Körperliche Betätigung führt zu einer deutlichen Zunahme meiner Müdigkeit	1	2	3	4	5
9. Ich bin aufgrund meiner Erschöpfung oft nicht in der Lage, klar zu denken.	1	2	3	4	5

Denken	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
10. Ich habe Schwierigkeiten, neue Dinge zu lernen.	1	2	3	4	5
11. Ich habe Schwierigkeiten, mich zu erinnern.	1	2	3	4	5
12. ich habe Schwierigkeiten, mich zu konzentrieren.	1	2	3	4	5
13. Ich habe Probleme, mehrere Dinge gleichzeitig zu machen.	1	2	3	4	5

Sehen	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
14. Ich habe Probleme mit dem Lesen.	1	2	3	4	5
15. Ich habe Probleme mit der Orientierung oder dem Erkennen anderer Menschen.	1	2	3	4	5

16. Ich kann gehen: *(an guten Tagen)* □ ohne Gehhilfe □ mit Gehhilfe

□ gar nicht
□ bis zu 10, 20, 50,100, 200, 300, 500, 1000 m *(Zutreffendes ankringeln)*
□ ..... km
□ unbegrenzt

Gehstrecke vor 1 Jahr: ……m/km vor 2 Jahren ……m/km

Beweglichkeit / untere Extremität	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
17. Ich habe Schwierigkeiten, Sport zu treiben oder schnell zu laufen.	1	2	3	4	5
18. Ich habe Schwierigkeiten Treppen zu steigen.	1	2	3	4	5
19. Ich habe Probleme beim Gehen innerhalb der Wohnung.	1	2	3	4	5
20. Ich habe Schwierigkeiten, sicher zu stehen.	1	2	3	4	5

Beweglichkeit / obere Extremität	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
21. Schreiben fällt mir schwer.	1	2	3	4	5
22. Es fällt mir schwer, die Wohnung zu putzen.	1	2	3	4	5
23. Ich habe Probleme, mir eine Mahlzeit zu machen.	1	2	3	4	5
24. Ich habe Probleme beim Waschen und Anziehen.	1	2	3	4	5
25. Alleine zu essen fällt mir schwer.	1	2	3	4	5

Blase / Darm	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
26. Ich habe Schwierigkeiten, meine Blase zu kontrollieren.	1	2	3	4	5
27. Ich habe unwillkürlichen Urinabgang.	1	2	3	4	5
28. Ich habe Schwierigkeiten, meinen Stuhlgang zu kontrollieren.	1	2	3	4	5

Kommunikation	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
29. Ich fühle mich von meine Freunden innerlich entfernt	1	2	3	4	5
30. Ich erhalte Unterstützung von Freunden oder Nachbarn.	1	2	3	4	5
31. Ich erhalte Unterstützung von meiner Familie.	1	2	3	4	5
32. Es ist schwierig, in der Familie von meiner Krankheit zu sprechen.	1	2	3	4	5

	gar nicht	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
33. Meine Krankheit beeinträchtigt den Kontakt zu anderen Menschen (Freunde, Verwandte, Familie).	1	2	3	4	5
34. Ich fühle mich ausgeschlossen.	1	2	3	4	5
35. Ich bin mit meinem Sexualleben zufrieden.	1	2	3	4	5

Stimmung	**gar nicht**	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
36. Ich bin deprimiert über meinen Gesundheitszustand.	1	2	3	4	5
37. Meine Krankheit macht mir Angst.	1	2	3	4	5
38. Ich kann mein Leben genießen.	1	2	3	4	5
39. Ich sehe einen Sinn in meinem Leben.	1	2	3	4	5
40. Ich habe Lust, etwas zu tun.	1	2	3	4	5
41. Haben sie sich in den letzten 2 Wochen an den meisten Tagen und die meiste Zeit des Tages deprimiert oder bedrückt gefühlt?	1	2	3	4	5
42. Haben sie in den letzten 2 Wochen kein Interesse, gehabt irgendetwas zu tun oder haben sie keine Freude an Dingen gehabt, die ihnen sonst Spaß gemacht haben?	1	2	3	4	5

Gesamtbild

43. Ich bin derzeit mit meiner Lebensqualität zufrieden.	1	2	3	4	5

44. Wie massiv beeinflußt insgesamt die MS ihre Fähigkeit ein normales Leben zu führen?
(Eine Markierung bei 1 würde bedeuten, daß die MS keinen Einfluß auf ihre Stellung im Leben, im Beruf, in der Familie hat. Eine Markierung bei 5 meint, daß die MS Sie völlig unfähig macht, ein normales Leben zu führen und damit völlig abhängig von ihrer Umwelt.)

gar nicht				**sehr**
1	2	3	4	5

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9.3.10 Demography

Fragebogen zum sozidemographischen Hintergrund		
Alter (Jahre):		1
Staatsangehörigkeit	(1) Deutsch (2) Andere	2
Familienstand	(1) ledig (2) verheiratet (3) geschieden/getrennt lebend (4) verwitwet	3
Leben Sie mit einem festen Partner?	(0) Nein (1) Ja	4
Wie viele Kinder haben Sie?		5
Wie viele Personen leben ständig in Ihrem Haushalt, Sie selbst eingeschlossen?		6
Wie viele davon sind über 18 Jahre?		7
Was ist Ihr höchster Schulabschluss?	(0) keinen Schulabschluss (1) Hauptschule/Volksschule (2) Realschule/mittlere Reife (3) Abitur/Allgemeine Hochschulreife (4) Polytechnische Oberschule (5) Fachhochschulreife (6) anderer Schulabschluss	8
Welche abgeschlossene Berufsausbildung haben Sie?	(0) keine Berufsausbildung (1) Lehre (berufliche – betriebliche Ausbildung) (2) Fachschule (Meister-, Technikerschule, Berufs-, Fachakademie) (3) Universität, Hochschule (4) andere Berufsausbildung	9
Sind Sie zurzeit erwerbstätig?	(1) Ja, ganztags (2) Ja, halbtags (3) Nein, Hausfrau/Hausmann (4) Nein, in Ausbildung (5) Nein, arbeitslos, erwerbslos (6) Nein, Erwerbs-, Berufsunfähigkeitsrente (7) Nein, Altersrente (8) Nein, anderes (z.B. Mutterschutz)	10
Berufstätigkeit in Stunden pro Woche	….bis….. Stunden:	11

Welche berufliche Stellung haben Sie?	(1) Angestellter/in (2) Beamter/in (3) Selbständige/r (4) sonstiges	12
Wie hoch ist ihr monatliches Bruttoeinkommen aus nicht selbständiger Arbeit? *(als Angestellter oder Arbeiter, nicht Rente)*	(1) unter 500 € (2) 501-1000 € (3) 1001-1500 € (4) 1501-2000 € (5) 2001-2500 € (6) 2501-3000 € (7) 3001-3501 € (8) 3501 € und mehr	13
Wie hoch ist das Gesamthaushaltseinkommen netto? *(Angabe nach allen Abzügen)*	(1) unter 500 € (2) 501-1000 € (3) 1001-1500 € (4) 1501-2000 € (5) 2001-2500 € (6) 2501-3000 € (7) 3001-3501 € (8) 3501 € und mehr	14
Arbeitsveränderungen durch MS		
Erfolgte eine Berentung/Arbeitszeitreduktion aufgrund der MS?	(0)Nein (1) Berentung (2) ….. bis …..Stunden Arbeitsreduktion	15
An wie vielen Tagen waren Sie MS bedingt in den letzten 3 Monaten krankgeschrieben	(0) nicht krankgeschrieben (1) ..…bis…. Tage krankgeschrieben	16
MS Demografie:		
Welche Verlaufsform liegt vor?	(1) Erstmanifestation einer MS (2) schubförmige MS (3) sekundär chronische MS (4) primär chronische MS mit Schüben (5) unklar	17
Hat sich die Krankheit in den letzten 12/24/36 Monaten gebessert/verschlechtert?	(1) deutlich gebessert (2) gebessert (3) gleich geblieben (4) schlechter (5) deutlich schlechter	18
Schübe (*jeweils Angabe der Anzahl*)		
Schubanzahl im letzten Jahr: Schubanzahl in den ersten 2 Jahren		19

Schubanzahl seit Diagnosebeginn:		20
davon kortisontherapiert (*Anzahl*):		21
MS-Management		
Von welchem Arzt lassen Sie sich in Sachen MS betreuen?	(1) Hausarzt (2) Neurologen (3) MS-Ambulanz (4) Augenarzt (5) Urologe (6) Hausarzt und Neurologe (7) Hausarzt und MS-Ambulanz (8) Neurologe und MS-Ambulanz (9) Hausarzt, Neurologe und MS-Ambulanz (10) andere Kombination (11) gar nicht	22
Wie oft haben Sie in den letzten 12/24/36 Monaten mit einem Arzt/MS-Ambulanz wegen Ihrer MS telefoniert?	(0) gar nicht (1) einmal (2) zweimal (3) mehr: …..	23
davon:	…-mal MS-Ambulanz …-mal Hausarzt *(Allgemeinarzt, Internist)* …-mal andere:	24
Nehmen Sie ein MS-spezifisches Immunmedikament ein? Oder haben Sie im Verlauf der Erkrankung eine Zeitlang ein MS-Spezifisches Medikament eingenommen?	(0) Nein (1) Betaferon® (2) Avonex® (3) Rebif® (4) Copaxone® (5) Immunglobuline (6) Azathioprin (Imurek®) (7) Mitoxantron (Novantron®) (8) Methotrexat (9) Cyclophosphamid (Endoxan®) (10) anderes:	25
Seit wann nehmen Sie dieses Medikament? Oder wie lange haben Sie das Medikament genommen?	seit…….. Monaten ……Monate	26
Andere Medikamente zur Behandlung von Beschwerden bei MS?	(0) Nein (1) Ja	27
Haben sie im letzten Jahr regelmäßig Physiotherapie	(0) Nein (1) Ja durchgehend	28

bekommen?	(2) Ja zeitlich begrenzt	
Wenn durchgehend eine Physiotherapie erfolgte, wie oft in der Woche fand sie statt?	(1) einmal (2) zweimal (3) öfter:……. *(Angabe der Anzahl)*	39
Wenn nur zeitweise eine Physiotherapie erfolgte, wie viele Einzelbehandlungen erfolgten im letzten Jahr?	.....bis..... Wochen im letzten Jahr ….. bis ….. Behandlungen pro Woche	30
Haben sie im letzten Jahr regelmäßig Ergotherapie bekommen?	(0) Nein (1) Ja	31
Haben sie im letzten Jahr regelmäßig Logopädie bekommen?	(0) Nein (1) Ja	32
Waren Sie MS-bedingt schon einmal in einer Klinik oder ambulanten Reha?	(0) Nein (1) Ambulante oder stationäre Reha (2) Klinik	33
Wenn ja: Was war der Grund für den Klinikaufenthalt? Wie lange war der Aufenthalt:	(1) Schubtherapie (2) andere MS-bedingte Gründe:…… ……..	34

9.3.11 Additional Questions

1. Wie sehr beeinträchtigt die MS ihre
   1. Freizeitaktivitäten (nicht/ wenig/ stark)
   2. Ihre sozialen Kontakte (nicht/ wenig/ stark)
   3. Ihre wirtschaftliche Situation (nicht/ wenig/ stark)
   4. Ihre alltäglichen Aktivitäten auf einer Skala 0(=gar nicht) bis 10(=sehr stark)
2. Wie gut können sie ihre Arbeit verrichten (gut, ok, nicht gut (anstrengend))
3. Würden sie sich als einen aktiven oder inaktiven Menschen beschreiben?
4. Wären sie gerne aktiver? (ja/nein)
5. Wenn ja fühlen sie sich durch die MS hier hingegen eingeschränkt? (ja/nein)
6. Wie glauben sie, dass ihre MS für Sie verläuft? (eher gutartig, neutral, eher bösartig)
7. Was verstehen sie unter einer gutartigen (benignen) MS Verlaufsform: .....

9.4 Comparison of outcomes

9.4.1 Frenchay activity index (FAI)

Addendum Table1: Comparison of Frenchay activity index (FAI) outcomes with a Stockholm MS population

Frenchay activity index (FAI)	**Current cohort**	**Einarsson et al. 2006**
n=	94	164
Question (Code in %)		
1 Preparing Meals (0/1/2/3)*	12/ 7/ 22/ 59	34/ 6/ 11/ 49
2 Washing up after meals (0/1/2/3)*	7/ 8/ 17/ 69	29/ 1/ 21/ 49
3 Washing clothes (0/1/2/3)**	10/ 6/ 11/ 74	38/ 2/ 9/ 51
4 Light housework (0/1/2/3)**	2/ 7/ 14/ 77	32/ 3/ 12/ 53
5 Heavy housework (0/1/2/3)**	13/ 21/ 29/ 37	61/ 4/ 8/ 26
6 Local shopping (0/1/2/3)**	4/ 2/ 10/ 84	34/ 2/ 10/ 54
7 social occasions(meeting friends, cinema…) (0/1/2/3)**	2/ 19/ 35/ 44	14/ 16/ 31/ 39
(8) walk outside for more than 15 minutes (0/1/2/3)**	1/ 7/ 62/ 31	59/ 2/ 6/ 33
9 actively pursuing hobby (0/1/2/3)**	15/ 13/ 12/ 58	49/ 2/ 9/ 40
10 driving car/going on bus (0/1/2/3)**	2/ 6/ 6/ 86	43/ 2/ 5/ 49
12 gardening (0/1/2/3)****	40/ 18/ 15/ 28	68/ 12/ 12/ 9
13 household maintenance (0/1/2/3)****	4/ 11/ 20/ 65	59/ 19/ 14/ 8
14 reading books (0/1/2/3)*****	12/14/14/59	38/ 17/ 29/ 17
15 gainful work(0/1/2/3)******	33/ 8/ 25/ 34	58/ 2/20/21

[1] Mean, [2] (SD),
* in the last 3 months (0: never; 1: <1x/week; 2: 1-2 x/ week; 3: during the most days)
** in the last 3 months (0: never; 1:1-2 x in 3 months; 2: 3-12x in 3 months; 4: at least 1x/week)
*** in the last 6 months (0: never, 1: 1-2x in 6 months; 2: 3-12x in 6 months; 4: at least every 14 days)
**** in the last 6 months (0: never, 1: 1-2x in 6 months; 2: 3-12x in 6 months; 3: at least every 14 days)
***** in the last 6 months (0: never, 1: 1x in 6 months; 2: <14 days in 14 days; 3 > 1x in 14 days)
****** in the last 6 months (0: never, 1: up to 10 hours/ week; 2: 10-30 hours per weeks; 3: at least 30 hours per week

9.4.2 Stern Leisure Activities

AddendumTable 2: Comparison of Stern leisure activity outcomes with a MS US cohort

Stern Leisure Activities		**Cohort** n= 94, (missing =3)	**Schwarz et al. 2013** n=1142
How often have you … in the past month?		%	%
1. Gone to lectures or concerts?	often	6	6
	sometimes	34	32
	never	60	62
2. Gone to the theatre or movies?	often	12	6
	sometimes	36	34
	never	52	60
3. Traveled or gone on tours?	often	33	10
	sometimes	43	35
	never	24	55
4. Gone for walks or rides?	often	58	30
	sometimes	17	48
	never	25	22
5. Done arts and crafts or hobbies?	often	15	20
	sometimes	13	38
	never	71	42
6. Sang or played a musical instrument?	often	18	14
	sometimes	7	28
	never	76	58
7. Visited with relatives, friends, or neighbors in your home or theirs?	often	41	37
	sometimes	44	56
	never	15	7
8. Taken part in sports, dancing or exercice?	often	42	27
	sometimes	21	34
	never	37	39
9. Cooked or prepared food as a hobby?	often	43,	27
	sometimes	25	37
	never	32	36
10. Participated as a member of a	often	30	28
	sometimes	13	37

group or organization?	never	57	34
11. Participated in church or religious activities?	often	13	26
	sometimes	10	20
	never	77	54
12. Done volunteer work?	often	19	26
	sometimes	13	20
	never	67	54

9.4.3 Overview: comparison with normative data from Literature

Test Items (range)	**BEGIMS Cohort** n, mean (SD)	**Healthy population** n, Mean (SD)	**MS population** n, EDSS, mean (SD)	**Reference**
T25FW	n=79	US Control group n=100	US Cohort n=400,	(Drake *et al.* 2010) ***
	$\bar{x}$=5.22±1.52sec	$\bar{x}$=4.3±1.0	EDSS $\tilde{x}$= 2.5 $\bar{x}$=8.5±11.6	
TTW	n=79		Hamburg Cohort n=2648	[1](J P Stellmann *et al.* 2014) ***
	$\bar{x}$=11.52±5.68sec		EDSS $\tilde{x}$= 3.8 (0-8) $\bar{x}$=11±6.7 sec	
6MWT	n=79	US control group n=20,	US-MS patients n=40,	(Goldman and Cohen 2008) ***
	$\bar{x}$=466±122.9m	$\bar{x}$=620±49.1m	EDSS 0-2.5: $\bar{x}$=603±48.5m EDSS 3-4: $\bar{x}$=507±103m EDSS 4.5-6.5: $\bar{x}$=389±77.7m	
SOC	n= 94	[1]German Cohort n= 2005 [2]Swedish Cohort n= 145	[3]Stockholm Cohort: n= 219	[1](Schumacher et al. 2000) [2] (Ytterberg *et al.* 2008)
-**29** items (29-203) -**13** items (13-91)	**SOC 29**: $\bar{x}$=146.8±24.5 *5.1±0.84	[1] **SOC 29**: $\bar{x}$=145.66±24.33 **SOC 13**: $\bar{x}$ =65.17±11.58	[2] **SOC 13:** EDSS $\bar{x}$=x $\bar{x}$=68-75(IQR 56-81) ****	
CSES	n=94		Slovakia Cohort n= 113	(Mikula *et al.*

				2014)
- **13** items (0-130) PO: 0-60 SO: 0-40 EO: 0-30 - **26** items (0-260) PO: 0-120 SO: 0-90 EO: 0-50	**CSES 13** $\bar{x}$=82.87±28.58 *6.38±2.19 PO: *6.55±2.33 SO: *7.12±2.31 EO: *5.55±2.77		**CSES 26** EDSS $\bar{x}$=3.3±1 $\bar{x}$=167.5(x) * 6.4 PO: 77.54±22.70;* 5.6 SO: 32,90±10; *****8.2 EO: 57,01±19.56; *****9.7	
HAQUAMS	n=94		Hamburg Cohort n=117	(Schäffler *et al.* 2013)
(0-5)	$\bar{x}$= 2.06±0.64		EDSS $\bar{x}$= 3.4 (range 0-8) $\bar{x}$= 2.21±0.79	
GLTQ	n=94	[1]Toronto Cohort n=306	[2]US-NARCOMS registry n=1142, [3]US Cohort: n= 567	[1](Godin and Shephard 1985) [2](Schwartz *et al.*, 2013) [3](Motl and Klaren 2014)
	$\bar{x}$=19.55±20.55	$\bar{x}$=45.8	[2] EDSS $\bar{x}$=x $\bar{x}$=12±21.2 [3] EDSS $\bar{x}$=x $\bar{x}$=26.3±21.4	
FAI	n=94	[1] UK-Cohort, n=281	[2]Stockholm Cohort n=196	[1](Turnbull *et al.* 2000) [2](Einarsson *et al.* 2006)
(0-45)	$\bar{x}$=31.19±6.68 $\tilde{x}$= 32(4-42)	$\bar{x}$=28(0-42)	EDSS =0-3 in 25% $\bar{x}$=21±12	
QIDS	n=94	Control group n= 10	MS exercise intervention cohort n=9	(Barry et al. 2018) *****
(0-27)	$\bar{x}$=6.31 ±4.53	$\bar{x}$=2.22 ±0.62	EDSS $\bar{x}$ =2.17 ± 0.40 $\bar{x}$=8.67±1.76	
MSNQ	n=94	New York control group n= 40	New York Cohort n=74	(Benedict *et al.* 2004) *****
(0-60)	$\bar{x}$= 18.52 (9.25)	$\bar{x}$= 16.0±6.2	EDSS $\tilde{x}$=2.5(0-7.5) $\bar{x}$=27.4±11.9	

FSMC	n=94		Neuropsychological intervention group n=50	(Rosti-otajärvi *et al.* 2013) *****
(20-100) **total score** 10-50 **cog. score** 10-50 **mot. score**	$\bar{x}$ 57.43 ± 21.5 cog $\bar{x}$ 27.34±11.25 mot $\bar{x}$= 30.1±11.07		EDSS =1-4 in 94% $\bar{x}$=64.2±18.7 cog $\bar{x}$=32.3±9.2 mot $\bar{x}$=31.9±10.2	

$\bar{X}$= mean, $\tilde{x}$ = median (range), x=missing, BEGIMS=our study cohort, PO=problem orientated coping, EO= emotional orientated coping, SO= coping with social support, f= female, MID= minimally important difference, cog= cognitive, mot=motor,
*mean/question. *** walking test are not adjusted to age. In this cohorts mean age were round about 40years. **** Swedish healthy reference (n= 145) (Langius and Björvell, 1993): **SOC 29**: mean= 151±18; **SOC 13**: mean=61±9

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11. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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