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COGNITIVE AND AFFECTIVE CHANGES IN MULTIPLE SCLEROSIS, A NOVEL GROUP PSYCHOTHERAPY IN THE EARLY PHASE OF THE DISEASE

PhD thesis

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List of Abbreviations

AAN	American Academy of Neurology
ACT	Acceptance and commitment therapy
ADLs	Activities of daily living
AT	Autogenic Training
AVLT	Auditory-Verbal Learning Test
BDI	Beck Depression Inventory
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BMS	Benign multiple sclerosis
BRB-N	Brief Repeatable Battery of Neuropsychological Tests
BVMT-R	Brief Visuospatial Memory Test Revised
CBT	Cognitive behaviour therapy
CFT	Rey-Osterrieth Complex Figure Test
CI	Cognitive impairment
CIS	Clinically isolated syndrome
CNS	Central nervous system
CSF	Cerebrospinal fluid
CVLT	California Learning Verbal Test
DAS	Dysfunctional Attitude Scale
DBT	Dialectical behaviour therapy
DD	Disease duration
D-KEFS	Delis-Kaplan Executive Function System
DMT	Disease-modifying therapy
DS	Digit Span
EDSS	Expanded Disability Status Scale
EQ-i	Emotional Quotient Inventory
FSS	Fatigue Severity Scale
HA	Health anxiety
HADS	Hospital Anxiety and Depression Scale
IQR	Interquartile range
MACFIMS	Minimal Assessment of Cognitive Function in MS

MFIS	Modified Fatigue Impact Scale
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
NICE	National Institute of Clinical Excellence
PASAT	Paced Auditory Serial Addition Test
PASAT-3	Paced Auditory Serial Attention Test 3 seconds
PPMS	Primary progressive multiple sclerosis
PST	Processing Speed Test
QoL	Quality of life
RAVLT	Rey Auditory Verbal Learning Test
RIS	Radiologically isolated syndrome
ROCFT	Rey-Osterrieth Complex Figure Test
RRMS	Relapsing remitting multiple sclerosis
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SDS	Zung Self-Rating Depression Scale
SHAI	Short Health Anxiety Inventory
SPMS	Secondary progressive multiple sclerosis
SRT	Selective Reminding Test
TAS-20	Toronto Alexithymia Scale
TH	Tower of Hanoi
ToM	Theory of mind
WCST	Wisconsin Card Sorting Test
WDST	Wechsler’s Digit Symbol Test

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> "[In] most of the patients affected by multi-locular sclerosis whom I have had occasion to observe … there is marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality. The dominant feeling in the patients appears to be a sort of almost cheerful indifference in reference to all things."
> (Charcot, 1877)

1. Introduction

Multiple sclerosis (MS), the most common neurological disease that causes disability in early life, does not only influence physical functioning but is also related to cognitive impairment, fatigue, depression, and anxiety and can significantly impact quality of life (QoL). Social dimensions such as education, work and income, social life, interpersonal relationships and family life are also involved in the process of adaptation to the chronic illness. People with MS might experience isolation and reduced social support. Patients may need to alter their working patterns, type of work or give up employment, creating a heavy economic cost to individuals and their families. Taken together, it is beyond question that this chronic disease imposes a significant burden on individual, family, community and on economy at large.

Understanding the complex interplay between various factors concerning the nature of MS is of utmost importance in the management of MS. Adjustment to disease burden in different life domains creates challenges for both patients and their family members. The need for MS specific psychological interventions cannot be called into question. However, literature on the development of interventions based on the biopsychosocial model of the disease is missing and even less attention has been paid to interventions dedicated to young adults with MS.

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1.1 About multiple sclerosis

1.1.1 Pathophysiology and symptoms

Multiple Sclerosis is a chronic autoimmune neurological disease that produces demyelination and axonal loss of the central nervous system (CNS). Multifocal inflammation results in the formation of CNS plaques in both white and grey matter. These lesions can influence the transmission of nerve impulses and lead to neuronal dysfunction such as sensorimotor defects, visual disturbances, ataxia, autonomic symptoms, fatigue, cognitive dysfunctions and emotional problems. MS symptoms are unpredictable and uncertain. They differ among individuals and over time. Symptoms can be mild or severe, and temporary or persistent. Common symptoms of MS include sensory disturbances (numbness, tingling, itching, burning), walking difficulties (due to fatigue, weakness, spasticity, loss of balance, tremor), vision problems (diplopia, blurred vision, pain on eye movement), dizziness and vertigo, intestinal and urinary system dysfunction (constipation, bladder dysfunction), cognitive impairment, depression, or sexual problems. Less common symptoms are dysarthria and dysphagia, breathing problems, hearing loss, seizures and headache (Gelfand, 2014).

The functional systems can be quantified with the Expanded Disability Status Scale (EDSS) in the range between 0 (normal neurological exam) and 10 (death due to MS) (Kurtzke, 1983). However, it is the most widely used disability score, cognitive impairment seems underrepresented, while neuropsychiatric and cognitive symptoms are a major cause of loss of employment, and poor QoL of patients (Clemens & Langdon, 2018).

1.1.2 MS types and courses

In MS pathophysiological changes occur before the first clinical sign of the disease (Kurtzke, 2000). The clinical heterogeneity of MS implicates that MS might be a spectrum of diseases representing different processes. MS can be categorized in different phenotypes, and can be subclassified according to its clinical and radiological activity (Lublin et al., 2014). These phenotypes are associated with hypothetically different

pathological disease mechanisms, including acute or chronic inflammation, axonal, neuronal loss and gliosis, and variable degrees of tissue recovery, including plasticity and clinical recovery (Macías Islas & Ciampi, 2019).

In case of radiologically isolated syndrome (RIS) – or asymptomatic MS – lesions are detected on magnetic resonance imaging (MRI) done for distinct reasons. Clinically isolated syndrome (CIS) refers to a first at least 24-hour-long neurological episode that can be mono- or poly-symptomatic (Dobson & Giovannoni, 2019). During the course, relapses are defined as new or deteriorating neurological symptoms lasting longer than 24 hours, in the absence of fever or infection.

Based on the course of the disease three major subtypes can be distinguished: relapsing remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).

RRMS is the most common form, affecting approximately 85% of MS patients. It is characterized by acute relapses followed by periods of remission, when symptoms improve or disappear. SPMS develops in around 65% of patients with RRMS 10-15 years after disease onset. The disease course continues to worsen to a slowly progressive disease. PPMS affects approximately 5-15% of MS patients. From the beginning it is characterized by gradually worsening symptoms (Lublin et al., 2014).

A subgroup of patients show little or no disease progression and minimal disability minimum a decade after the clinical onset. This condition is named as benign MS (BMS). As BMS remains an “a posteriori” definition based on the EDSS, it has been receiving growing attention in order to accurately diagnose and predict benign cases (Correale, Ysrraelit, et al., 2012; Razzolini et al., 2018). Despite preservation of motor functioning, the prevalence of significant cognitive impairment, depression and fatigue in BMS is comparable to those reported in MS patients at large (Correale, Peirano, et al., 2012) which may be as disabling as motor impairment resulting in an adverse effect on QoL (Gajofatto et al., 2016). These findings confirm that a simple definition of BMS on the basis of EDSS score may be misleading and the proportion of benign subjects may be overestimated (Amato et al., 2006).

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1.1.3 Epidemiology and aetiology

MS is the most common disabling neurological disease, usually diagnosed in young adulthood. The prevalence of MS in Hungary has been reported to be 130.8/100000. The female/male ratio of prevalent cases is 2.6 (Iljicsov et al., 2020).

The aetiology of the disease is multifactorial and there is a complex interplay between genetic and environmental factors – not yet fully understood. Migration studies indicate that the susceptibility is determined by the residence of the childhood. Viral infections, such as Epstein-Barr virus, and certain autoimmune diseases have been linked to MS. Low vitamin D level, cigarette smoking and obesity have been identified as risk factors (Thompson, Baranzini, et al., 2018).

1.1.4 Diagnosis and treatment

There is no definite measure or laboratory marker for the diagnosis of MS. It is based on the diagnostic criteria proposed by McDonald in 2001, revised in 2005, 2010, and 2017. The diagnosis relies on the clinical features of the disease, comprehensive history taking, neurological examination and paraclinical tests, such as MRI, evoked potential studies and cerebrospinal fluid (CSF) analyses in the absence of a better explanation (Thompson, Banwell, et al., 2018).

Management of MS includes treatment of relapses, disease-modifying therapies (DMT) and controlling symptoms associated with the illness. DMTs have proven to be beneficial in reducing the rate of relapses and MRI activity affecting their QoL (Gombos et al., 2017), with a more discrete efficacy over reducing disability progression or the brain atrophy (Montalban et al., 2017; Thompson, Banwell, et al., 2018). A recent study provides evidence that, for RRMS patients, long-term – over 15 years – exposure to immunotherapy is effective in improving disability outcomes (Kalincik et al., 2021). New therapies with higher-efficacy and more convenient administration in treatment of all forms of MS have improved tolerability and adherence (Hauser & Cree, 2020).

1.2 Cognitive impairment in MS

Cognition includes several correlated and interdependent cognitive domains:

- complex attention: sustained attention, divided attention, selective attention, processing speed,
- executive functions: planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility,
- learning and memory: immediate and recent memory, including free recall, cued recall and recognition memory, very-long-term memory, including semantic, autobiographical memory, implicit learning,
- language: expressive language including naming, word finding, fluency and grammar, and syntax, and receptive language,
- perceptual-motor function: visual perception, visuo-constructional, perceptual-motor, praxis and gnosis, and
- social cognition: recognition of emotions, theory of mind (American Psychiatric Association, 2013).

Dysfunction of different domains may result in impairment of the global cognitive function (Woodruff, 2011).

Cognitive impairment (CI) affects 40-65% of MS patients (Amato et al., 2006), partly independent from the course and stage of the disease (Johnen et al., 2017). Most frequently involved cognitive domains are information processing speed, learning and episodic memory with additional difficulties in executive functions, working memory, verbal fluency and word list generation, complex attention, and visuospatial skills (Benedict et al., 2006; Benedict et al., 2002). Core language abilities (Chiaravalloti & DeLuca, 2008), semantic memory, and attention span are rarely impaired (Hegedüs, Kárpáti, Szombathelyi, Simó, 2015; Benedict et al., 2020). However, among elderly patients semantic fluency seems to be more affected that may suggest other aetiology (Jakimovski et al., 2019). Social cognition has been demonstrated to be affected, as well, with a larger impact in theory of mind (ToM) and in the recognition of negative facial emotional expressions (Cotter et al., 2016). This cognitive domain plays an important role in developing and maintaining deep social interactions (Labbé et al., 2018) and affects moral evaluation of others' actions (Patil et al., 2017).

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Table 1 Cognitive dysfunction in MS: frequency of cognitive impairment in different cognitive domains.
(Benedict et al., 2006; Chiaravalloti & DeLuca, 2008; Jack Cotter et al., 2016; Macías Islas & Ciampi, 2019; Rao et al., 1991)

Cognitive domain	Frequency (%)
Complex attention	5-25
Information processing speed	15-50
Executive function	15-25
Working memory	15-60
Inhibitory control	15-30
Learning and memory	40-65
Visual episodic memory	20-75
Verbal episodic memory	15-80
Language	20-58
Verbal fluency	15-25
Visuospatial skills	12-19
Social cognition	20-40

Recently word-finding difficulty (Brandstadter et al., 2020) and multitasking deficit (Glukhovsky et al., 2020) have been reported in early MS. Considering the life task of young adulthood (effectively managing multiple simultaneous aims), multitasking is more related to real-world functioning compared to monotasking. Hence it would be an important field to explore (Sumowski et al., 2018).

Information processing speed is one of the basic elemental cognitive functions, therefore it may interfere with higher cognitive processes such as learning, memory, word retrieval, and executive functions (Benedict et al., 2017; Costa et al., 2017) which has an implication regarding rehabilitation. Furthermore, it can be the first cognitive domain to be affected in MS (Van Schependom et al., 2015).

Impaired learning of new information seems to be the primary problem for explaining memory deficits (Deluca et al., 2013), while encoding, storing, and recall from long-term storage seems to be less affected in MS patients. Apart from slow processing speed, executive dysfunction and perceptual deficits may also influence it (Macías Islas

& Ciampi, 2019). Furthermore, impaired executive functions may be explained by a general fluid intelligence loss (Goitia et al., 2020).

1.2.1 Prevalence of cognitive impairment in different MS phenotypes

Cognitive impairment can occur in all MS subtypes even in the absence of other neurological symptoms (Johnen et al., 2017; Ruano et al., 2016): prevalence rates are 20-25% in RIS and CIS, 30–45% in RRMS, and 50–75% in SPMS. While prevalence in PPMS varies greatly due to small proportion and sample sizes in studies. In BMS patients the prevalence of significant CI is comparable to those reported in MS patients at large (Correale, Peirano, et al., 2012). In a 12-year follow-up study (Portaccio et al., 2009; Razzolini et al., 2018), patients with BMS and cognitive impairment were more likely to have clinical progression on the basis of EDSS scores (defined as no longer benign) than were MS patients with preserved cognition.

Regarding neuropsychological profile, information processing speed is mainly involved in patients with RIS, CIS or RRMS, whereas, attention, memory and executive functions are more affected in progressive subtypes (Branco et al., 2019). A recent meta-analysis has shown that PPMS patients exhibit significantly more CI in almost every cognitive domain compared to RRMS patients, particularly verbal learning and verbal memory are affected (Johnen et al., 2017).

Detected differences seem to be related to patient age and physical disability (Ruano et al., 2016). However, the phenotype itself, probably because of its specific pathological mechanism, might play an important role in the cognitive profile of patients (Brochet & Ruet, 2019).

1.2.2 Assessment of cognitive functioning

Assessment of cognitive functioning in MS patients targets the continuous monitoring of cognitive abilities in the routine clinical practice. After diagnosing MS, a systematic neuropsychological assessment should be carried out and cognitive dysfunction should be routinely screened throughout the disease course to detect clinically meaningful changes.

Neuropsychological tests included in a screening battery should be standardized, reliable, sensitive, specific, and accurate in the discrimination of patients from healthy individuals, have normative data and alternative forms (Benedict et al., 2002).

Cognitive impairment is defined as a performance that falls 1.5-2 standard deviations (SD) below normative expectation, after accounting for demographics such as age and education, in one or more cognitive domains (Macías Islas & Ciampi, 2019).

1.2.2.1 Assessment of cognitive processing speed

The Symbol Digit Modalities Test (SDMT) effectively represents the core cognitive domain of information processing speed. It is the most sensitive measure to MS cognitive dysfunction and correlates with MRI measures of atrophy, lesion burden, and microstructural pathology. It has an excellent test-retest reliability, with a sensitivity of 82% and a specificity of 60%. In order to eliminate incidental learning, alternate forms are available that are equivalent in difficulty and in reliability (Benedict et al., 2012; Benedict et al., 2017). However, the performance on SDMT is also determined by patient's working memory, paired-associate learning, and visual scanning. This is the reason why it can be the most sensitive measure in MS (Rocca et al., 2015).

Evolving from the Wechsler Digit Symbol Test (WDST) (Wechsler, 1944), the test consists of single digits paired with abstract symbols at the top of a page, with rows of the nine symbols arranged pseudo-randomly with a blank space underneath. For 90 seconds, the patient needs to write the number that corresponds with each symbol. The SDMT can be completed within 5 minutes, including instructions, practice, and testing (Smith, 1982). Oral version is administered in case of upper extremity weakness and ataxia. It is well tolerated by patients.

Regarding interpretation, there are available benchmarks: MS work disabled – 45, MS employed but work challenged – 55, MS employed and stable – 63 (Benedict et al., 2016) and a raw score change of 4 points, or a 10% in magnitude, can be understood as clinically meaningful change (Benedict et al., 2017). The test's ecological validity has been proven as SDMT scores significantly correlate with several activities of daily living (ADLs) and employment status (Benedict et al., 2017). Therefore SDMT is recommended for baseline testing, and for regular screening in clinical practice (Sumowski et al., 2018).

Processing Speed Test (PST) application is a self-administered version of SDMT. Its advantages are its efficient administration, scoring without technician, and potential for medical record or research database integration. Additional data (e.g., inter-response times and learning curves) can be measured. It has multiple forms to minimize practice effects. Its psychometric properties are comparable with the ones of SDMT. Therefore PST could be a practical tool for routine screening of cognitive processing speed (Rao et al., 2014; Rao et al., 2017).

As ocular motor functions and visual acuity can influence the SDMT performance (Costa et al., 2017), Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977) is recommended instead to assess cognitive processing speed in case of visual impairment (Sumowski et al., 2018). It measures specifically auditory information processing speed and flexibility, working memory, and sustained attention. Although the performance might be influenced by calculation ability. PASAT has high sensitivity, however, continuous utilization might reduce its validity (Tombaugh, 2006). Two alternate forms are available.

In PASAT, single digits are presented either every 3 s (or every 2 s) and the patient has to add 60 pairs by adding each digit to the immediately preceding one. The test score is the number of correct sums given in each trial (Rao et al., 1989).

Although it has been widely used in MS studies and neuropsychological batteries, it is not recommended for cognitive monitoring in clinical practice, nor for clinical trials designed with multiple administrations because of practice effect, poor tolerability by patients, and test-related anxiety (Sumowski et al., 2018).

1.2.2.2 Assessment of episodic verbal memory

California Verbal Learning Test-II (CVLT) is a verbal learning and memory test (Delis et al., 2000). It has high sensitivity with age and sex adjusted normative data (Sumowski et al., 2018). One standard and one alternate form is available. It uses a 16-item word list, with four items belonging to four semantic categories, arranged randomly. The list is read aloud five times in the same order to the patient. In each trial, the participant is required to recall as many items as possible, in any order. It is followed by an immediate and a delayed recall task, in which the patient recalls the same information

without another exposure to the word list. Scores include the sum of words recalled within each trial, and the sum of words recalled across the first five trials. It is recommended for clinical use, however, practice effect shall be considered when more than two administrations are required (Macías Islas & Ciampi, 2019).

A valid and cost-effective alternative to the CVLT-II is the Rey Auditory Verbal Learning Test (RAVLT) (Beier et al., 2019). It is a widely-used and reliable assessment of auditory verbal learning and memory (Lezak, 1995). It has been validated in different neurological populations (Schoenberg et al., 2006). The only difference compared to CVLT-II is that 15 unrelated words are presented in the first five trials.

As a result of the learning-deficit hypothesis of memory impairment in MS (Deluca et al., 2013), the first five trials of verbal memory tests are used in clinical practice for screening. Even an abbreviated version of the CVLT-II, the first two learning trials, has an accuracy of 97.5% compared with all five learning trials (Gromisch et al., 2013).

Selective Reminding Test (SRT) allows to separate long-term storage, retrieval from long-term storage, and recall from short-term storage in verbal-list learning tasks (Buschke, 1973). The test has high sensitivity (Benedict et al., 2017). Several alternate forms are available, however, further validation in MS is needed (Sumowski et al., 2018). Usually 12 unrelated words are presented in the first SRT trial. On the immediately preceding trial, only the items not recalled are said while the subject needs to repeat both reminded and not reminded words. The procedure is repeated until the recall of all 12 words for three consecutive trials or the completion of 12 trials in case of unattainable performance.

1.2.2.3 Assessment of episodic visuospatial memory

Brief Visuospatial Memory Test Revised (BVMT-R) is a visual learning and memory test (Benedict, 1997). Among memory tests used in MS, it is the most sensitive. It has high sensitivity, good reliability and validity. It has six alternate forms. It is time efficient, and well tolerated by patients although severe motor impairment influences the assessment (Sumowski et al., 2018). It is nearly as effective as SDMT at distinguishing cognitive impairment in MS patients from otherwise healthy individuals (Benedict et al.,

2020). Similarly to CVLT, only the learning trials of BVMT-R is recommended for routine clinical practice (Langdon et al., 2012).

In the first three learning trials of BVMT-R, a 2x3 matrix of abstract geometric figures is presented for 10 s. After exposure, the patient is required to draw the matrix with the correct shapes in the correct position and to retain the same information over 20-30 minutes.

Rey-Osterrieth Complex Figure Test (ROCFT) (Rey, 1941; Osterrieth, 1944) examines perceptual organization and visual memory involving attention and executive functions (decision making, planning strategies), as well. Its advantages are the availability, easy application, standardization and language independence. In case of motor deficit of the dominant hand, non-dominant hand can be used as it does not influence test performance in memory task (Yamashita, 2010). ROCFT can differentiate patients with MS and healthy subjects (Dimitrov et al., 2015). It has an alternate form (Modified Taylor Complex Figure), which is considered similar to ROCF in terms of copy and recall scores (Hubley & Jassal, 2006). During the test, the patient is required to copy a complex figure with 18 elements, then to draw the same figure by memory, and later to reproduce it after an interference period.

1.2.2.4 Assessment of executive functions

Delis-Kaplan Executive Function System (D-KEFS) (Fine & Delis, 2011) Sorting Test serves as a measure of reasoning, categorization abilities, problem solving, abstraction, flexibility of thinking and concept-formation skills. It has good validity, adequate reliability, and moderate sensitivity. Alternate forms are available. As administration time is long, it is recommended for a comprehensive clinical evaluation (Sumowski et al., 2018). Compared to Wisconsin Card Sorting Test (WCST) (Lezak, 2012), that has comparable results in MS (Parmenter et al., 2007), D-KEFS Sorting Test discriminates verbal and non-verbal modalities of concept formation and does not employ the right/wrong feedback procedure that could be discouraging. It can differentiate MS patients with increased self-perception of cognitive decline, depression and higher physical disability (Riccardi et al., 2019).

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1.2.2.5 Assessment of social cognition

An experts' consensus is needed regarding the assessment of social cognition in MS with exploring sensitivity, specificity and reliability (Macías Islas & Ciampi, 2019). Usually Face Emotion Recognition Test (Ekman & Friesen, 1976) is used for social perception and Faux Pas Test (Stone et al., 1998) for ToM abilities. The Face Emotion Recognition consists of pictures of faces displaying the six primary emotions. The participant needs to recognize and point the label that best describes the facial expression. While the Faux Pas Test is comprised by ten short stories in which a character involuntarily hurts or offends another. Using ToM, patient is expected to recognize the other's mental state, beliefs and emotions. Half of the test contains control stories.

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Table 2 Summary of neuropsychological tests used in MS by cognitive domains.

Cognitive domain	Test	Validated in Hungarian
Cognitive processing speed	SDMT	Y
Cognitive processing speed, working memory, complex attention	PASAT	Y
Verbal memory	CVLT-II	Y
	RAVLT	Y
	SRT	N
Visuospatial memory	BVMT-R	Y
	10/36 SPART	N
	RCFT	Y
Visuospatial processing	JLO	Y
Verbal fluency	COWAT	Y
	Word List Generation Test	Y
Executive function	D-KEFS Sorting Test	N
Social cognition	Face Emotion Recognition	Y
	Faux Pas Test	Y

BVMT-R = Brief Visuospatial Memory Test, Revised; COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test, second edition; D-KEFS = Delis-Kaplan Executive Function System; JLO = Judgment of Line Orientation; PASAT = Paced Auditory Serial Addition Test; RAVLT = Rey Auditive Verbal Learning Test; RCFT = Rey Complex Figure Test; SDMT = Symbol Digit Modalities Test; SPART = Spatial Recall Test; SRT = Selective Reminding Test.

Y = yes; N = no.

1.2.2.6 Neuropsychological batteries in MS

The three most frequently used and validated neuropsychological test batteries for the assessment of cognitive impairment in MS are:

(1) the 45-min Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Rao, 1991),

(2) the 90-min Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2006), and

(3) the 15-min Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Langdon et al., 2012).

The subtests of these batteries are shown in Table 3.

Table 3 Summary of neuropsychological batteries for patients with MS.

Cognitive domain	BRB-N	MACFIMS	BICAMS
Cognitive processing speed	PASAT, SDMT	PASAT, SDMT	SDMT
Verbal memory	SRT	CVLT-II	CVLT-II five recall trials
Visuospatial memory	10/36 Spatial Recall Test	BVMT-R	BVMT-R three recall trials
Visuospatial processing	-	JLO	-
Verbal fluency	COWAT	COWAT	-
Executive function	-	D-KEFS Sorting Test	-

BRB-N: Brief Repeatable Battery of Neuropsychological Tests, MACFIMS: Minimal Assessment of Cognitive Function in MS, BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis, PASAT: Paced Auditory Serial Addition, SDMT: Symbol Digit Modalities Test, SRT: Selective Reminding Test, CVLT-II: California Verbal Learning Test, BVMT-R: Brief Visuospatial Memory Test Revised, COWAT: Controlled Oral Word Association Test, JLO: Judgement of Line Orientation test, D-KEFS: Delis-Kaplan Executive Function System.

The advantages of MACFIMS are that it has a strong psychometric foundation and includes assessment of visuospatial processing and higher executive functions, however, the administration takes longer compared to the other batteries. While BICAMS is recommended to use for annual or bi-annual cognitive monitoring (Rocca et al., 2015), it allows to identify patients with possible CI (Corfield & Langdon, 2018). There is an attempt to develop the digital versions of the battery (Beier et al., 2020; Petrova-Antonova et al., 2020) in order to ease administration, scoring, collection and comparison of data.

1.2.3 Correlates of cognitive impairment

A large interpatient variability can be seen in the pattern and severity of cognitive deficits in MS. Therefore a number of biological and psychological factors has been investigated in order to explain this phenomenon. Fatigue and depression has been shown to be the main correlates of cognitive impairment in MS with domain-specific associations (Heesen et al., 2010).

Symptoms of depression have been linked to cognitive multitasking in early MS (Glukhovsky et al., 2020), to memory (Heesen et al., 2010; (Hegedüs, Kárpáti, Szombathelyi, Simó, 2015), attention, executive functions (cognitive efficiency, executive control of attention, and planning) and information processing speed (Glukhovsky et al., 2020).

Although the role of fatigue is still a matter of debate (Benedict et al., 2017), it has been linked to worse attention (Heesen et al., 2010) and to slower processing speed (Andreasen et al., 2010). Furthermore, patients' perception about their cognitive functioning is related to depression and fatigue and it does not reflect the objective neuropsychological performance (Benedict et al., 2017).

Nevertheless, the complex interplay among cognitive impairment, depression and fatigue needs to be hypothesized in patients with MS (Rocca et al., 2015).

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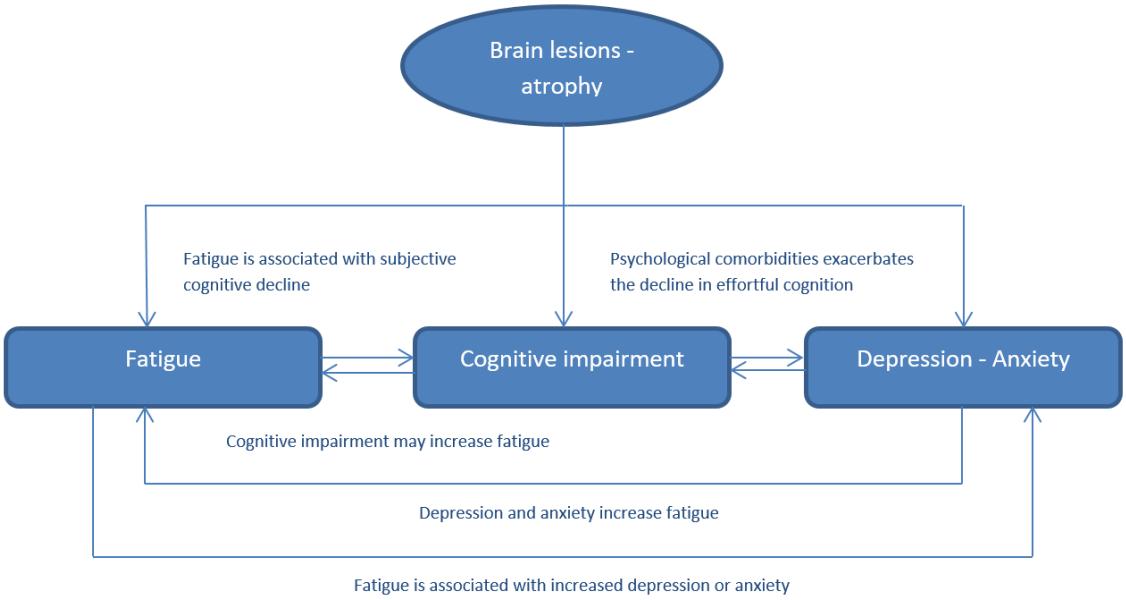

Figure 1 Interplay between cognitive impairment, fatigue and depression/anxiety. (Bradshaw, 2008; Solaro et al., 2018)

Further explanation for this variability could be the phenomenon of cognitive reserve, as both years of education and reading level are proved to improve predictions of cognitive decline over 5 years (Benedict et al., 2010). Individuals with intellectual enrichment, namely with greater vocabulary knowledge, and/or greater early life participation in cognitive leisure activities (e.g. reading, hobbies) are better able to cope with MS disease without cognitive impairment (Sumowski & Leavitt, 2013).

1.3 Psychological consequences

Among individuals with MS, mental health comorbidities contribute to secondary disability and detract from QoL. A significant incidence and prevalence of psychological disorders in MS has been described. Depression is the predominant psychological disturbance. Anxiety is also frequent, occurs in newly diagnosed patients, and its co-morbidity with depression contributes to the increase of the rate of suicidal ideation. Other psychiatric illnesses, as bipolar affective disorder, pathological laughing and crying, or psychosis, occur less frequently in MS. Therapeutic strategies include psychotherapy, strengthen of coping mechanism, and specific medications (Sa, 2008).

1.3.1 Depression and suicide

The prevalence of depression is higher in the population with MS than in general public or in many other chronic patient populations (Feinstein et al., 2014). The accurate quantification is difficult because of different assessment methods used in the literature. In general, up to 50% of people with MS is reported to experience major depressive disorder in their lifetime (Solaro et al., 2016). Regarding benign MS patients, around one in five patients has been found to have moderate to severe depression when longitudinally followed (Sayao et al., 2011) that is comparable with the yearly proportion of 20 % in the whole MS population (Sa, 2008). Women and people younger than 45 years seem to be more at risk for depression (Masuccio et al., 2021).

Results concerning its prevalence within the different forms of MS are inconsistent. A higher rate in SPMS has been reported than in RRMS or in PPMS, independently from disease duration (DD) and physical disability (Solaro et al., 2016), whereas a lower life time risk of depressive disorders has been found in PPMS compared with RRMS (Zabad et al., 2005), or no association between the prevalence of depression and the disease course has been established (Koch et al., 2015).

The suicide risk in the MS population is twice larger than that in the general population. Risk factors for suicidality in MS include a high incidence of depression, social isolation, and reduced function, or independence (Kalb et al., 2019). Young males within the first 5 years of their MS diagnosis are particularly vulnerable. While the frequency with which intent is followed by suicide is not known (Feinstein & Pavisian, 2017).

Aetiology of depression in MS is multifactorial with a complex interplay between biological and psychosocial variables. It might be a natural reaction to the unpredictable course of the disease. MS patients could be predisposed for depression by several psychosocial risk factors such as insufficient social support (Boeschoten et al., 2017) or emotion-focused coping (Lynch et al., 2001; Solaro et al., 2018). These inadequate coping styles seem not to improve over time (Lode et al., 2010). Lower emotional and social intelligence – as the ability to evaluate one's own and others' emotions and utilizing essential information for determining thoughts and actions – and alexithymia – characterized by difficulty identifying and describing feelings – are present in patients

with MS. Difficulty in social interaction could be a risk of future affective disorders (Ghajarzadeh et al., 2014; Jougleux et al., 2021).

Gay et. al. (2010) studied physical and psychological factors in one model in order to find predictors of depression in MS. They found that physical status, trait anxiety, alexithymia and satisfaction with social support system were predicting factors. Trait anxiety and physical status were two predictors that independently and simultaneously led to the appearance of depression symptoms, with trait anxiety playing a predominant role. Alexithymia and social support indirectly influenced the appearance of these symptoms.

Furthermore, genetic and immune-inflammatory factors (Solaro et al., 2018), and structural and functional brain impairment might be potential causes of depression, as well. In fact, depression itself can be a symptom with a neuro-biological basis (Masuccio et al., 2021). Brain MRI variables might contribute to approximately 40% of the depression variance (Feinstein et al., 2010), a percentage corresponding to a constellation of psychological factors (Lynch et al., 2001).

Depression has been associated with interpersonal isolation and working problems (Dorstyn et al., 2019), cognitive impairment (Portaccio, 2016), especially, in the field of working memory, executive function and information processing speed (Feinstein et al., 2014), and elevated suicide risk (Kalb et al., 2019). Depression may adversely affect health status by increasing symptom burden, decreased medication adherence or by direct pathophysiological effects on immunity (Katon et al., 2007; Solaro et al., 2018). Regarding QoL, its lower level is related to depression, along with depressive temperament and anxiety (Gil-González et al., 2020).

Among the scales available for scoring depressive symptoms, Beck Depression Inventory (BDI) (Beck et al., 1961) is recommended for evaluating depression in MS according to the evidence-based guidelines of the American Academy of Neurology (AAN) (Minden et al., 2014). The question of the possible overestimation of the prevalence of symptoms of depression due to the overlap with MS symptoms, such as fatigue, sleeping problems, etc., has been investigated: the clinical phenotype of “idiopathic” major depressive disorder and MS-associated depression appears similar. Therefore the screening tools employed to identify depression in patients without MS might be used to measure depression also in MS (Hasselmann et al., 2016).

1.3.2 Anxiety

Although depression is the dominant mental health comorbidity in MS, the high levels of stress and perceived lack of control due to the nature of the disease may lead to anxiety. The lifetime prevalence of anxiety symptoms and disorders is reported to be 35.7%. The most commonly recognized disorders are generalized anxiety disorder (18.6%), panic disorder (10%), and obsessive compulsive disorder (8.6%) (Korostil & Feinstein, 2007). When analysing data regarding the prevalence of clinically significant anxiety symptoms (34%) compared to the prevalence of anxiety disorders (10%), a higher rate can be found (Boeschoten et al., 2017). The rates of anxiety are more elevated among people with MS compared to both the general population and people with other chronic disorders, as observed in case of depression (Gill et al., 2018). The comorbidity rates between anxiety and depression are high: 65% for depression among those meeting criteria for anxiety symptoms and 75% for anxiety among those meeting criteria for depressive symptoms (Askari et al., 2014; Jones et al., 2014).

Anxiety plays a large role in individuals' perceived health and well-being, which subsequently impacts the severity of symptoms and overall QoL. Regarding predictors, social support appears to be an important factor (Berrigan et al., 2016; Hanna & Strober, 2020).

Data concerning associations of anxiety are contradictory. Higher levels of anxiety symptoms were associated with longer disease duration (Hartoonian et al., 2015), while younger age and shorter disease duration were found to be related to anxiety in another study (Hanna & Strober, 2020). It may be more common in SPMS (Askari et al., 2014) and among women with RRMS (Jones et al., 2014; Théaudin et al., 2016). Furthermore, adverse health behaviours (alcohol dependence and smoking) may be associated with anxiety (McKay et al., 2016).

Unfortunately valid and reliable anxiety screening measures are lacking for use with people with MS. Commonly applied tool is the Hospital Anxiety and Depression Scale (HADS) (Turner et al., 2016; Zigmond & Snaith, 1983).

As high level of anxiety can lead to temporary physiological symptoms that mirror those of the illness, it can easily result in the misinterpretation of these symptoms as signs of severe threat, i.e. as signs of MS relapse, in which case health anxiety (HA) evolves

(Carrigan et al., 2018). The rate of HA in MS is found to be approximately 25% (Kehler & Hadjistavropoulos, 2009), and it is associated with lower QoL independent of physical disability (Hayter et al., 2016).

The level of HA can be assessed with a modified version of the Short Health Anxiety Inventory (SHAI). The SHAI is a reliable and valid measure among the general population and the modified version, which includes the statement 'other than MS', can be interpreted by MS patients (Kehler & Hadjistavropoulos, 2009; Köteles et al., 2011).

1.3.3 Psychological interventions

Psychological treatment may be beneficial for people with MS to gain skills to cope with emotions, thoughts and to adjust to MS diagnosis and symptoms. Several studies show the effectiveness of different psychological interventions (Malcomson et al., 2007; Thomas et al., 2006), e.g. cognitive behaviour therapy (CBT) (Askey-Jones et al., 2013; Dennison & Moss-Morris, 2010; Graziano et al., 2014; Hind et al., 2014; Lincoln et al., 2011; Moss-Morris et al., 2013), acceptance and commitment therapy (ACT) (Moss-Morris et al., 2009; Nordin & Rorsman, 2012), dialectical behaviour therapy (DBT) (Blair et al., 2017), stress management (Artemiadis et al., 2011; Artemiadis et al., 2012; Reynard et al., 2014), relaxation techniques (Ghafari et al., 2009; Sutherland et al., 2005), or mindfulness based intervention (Simpson et al., 2014).

Apart from reducing depressive symptoms and anxiety (Fiest et al., 2016; Sesel et al., 2018), positive impacts may include outcomes such as prevention of new brain lesions in patients with MS (Mohr et al., 2012), improvement in adherence to treatment, decrease in fatigue, and increase in mental and total health related QoL (Mohr et al., 1997; Sesel et al., 2018).

A significant finding is that peers and peer support is an important component in rehabilitation from the perspective of individuals (Salminen et al., 2014) therefore group-based intervention might have an extra benefit (Borghi et al., 2018). Further suggested consideration when developing psychosocial interventions for people with MS is that sharing one's thoughts and feelings, and learning specific strategies for living with MS proved to be important processes for change (Dennison et al., 2013).

The AAN guidelines (Minden et al., 2014) state that there is an evidence supporting the efficacy of pharmacologic and non-pharmacologic therapies for depressed mood and anxiety in individuals without MS. Despite the lack of evidence in individuals with MS, these therapies are frequently used to treat emotional disorders in this population. They recommend a 16-week program of individual telephone-administered CBT to treat depressive symptoms in MS.

Although the United Kingdom National Institute of Clinical Excellence (NICE) encourages the routine psychosocial management in the care of MS patients, when it comes to the treatment of psychological disturbances it refers to NICE guideline on depression in adults with a chronic physical health problem and NICE guideline on generalised anxiety disorder and panic disorder in adults (National Institute for Health and Care Excellence, 2014).

The importance of psychological support of MS patients including MS-specific considerations is justifiable. As the adjustment process including perceived disease burden starts with the diagnosis, the early stage of MS can be considered a good time for a psychological intervention (Calandri et al., 2017).

1.4 Fatigue

Fatigue is a complex and multifactorial symptom of MS that is defined as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Patients report it to be the most debilitating symptom which influences cognitive, psychological, social, and physical functioning, while significantly impacts QoL and employment (Bakshi, 2003; Moore et al., 2013).

Depending on study populations and applied outcome measures, prevalence of fatigue varies between 40% and 70%, with a higher prevalence rate in progressive forms of MS (Fiest et al., 2016; Rooney, McFadyen, et al., 2019; Rooney, Wood, et al., 2019).

Fatigue can be a consequence of the primary pathological mechanisms of MS including inflammation and neurological damage (Langeskov-Christensen et al., 2017), while secondary mechanisms independent of MS pathophysiology, such as sleep problems, depression or disability, may contribute to the development of fatigue.

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However, the association between these factors may be a bi-directional relationship, as higher level of fatigue could be the cause or consequence of impaired physical, cognitive, and psychological functioning (Kos et al., 2008).

Due to the subjective nature of fatigue, patient reported outcome measures are commonly used in studies to assess the severity and impact of fatigue. Two of the most frequently used are the Fatigue Severity Scale (FSS) (Krupp et al., 1989) and the Modified Fatigue Impact Scale (MFIS) (Fisk et al., 1994; Ritvo, 1997). The clinical features of MS have been found to be more strongly associated with fatigue impact in comparison to fatigue severity, which may suggest that the MFIS is a more sensitive measure of MS-related fatigue due to its multidimensional nature (Rooney, Wood, et al., 2019).

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2. Aims

2.1 Neuropsychological characteristics of BMS patients[1]

The aim of our two-year follow-up study (Hegedüs et al., 2019) was to investigate the pattern of cognitive functioning and depression in patients with BMS compared to a comparison group of treated RRMS patients and healthy controls. We were hoping to provide further insight into the different aspects of truly remained benign cases. We were interested in the difference between the cognitive status of patients with benign course without any DMT and the profile of RRMS patients treated from the beginning of the disease onset.

We hypothesized that cognitive functions of BMS patients would differ from those of healthy controls, whereas RRMS patients would present the same cognitive performance. The level of depression would be higher in both MS groups than in the healthy group and it would not differ in the two patient groups. As for the two-year follow-up, we hypothesized that there would not be any change in cognitive performance of treated patients, that is, therapeutic efficacy of DMT on somatic symptoms would not be confirmed in relation to cognitive functions. In BMS group the cognitive performance would remain stable. Without treatment, the level of depression would not change.

2.2 Psychological characteristics of MS patients

Considering that the prevalence of depression is higher in the population with MS than in general public and it is associated with several psychological factors, we aimed to study the nature of the interactions between factors, as well as their impact on depression. Thus the aim of our study was to explore the differences in psychological characteristics (anxiety, fatigue, coping style, dysfunctional attitudes, emotional-social intelligence and alexithymia) between MS patients and healthy population, to determine the correlates of

[1] Incorporated publication: Hegedüs K, Kárpáti J, Iljicsov A, Simó M. (2019) Neuropsychological characteristics of benign multiple sclerosis patients: A two-year matched cohort study. Mult Scler Relat Disord. 35: 150-155.

depression and to clarify the relationship between depression and the factors associated with it.

2.3 Integrative group therapy for people in early MS

There is growing evidence that psychological interventions have a significantly positive impact on depressive symptoms, anxiety, fatigue, and health related QoL. They can improve adherence to treatment (Sesel et al., 2018). Regarding cost-effectiveness, group psychotherapy could be a more favourable setting compared to face-to-face intervention. Besides, group intervention could embrace peer support that is an important component in rehabilitation from the perspective of individuals (Salminen et al., 2014). The importance of psychological support for MS patients, including MS-specific considerations, has been proved. The early stage of MS could be a reasonable time to support patients' adjustment to the illness (Calandri et al., 2017), preventing further severe psychological consequences, and reducing the risk of suicide (Hind et al., 2014).

The aim of this study was to design an integrative intervention group protocol for MS patients in the early stage, having depressive symptoms or anxiety. Furthermore, we aimed to evaluate the feasibility of the program before conducting a study focusing on effectiveness.

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3. Materials and methods

3.1 Neuropsychological characteristics of BMS patients[2]

3.1.1 Participants and study design

The study was conducted based on the analysis of clinical data acquired from a registry of 400 MS outpatients from the year of 2014 at the Department of Neurology in Semmelweis University. Patients were included in the BMS group based on a definite diagnosis of MS (according to 2010 McDonald diagnostic criteria) and a benign course defined as an EDSS score ≤ 3.0 after at least 10 years from the clinical onset of the disease (Polman et al., 2011). These patients have never been treated with immunomodulatory drugs. They follow the natural course of the disease. Of 30 eligible patients (7.5%), 22 gave consent for neuropsychological assessment.

A comparison group of 22 MS patients was recruited. Inclusion criteria were: (1) a definite diagnosis of MS (according to 2010 McDonald diagnostic criteria); (2) relapsing remitting course (Polman et al., 2011); (3) receiving of disease modifying treatment. In the beginning of disease course, the disease activity was higher in this group compared to BMS group. Therefore each patient started drugs after their first relapse in the setting of everyday clinical practice (based on the legislation of National Health Insurance Fund of Hungary). Controlling for demographic and clinical characteristics, cases in the patient groups were matched in terms of age, gender, education and disease duration.

Exclusion criteria for both MS groups included: (1) an acute MS relapse; (2) corticosteroid treatment within 90 days before the cognitive assessment; (3) other significant neurologic or psychiatric illnesses; (4) treatment with psychoactive drugs for depression or fatigue and (5) alcohol or drug abuse.

[2] Incorporated publication: Hegedüs K, Kárpáti J, Iljicsov A, Simó M. (2019) Neuropsychological characteristics of benign multiple sclerosis patients: A two-year matched cohort study. Mult Scler Relat Disord. 35: 150-155.

After a 2-year period patients were clinically re-evaluated. In both groups patients had the same disease course remaining in the same MS group. RRMS patients continued to receive the DMT. None of them were treated especially for cognitive impairment or depression. They were reassessed through the use of the same neuropsychological testing battery that had been initially administered.

Healthy volunteers matched with the sample for gender, age and education were also studied at baseline. None of them referred to any previous neurological or systemic diseases potentially affecting the CNS function, and the neurological exam was normal in all cases.

All participants gave an informed consent. The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics.

3.1.2 Neuropsychological assessment

Participants underwent a neuropsychological evaluation exploring the cognitive domains most frequently impaired in MS: complex attention [Paced Auditory Serial Attention Test 3 seconds (PASAT-3)] (Rao et al., 1989); visuo-spatial memory [Rey-Osterrieth Complex Figure Test (CFT)]; learning, verbal memory [Auditory-Verbal Learning Test (AVLT)]; working memory [Digit Span (DS)]; information processing speed [Wechsler's Digit Symbol Test (WDST)]; and executive function [Tower of Hanoi (TH)] (Lezak, 2012). The neuropsychological battery was administered in 45 minutes by a trained psychologist in a preordered sequence.

Our evaluation incorporated the recommendations of the latest battery for cognitive assessment to be applied in clinical routine, the BICAMS (Benedict et al., 2012; Langdon et al., 2012; Sandi et al., 2015). It detects cognitive changes in the domains of information processing speed, verbal and visual memory including SDMT, CVLT and BVMT-R. It was completed with testing complex attention, working memory and executive function.

Test failure was defined as a performance of <1.5 SD below healthy control subjects (Borghi et al., 2013; Jonsson et al., 2006). Patients failing at least two tests or subtests were considered cognitively impaired, failing 0–1 test meant cognitively

preserved status (Amato et al., 2010; Lopez-Gongora et al., 2015). The neuropsychological performance was classified as worsened at 2-year follow-up if the patient failed at least two more tests compared to baseline assessment (Sayao et al., 2011).

3.1.3 Depression assessment

Depression was assessed using the Zung Self-Rating Depression Scale (SDS) (Zung, 1965). It is a 20-item questionnaire that has been shown to have good construct validity for measuring depression in medically ill populations and has been used for patients with MS (Skokou et al., 2012). SDS scores are classified as normal (<50), mild depression (50 to 59), moderate to marked major depression (60 to 69), and severe to extreme major depression (>70).

3.1.4 Statistical analysis

Demographic and clinical characteristics of the participants were summarized as mean ± SD. Data were tested for normal distribution using the Shapiro-Wilk test. Group differences in EDSS score were determined using non-parametric Mann-Whitney U-test. Differences in cognitive parameters and depression between groups were determined using the multivariate analysis of variance tests. At baseline, Kruskal-Wallis H test was applied in case the assumption of normal distribution failed. The Bonferroni correction adjusted multiple comparisons between groups. Analysing follow-up data, between group comparisons were assessed using the 2-tailed t-test for unpaired samples or the non-parametric Mann-Whitney U-test. The Wilcoxon test or 2-tailed t-test for paired samples was used for within group comparisons. Pearson's correlation was performed to evaluate the association between depression and the different cognitive domains. All analyses were carried out using the SPSS software (version 25.0 for Windows; SPSS Inc., Chicago, Illinois, USA). In all cases p values < 0.05 were taken as significant.

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3.2 Psychological characteristics of MS patients

3.2.1 Participants and study design

Patients attending regularly scheduled appointments at the Department of Neurology of Semmelweis University were asked to participate in the study. Patients were recruited consecutively provided they matched the inclusion criteria: (1) a definite diagnosis of MS (according to 2010 McDonald diagnostic criteria); (2) relapsing remitting course (Polman et al., 2011) for homogeneity of the population. Exclusion criteria included: (1) an acute MS relapse; (2) corticosteroid treatment within 90 days before the assessment; (3) other significant neurologic or psychiatric illnesses; (4) treatment with psychoactive drugs for depression or fatigue and (5) alcohol or drug abuse. The battery required approximately one hour to complete and patients completed it by the end of their clinic appointment or returned it in a distributed envelope by mail.

The sample consisted of 68 patients (51 females, 17 males), who ranged in age from 22 to 60 with the mean level of education of 14 years. Disease duration ranged from 1 year to 21 years and EDSS scores ranged from 0.0 to 6.0. Sixty-two percent of the patients were receiving disease modifying treatment.

Sixty-six healthy volunteers matched with the sample for gender, age and education were recruited. None of them referred to any previous neurological or systemic diseases potentially affecting the CNS function, and the neurological exam was normal in all cases.

All participants gave an informed consent. The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics.

3.2.2 Measures

In addition to an initial page eliciting demographic and disease-related information, the battery included the following questionnaires and measures:

Beck Depression Inventory (BDI) (Beck et al., 1961) to measure the level of depression. It is an objective self-report assessment tool comprising 21 items, and it is recommended by AAN.

Short Health Anxiety Inventory (SHAI) (Köteles et al., 2011; Salkovskis et al., 2002) to assess the level of health anxiety. The SHAI is a reliable and valid measure among the general population and the modified version, which includes the statement 'other than MS', can be interpreted by MS patients (Kehler & Hadjistavropoulos, 2009).

Modified Fatigue Impact Scale (MFIS) to assess the effects of fatigue. It is a 21-item questionnaire, which is a modified version of the 40-item Fatigue Impact Scale (FIS). The FIS was originally developed to assess the effects of fatigue on the QoL of patients with chronic diseases, specifically MS. By eliminating items which appeared both content-redundant and had high inter-item correlations MFIS evolved (Fisk et al., 1994; Ritvo PG, 1997; Losonczi et al., 2011). It is recommended by the clinical practice guidelines of the Consortium of Multiple Sclerosis Centres (Ayache & Chalah, 2017). Items on the MFIS can be gathered into three subscales (physical, cognitive, and psychosocial), as well as into a total MFIS score.

Ways of Coping (Folkman & Lazarus, 1980), a 22-item questionnaire to analyse the coping strategies, which people use in stressful situation: problem-focused strategies (problem analysing, goal directed behaviour) and emotion-focused strategies (emotion-centred behaviour, adaptation, support seeking, emotional balance seeking and withdrawal).

Dysfunctional Attitude Scale (DAS) (Burns, 1980; Weissman & Beck, 1978). The 35-item scale is used to identify and measure cognitive distortion in seven major value systems: approval, love, achievement, perfectionism, entitlement, omnipotence and autonomy.

Emotional Quotient Inventory (EQ-i) (Bar-On, 2006) to assess emotional-social intelligence. According to Bar-On, "it includes the following key components: (a) the ability to recognize, understand and express emotions and feelings; (b) the ability to understand how others feel and relate with them; (c) the ability to manage and control emotions; (d) the ability to manage change, adapt and solve problems of a personal and interpersonal nature; and (e) the ability to generate positive affect and be self-motivated" (Bar-On, 2006). It consists of five scales and 15 subscales, as follows: I-Intrapersonal

(self-regard, emotional self-awareness, assertiveness, dependence, and self-actualization), II-Interpersonal (empathy, social responsibility, and inter-personal relationship), III-Stress Management (stress tolerance and impulse control), IV-Adaptability (reality testing, flexibility, and problem solving), and V-General Mood Scale (optimism and happiness).

Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994). This 20-item measure evaluates three dimensions of alexithymia: difficulty in identifying feelings (DIF), difficulty in describing feelings (DDF) and externally oriented thinking (EOT).

3.2.3 Statistical analysis

Demographic and clinical characteristics of the participants were summarized as mean (SD) or median (interquartile range). Data were tested for normal distribution using the Shapiro-Wilk / Kolmogorov-Smirnov normality test. Analysing data, between group comparisons were assessed using the 2-tailed t-test for unpaired samples or the non-parametric Mann-Whitney U-test. The prevalence of psychological symptoms was estimated by cut-off scores: BDI score ≥ 10 (Butcher et al., 1998), SHAI score ≥ 27 for HA (Deacon & Abramowitz, 2008), SHAI score ≥ 15 for A (Kocjan, 2016; Salkovskis et al., 2002), and MFIS score ≥ 38 (Larson, 2013). Regarding alexithymia, cut-off values were: no-clinical alexithymic (scores ≤51), borderline alexithymic (scores of 52-60), or alexithymic (scores >60) (Bagby et al., 1994). Correlation analyses (using Pearson's r for variables with a normal distribution or Spearman's rank correlation for non-parametric variables) were performed to evaluate the association between depression / anxiety / fatigue and the different psychosocial variables. Additionally, variables with a p-value below 0.20 in a bivariate analysis were selected for multivariate forward stepwise linear regression analysis to explain depressive symptoms. All analyses were carried out using the SPSS software (version 25.0 for Windows; SPSS Inc., Chicago, Illinois, USA). In all cases p values < 0.05 were taken as significant.

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3.3 Integrative group therapy for people in early MS

3.3.1 Patients and process

The pilot study was conducted at the Department of Neurology, Semmelweis University, Budapest and it was approved by Semmelweis University Regional and Institutional Committee of Science and Research Ethics.

The recruitment process intended to imitate clinical practice for identifying MS patients in the early stage who needed psychological counselling due to depressive symptoms or anxiety. After giving informed consent, patients were referred to a baseline evaluation conducted by a psychologist. Inclusion criteria were a definite diagnosis of MS (according to 2010 McDonald diagnostic criteria) (Polman et al., 2011), early stage (disease duration: 0.5-5 years) and subthreshold to moderate depressive symptoms on a validated depression scale and/or symptoms of health anxiety on a validated health anxiety inventory. Exclusion criteria were any other significant neurological or psychiatric illnesses, treatment with psychoactive drugs for depression or fatigue, and alcohol or drug abuse.

After examining inclusion and baseline assessment, six patients were assigned to the group intervention therapy. They were reassessed at post-intervention (six months after pre-treatment evaluation) and six months after post-intervention including the same tests as in the baseline data collection.

Primary outcome measures were: (1) 21-item Beck Depression Inventory (BDI) (Beck et al., 1961), to measure the level of depression; (2) Short Health Anxiety Inventory (SHAI) (Kehler & Hadjistavropoulos, 2009; Köteles et al., 2011), to assess the level of health anxiety; and (3) Modified Fatigue Impact Scale (MFIS) (Fisk et al., 1994; Ritvo PG, 1997; Losonczi et al., 2011), to assess the effects of fatigue. Secondary outcome measures were: (1) Emotional Quotient Inventory (EQ-i) (Bar-On, 2006), to assess emotional-social intelligence; (2) Ways of Coping (Folkman & Lazarus, 1980), to analyse the coping strategies; and (3) Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994), to evaluate the level of alexithymia.

Feasibility of the designed integrative group intervention protocol was characterized by recruitment rate, number of cancellations, attrition rate, and potential adverse events.

3.3.2 Intervention

The intervention consisted of 20 group sessions administered on a weekly basis for 1.5 hour. All group sessions were conducted by a psychologist having five years of experience in group therapy, which was supervised by two clinical neuropsychologists.

The intervention group program was designed for people with MS based on the information gathered from previous studies (Fiest et al., 2016; Hind et al., 2014; Reynard et al., 2014; Sesel et al., 2018), based on the results of our study on psychological characteristics of MS patients and based on the experience in relaxation and supportive group therapy for MS patients at the Department of Neurology, Semmelweis University (Hegedüs, Kárpáti, Szombathelyi, Iljicsov, Simó, 2015). The goal was to introduce a combination of evidence-based therapies in order to better serve the needs of MS people in the early stage and to ease the adjustment difficulties associated with depression or anxiety.

The series of sessions meant to be an integrative group therapy based on psycho-educational, cognitive behavioural framework (including elements of acceptance and commitment therapy, and dialectical behaviour therapy) combined with autogenic training, imagination, stress and change management, and peer support. The sessions were designed to encourage acceptance of MS, promote adequate coping mechanism and adjustment, increase self-efficacy, self-motivation and optimism, experience positive emotions, facilitate the development of social support, identifying, expressing and sharing feelings, addressing maladaptive thoughts, beliefs and behaviours, developing social skills for dealing with other people's reactions and preparing for difficulties in the future.

The topics covered are presented in Table 4. The sessions involved an opening relaxation exercise, homework reflection and presentation, discussion and practice of a new topic involving new skills. Homework based on session topics was assigned to encourage the participants to practice new skills at home. They were asked to perform relaxation exercises every day.

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Table 4 Topics of the intervention sessions.

Session	Topic	Description
1	Introduction	Introduction of MS and adjusting to MS. Assessment of current strengths and difficulties. Keeping a diary.
2	Target setting	Problem sheet and realistic target setting in different areas of life. How to relax? Introduction of Autogenic Training (AT). Contact with the present moment.
3-5	Representation of illness	Experience of MS diagnosis. Concealment. Representation of illness and self – PRISM (Buchi & Sensky, 1999). Identity/role change and redefinition of identity. Gaining self-efficacy over symptoms. Identifying the benefits. AT – Heaviness exercise.
6-7	Mood, emotions	Identifying and describing feelings. Dealing with negative emotions, e.g. sadness, grief, loss, frustration, anger, anxiety, depression, shame, and embarrassment. Acceptance. Values. Emotion-regulation strategies. AT – Warmth exercise.
8-9	Cognition	Cognitive behavioural model of adjusting. Cognitive restructuring. Management of negative thoughts and beliefs. Analysing thinking errors. AT – Heart exercise.
10-11	Behaviour	Behaviour evaluation. Dysfunctional attitudes.

Session	Topic	Description
		What are health behaviours (positive activities, exercise, diet, rest, sleep, etc.)?
		AT – Breathing exercise.
12-13	Stress	What is stress?
		Distress tolerance.
		Analysing stressful situations.
		Identifying warning signs.
		AT – Abdominal exercise.
14-15	Coping	Stress/change management: problem solving, planning, prioritizing, external and internal distraction.
		Acceptance.
		Committed actions.
		AT – Forehead exercise.
16-17	Interpersonal effectiveness	Social support network.
		Assertive communication.
		Saying no.
		Asking for help.
		AT – Self-generated formula.
18-19	Needs and goals	Definition of needs.
		Accepting limitations.
		Definition of new, realistic and meaningful life goals.
		Reinforcing a sense of coherence.
		Relaxation combined with imagination exercises (inner pictures of nature, e.g. medicinal spring, mountain).
20	Future	Summary of strategies to reach goals.
		Summary of strengths, values, newly acquired useful aspects and skills.
		Sense of personal realization.
		How to face and cope with difficult situations or problems in the future.
		Formation of a peer support group.

In order to evaluate the group experience, participants who had attended the intervention group were asked to fill out a questionnaire that included the following questions:

1. How satisfied are you with the experience? (5-point scale.)
2. Do you think this experience is useful for your life? (5-point scale.)
3. Did you perceive a positive personal change after the group experience? (Yes/no/don't know.)
4. Would you repeat this experience? (Yes/no/don't know.)
5. Would you recommend this experience to other patients? (Yes/no/don't know.)

3.3.3 Statistical analysis

Demographic and clinical characteristics of the participants were summarized using mean (SD) or median (IQR). Mean differences in outcome measures from baseline to 6-month follow-up were calculated. Descriptive statistics were used to analyse outcome variability.

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4. Results

4.1 Neuropsychological characteristics of BMS patients[3]

Demographic and main clinical data of the subjects included in the study at baseline and at 2-year follow-up are shown in Table 5 and Table 6. The mean level of EDSS was 1.2 (SD=0.9) in BMS group and 1.7 (SD=1.5) in RRMS group. There was no significant difference between them. Clinical characteristics including EDSS scores of MS patients did not change after two years (1.2, SD=0.9; 1.8, SD=1.7), they were considered still benign or relapsing-remitting.

The mean level of depression was elevated in the BMS group compared to the RRMS group, however, significant differences were found only between BMS and healthy groups (43.4 (SD=10.1) vs. 35.9 (SD=5.7), p=0.008). At two-year follow-up, mean level of depression did not change significantly in the MS groups.

Table 5 Demographic and clinical characteristics of the study sample, baseline (Hegedüs et al., 2019).

	BMS-1 n=22	RRMS-2 n=22	Control-3 n=22	*p*: 1-2	1-3	2-3
Gender, n (men/women)	5/17	5/17	5/17	n.s.	n.s.	n.s.
Age, y, mean (SD)	44.9 (9.5)	45.1 (9.2)	44.9 (9.6)	n.s.	n.s.	n.s.
Education, y, mean (SD)	13.6 (2.1)	14.1 (2.2)	13.9 (2.5)	n.s.	n.s.	n.s.
Disease duration, y, mean (SD)	14.9 (6.1)	13.7 (6)	n.r.	n.s.	-	-
EDSS score, mean (SD)	1.2 (0.9)	1.7 (1.5)	n.r.	n.s.	-	-
DMT, n						
Interferon beta 1b	0	5	n.r.	n.r.	-	-
Glatiramer acetate	0	6	n.r.	n.r.	-	-
Natalizumab	0	2	n.r.	n.r.	-	-

[3] Incorporated publication: Hegedüs K, Kárpáti J, Iljicsov A, Simó M. (2019) Neuropsychological characteristics of benign multiple sclerosis patients: A two-year matched cohort study. Mult Scler Relat Disord. 35: 150-155.

	BMS-1 n=22	RRMS-2 n=22	Control-3 n=22	*p*: 1-2	1-3	2-3
Fingolimod	0	1	n.r.	n.r.	-	-
Teriflunomide	0	3	n.r.	n.r.	-	-
Dimethyl fumarate	0	5	n.r.	n.r.	-	-
Depression score, mean (SD)	43.4 (10.1)	39.4 (7.5)	35.9 (5.7)	n.s.	0.008	n.s.

Note. y: years, SD: standard deviation, EDSS: expanded disability status scale, DMT: disease modifying treatment, Depression score measured by SDS, n.s.: not significant, n.r.: not relevant.

Table 6 Demographic and clinical characteristics of the study sample, 2-year follow-up (Hegedüs et al., 2019).

	BMS n=22	RRMS n=22	*p*-value
Gender, n (men/women)	5/17	5/17	n.s.
Age, y, mean (SD)	46.9 (9.5)	47.1 (9.2)	n.s.
Education, y, mean (SD)	13.6 (2.1)	14.1 (2.2)	n.s.
Disease duration, y, mean (SD)	16.9 (6.1)	15.7 (6)	n.s.
EDSS score, mean (SD)	1.2 (0.9)	1.8 (1.7)	n.s.
DMT, n			
Interferon beta 1b	0	5	n.r.
Glatiramer acetate	0	6	n.r.
Natalizumab	0	2	n.r.
Fingolimod	0	1	n.r.
Teriflunomide	0	3	n.r.
Dimethyl fumarate	0	5	n.r.
Depression score, mean (SD)	44.6 (9.0)	40.9 (7.9)	n.s.

Note. y: years, SD: standard deviation, EDSS: expanded disability status scale, DMT: disease modifying treatment, Depression score measured by SDS, n.s.: not significant, n.r.: not relevant.

Cognitive scores at baseline are presented in Table 7. Non-significant differences between MS groups were noted in the measured cognitive domains. In comparison with the healthy control group, there were significant differences in the BMS group in the following mean scores and domains: CFT (18.34 (SD=5.3) vs. 24.43 (SD=7.5), p=0.005) – visuo-spatial memory; AVLT-L (51.82 (SD=8.8) vs. 58.23 (SD=8.4), p=0.04) – auditory-verbal learning; and WDST (42.05 (SD=10.5) vs. 52.00 (SD=10.8), p=0.017) – information processing speed. Scores of complex attention, verbal memory, working memory and executive function did not differ significantly between the two groups. In RRMS group significant differences were found compared to healthy group in terms of PASAT-3 (35.55 (SD=12.5) vs. 45.82 (SD=11.5), p=0.032) – complex attention; CFT (19.72 (SD=5.7) vs. 24.43 (SD=7.5), p=0.044) – visuo-spatial memory; and WDST (38.23 (SD=13.2) vs. 52.00 (SD=10.8), p=0.001) – information processing speed. Scores of verbal learning, verbal memory, working memory and executive function did not differ significantly between the two groups.

Table 7 Neuropsychological scores at baseline, comparison between groups (Hegedüs et al., 2019).

Domain and test	BMS 1 n=22	RRMS 2 n=22	Control 3 n=22	*p*-value 1-2	1-3	2-3
Complex attention						
PASAT-3	40.09 (11.1)	35.55 (12.5)	45.82 (11.5)	n.s.	n.s.	0.015
Memory						
CFT	18.34 (5.3)	19.72 (5.7)	24.43 (7.5)	n.s.	0.005	0.044
AVLT-L	51.82 (8.8)	55.14 (8.8)	58.23 (8.4)	n.s.	0.04	n.s.
AVLT	10.73 (3.3)	11.41 (3.2)	12.36 (2.6)	n.s.	n.s.	n.s.
DS	12.05 (2.1)	12.27 (2.2)	12.18 (2.3)	n.s.	n.s.	n.s.
Information processing speed						
WDST	42.05 (10.5)	38.23 (13.2)	52.00 (10.8)	n.s.	0.017	0.001
Executive function						
TH*	26.86 (4.1)	29.23 (4.5)	28.00 (5.4)	n.s.	n.s.	n.s.

Note. Scores are mean (SD).

PASAT-3: Paced Auditorial Serial Attention Test 3 seconds; CFT: Rey-Osterrieth Complex Figure Test; AVLT-L: Auditory-Verbal Learning Test, learning; AVLT: Auditory-Verbal Learning Test, verbal memory; DS: Digit Span; WDST: Wechsler's Digit Symbol Test; TH: Tower of Hanoi.

n.s.: not significant

*Lower value means better performance

Cognitive scores at two-year follow-up compared to baseline are shown in Table 8. The cognitive evaluation showed no significant differences between BMS patients and RRMS patients. In BMS group, significantly higher mean scores were found on AVLT-L subtest (51.82 (SD=8.8) vs. 55.77 (SD=10.1), p=0.024) and on WDST test (42.05 (SD=10.5) vs. 45.43 (SD=12.0), p=0.022) at two-year follow-up cognitive evaluation compared to baseline performance. Auditory-verbal learning and information processing speed improved. The cognitive performance of RRMS patients remained stable.

Cognitive scores of different domains were not correlated with depression scores either at baseline or at two-year follow-up.

Table 8 Neuropsychological scores, 2-year follow-up, comparison within groups and between groups (Hegedüs et al., 2019).

Domain and test	BMS 1(t_1) n=22	BMS 1(t_2) n=22	*p*	RRMS 2(t_1) n=22	RRMS 2(t_2) n=22	*p*	*p*-value 1(t_2)-2(t_2)
Complex attention							
PASAT-3	40.09 (11.1)	41.68 (10.8)	n.s.	35.55 (12.5)	39.23 (12.7)	n.s.	n.s.
Memory							
CFT	18.34 (5.3)	19.27 (6.5)	n.s.	19.72 (5.7)	19.43 (6.0)	n.s.	n.s.
AVLT-L	51.82 (8.8)	55.77 (10.1)	0.024	55.14 (8.8)	56.45 (9.4)	n.s.	n.s.

Domain and test	BMS 1(t_1) n=22	BMS 1(t_2) n=22	*p*	RRMS 2(t_1) n=22	RRMS 2(t_2) n=22	*p*	*p*-value 1(t_2)-2(t_2)
AVLT	10.73 (3.3)	11.23 (3.8)	n.s.	11.41 (3.2)	11.36 (3.3)	n.s.	n.s.
DS	12.05 (2.1)	11.45 (2.3)	n.s.	12.27 (2.2)	11.86 (2.4)	n.s.	n.s.
Information processing speed							
WDST	42.05 (10.5)	45.43 (12.0)	0.022	38.23 (13.2)	39.57 (14.5)	n.s.	n.s.
Executive function							
TH*	26.86 (4.1)	28.59 (5.1)	n.s.	29.23 (4.5)	29.73 (7.9)	n.s.	n.s.

Note. Scores are mean (SD).

PASAT-3: Paced Auditorial Serial Attention Test 3 seconds; CFT: Rey-Osterrieth Complex Figure Test; AVLT-L: Auditory-Verbal Learning Test, learning; AVLT: Auditory-Verbal Learning Test, verbal memory; DS: Digit Span; WDST: Wechsler's Digit Symbol Test; TH: Tower of Hanoi, t_1: baseline; t_2: 2-year follow-up, n.s.: not significant.

*Lower value means better performance.

Cognitive impairment related data by domains are summarized in Table 9. In BMS group at baseline assessment, the most frequently involved tests were those assessing information processing speed (WDST, 32%), verbal learning and memory (AVLT-L, 27%; AVLT, 27%), visual memory (CFT, 23%) and complex attention (PASAT-3, 18%). Working memory and executive function was found to be less affected. At two-year follow-up slight improvement were observed in information processing speed (WDST, 27%), verbal learning and memory (AVLT-L, 23%; AVLT, 18%) and visual memory (CFT, 18%). In RRMS group the most frequently involved domains were information processing speed (WDST, 45%), complex attention (PASAT-3, 32%), visual memory (CFT, 23%) and verbal memory (AVLT, 18%). At two-year follow-up the number of

failed tests decreased in the field of information processing speed (WDST, 32%), complex attention (PASAT-3, 27%) and visual memory (CFT, 14%).

Table 9 Neuropsychological test results in BMS and in RRMS patients at baseline and at 2-year follow-up (Hegedüs et al., 2019).

Number of failed cognitive tests in study groups, n (%)				
	Baseline		2-year follow-up	
Domain and test	BMS n=22	RRMS n=22	BMS n=22	RRMS n=22
Complex attention				
PASAT-3	4 (18%)	7 (32%)	4 (18%)	6 (27%)
Memory				
CFT	5 (23%)	5 (23%)	4 (18%)	3 (14%)
AVLT-L	6 (27%)	3 (14%)	5 (23%)	2 (9%)
AVLT	6 (27%)	4 (18%)	4 (18%)	4 (18%)
DS	1 (5%)	2 (9%)	2 (9%)	1 (5%)
Information processing speed				
WDST	7 (32%)	10 (45%)	6 (27%)	7 (32%)
Executive function				
TH	1 (5%)	2 (9%)	1 (5%)	3 (14%)

Note. PASAT-3: Paced Auditorial Serial Attention Test 3 seconds; CFT: Rey-Osterrieth Complex Figure Test; AVLT-L: Auditory-Verbal Learning Test, learning; AVLT: Auditory-Verbal Learning Test, verbal memory; DS: Digit Span; WDST: Wechsler's Digit Symbol Test; TH: Tower of Hanoi

Table 10 shows the individual cognitive status and severity of impairment. The neuropsychological assessment allowed for the identification (failed at least two cognitive tests or subtests) of ten cognitively impaired BMS patients (45%), eight cognitively impaired RRMS patients (36%) at baseline and seven cognitively impaired BMS patients (32%), six cognitively impaired RRMS patients (27%) at two-year follow-up. In BMS

group one case, in RRMS group no case was found for worsening. Improvement was detected in three cases in both groups.

Table 10 Number of failed cognitive tests per individual in patient groups at baseline and at 2-year follow-up (Hegedüs et al., 2019).

	Baseline, n (%)		2-year follow-up, n (%)	
Number of failed cognitive tests	BMS n=22	RRMS n=22	BMS n=22	RRMS n=22
0	10 (45%)	10 (45%)	11 (50%)	11 (50%)
1	2 (9%)	4 (18%)	4 (18%)	5 (23%)
2	5 (23%)	4 (18%)	2 (9%)	3 (14%)
3	2 (9%)	1 (5%)	2 (9%)	0
4	3 (14%)	0	3 (14%)	1 (5%)
5	0	1 (5%)	0	1 (5%)
6	0	1 (5%)	0	1 (5%)
7	0	1 (5%)	0	0
CI, n (%)	10 (45%)	8 (36%)	7 (32%)	6 (27%)

Note. CI: cognitively impaired.

4.2 Psychological characteristics of MS patients

Demographic and main clinical data of the subjects included in the study are shown in Table 11. A total of 68 RRMS patients (17 men, 51 women) and 66 healthy controls (19 men, 47 women) participated in this study. Mean age was 36.4±8.9 for the patients and 35.5±9.9 for the control participants. Level of education was 14.4±2.1 years for the patients and 14.8±1.9 for the controls. In RRMS group, mean disease duration was 6.6±5.3 and median EDSS score was 1.0 (0.0, 2.0). Sixty-two percent of the patients received disease modifying therapy.

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Table 11 Demographic and clinical characteristics of the study sample.

	RRMS n=68	Control n=66	*p*-value
Gender, n (men/women)	17/51	19/47	n.s.
Age, y, mean (SD)	36.4 (8.9)	35.5 (9.9)	n.s.
Education, y, mean (SD)	14.4 (2.1)	14.8 (1.9)	n.s.
Disease duration, y, mean (SD)	6.6 (5.3)	n.r.	n.r.
EDSS score, mean (SD)	1.2 (1.4)	n.r.	n.r.
EDSS score, median (IQR)	1.0 (0.0,2.0)		
DMT, n			
Cladribine	1	n.r.	n.r.
Interferon beta-1a	8	n.r.	n.r.
Interferon beta-1b	1	n.r.	n.r.
Glatiramer acetate	5	n.r.	n.r.
Natalizumab	21	n.r.	n.r.
Fingolimod	1	n.r.	n.r.
Teriflunomide	2	n.r.	n.r.
Dimethyl fumarate	3	n.r.	n.r.
None	26	n.r.	n.r.

Note. y: years, SD: standard deviation, EDSS: expanded disability status scale, IQR=interquartile range,

DMT: disease modifying treatment, n.s.: not significant, n.r.: not relevant.

Concerning psychological characteristics, RRMS patients had a higher mean depression score (11.57±8.48 vs. 5.74±5.2, p<0.001), a higher mean health anxiety score (19±8.89 vs. 15.33±6.61, p=0.009) and a higher mean fatigue score (29.75±21.09 vs. 19.67±15.13, p=0.006) – including physical and psychosocial but not cognitive subscores – than controls (Table 12). Depressive symptoms occurred in 54.4% (n=37) of RRMS patients, and 67.6% (n=46) were considered anxious, out of them 13 patients (19.1%) had health anxiety. 38.2% of patients reported fatigue. In control group, 18.2% (n=12) had depressive symptoms, 48.5% (n=32) anxiety and 10.6% (n=7) health anxiety. The prevalence of fatigue was 10.6%.

In comparison with control group, RRMS patients used less problem-focused strategies (1.71±0.54 vs. 1.9±0.53, p=0.045), in general, and support seeking strategy (1.57±0.67 vs. 1.86±0.8, p=0.017) and were more prone to use withdrawal strategy (1.5±0.64 vs. 1.12±0.67, p=0.001). RRMS patients exhibited more elevated dysfunctional attitudes in the value systems of love (0.97±4.79 vs. -0.77±4.31, p=0.028), entitlement (3.33±4.37 vs. 1.86±4.1, p=0.025) and autonomy (0.79±4.11 vs. -1.44±3.69, p=0.002).

The patients' mean EQ-i score was significantly lower than that of the controls (418.28±56.76 vs. 457.95±46.13, p<0.001). The differences were significant in all five EQ-i scales – intrapersonal (120.24±23.33 vs. 134.92±19.15, p<0.001), interpersonal (90.54±12.4 vs. 97.12±9.86, p=0.001), stress management (56.56±8.91 vs. 60.76±8.21, p=0.005), adaptability (91.12±11.79 vs. 97.86±11.26, p= 0.001) and general mood (91.12±11.79 vs. 97.86±11.26, p=0.001) – and in almost all subscales, except for empathy, social responsibility, impulse control and problem solving.

Relative to controls, RRMS patients had a significantly higher mean global score of alexithymia (48.57±13.35 vs. 40.12±9.57, p<0.001) and had significantly more difficulties to identify emotions (13.56±4.87 vs. 10.45±3.57, p<0.001), to describe feelings (16.35±5.08 vs. 11.92±4.02, p<0.001) and were characterized by significantly more externally oriented thinking (19.26±4.61 vs. 17.65±4.51, p=0.043). Alexithymia was found in 13 (19.1%) patients, 13 (19.1%) patients showed borderline alexithymia. In control group, two individuals (3%) were alexithymic and five persons were borderline alexithymic (7.6%).

Table 12 Comparison of psychological characteristics between RRMS patients and controls.

	RRMS n=68	Control n=66	*p*-value
BDI	11.57 (8.48)	5.74 (5.2)	**<0.001**
SHAI	19 (8.89)	15.33 (6.61)	**0.009**
MFIS	29.75 (21.09)	19.67 (15.13)	**0.006**
Physical subscale	15.1 (11.3)	7.61 (6.45)	**<0.001**
Cognitive subscale	11.9 (10.06)	10.33 (8.41)	0.530
Psychosocial subscale	2.75 (2.37)	1.73 (1.78)	**0.015**

	RRMS n=68	Control n=66	*p*-value
Ways of Coping			
Problem-focused strategies	1.71 (0.54)	1.9 (0.53)	**0.045**
Problem analysing	1.91 (0.67)	2.18 (0.56)	0.072
Goal directed behaviour	1.51 (0.66)	1.62 (0.71)	0.456
Emotion-focused strategies	1.34 (0.33)	1.25 (0.4)	0.143
Emotion-centred behaviour	0.93 (0.63)	0.8 (0.55)	0.234
Adaptation	1.41 (0.54)	1.37 (0.52)	0.381
Support seeking	1.57 (0.67)	1.86 (0.8)	**0.017**
Emotional balance seeking	1.29 (0.68)	1.11 (0.68)	0.082
Withdrawal	1.5 (0.64)	1.12 (0.67)	**0.001**
DAS			
Approval	0.69 (3.99)	-0.74 (3.51)	0.039
Love	0.97 (4.79)	-0.77 (4.31)	**0.028**
Achievement	-0.51 (6.22)	-2.44 (5.09)	0.051
Perfectionism	0.37 (4.86)	-0.89 (3.16)	0.141
Entitlement	3.33 (4.37)	1.86 (4.1)	**0.025**
Omnipotence	1.1 (4.58)	0.39 (3.69)	0.294
Autonomy	0.79 (4.11)	-1.44 (3.69)	**0.002**
EQ-i	418.28 (56.76)	457.95 (46.13)	**<0.001**
1-Intrapersonal	120.24 (23.33)	134.92 (19.15)	**<0.001**
Assertiveness	18.81 (4.51)	20.64 (3.85)	**0.008**
Emotional self-awareness	25.16 (5.81)	27.83 (4.92)	**0.005**
Self-regard	28.01 (8.08)	32.64 (7.54)	**<0.001**
Dependence	21.87 (4.63)	24.33 (4.72)	**0.004**
Self-actualization	26.38 (5.35)	29.76 (3.97)	**<0.001**
2-Interpersonal	90.54 (12.4)	97.12 (9.86)	**0.001**
Empathy	18.38 (3.14)	19 (2.81)	0.195
Social responsibility	35.9 (4.46)	37.21 (3.98)	0.074
Inter-personal relationship	36.26 (8.04)	40.91 (6.44)	**0.001**
3-Stress Management	56.56 (8.91)	60.76 (8.21)	**0.005**

	RRMS n=68	Control n=66	*p*-value
Stress tolerance	27.06 (4.16)	30.15 (3.9)	**<0.001**
Impulse control	29.35 (6.89)	30.61 (6.63)	0.286
4-Adaptability	91.12 (11.79)	97.86 (11.26)	**0.001**
Reality testing	35.5 (5.59)	37.7 (5.3)	**0.008**
Flexibility	24.75 (5.95)	27.79 (5.38)	**0.002**
Problem solving	30.87 (4.17)	32.38 (4.37)	0.065
5-General Mood	91.12 (11.79)	97.86 (11.26)	**0.001**
Optimism	27.81 (5.46)	31.09 (5.22)	**<0.001**
Happiness	32.49 (7.13)	36.7 (5.28)	**<0.001**
TAS-20	48.57 (13.35)	40.12 (9.57)	**<0.001**
DIF	13.56 (4.87)	10.45 (3.57)	**<0.001**
DDF	16.35 (5.08)	11.92 (4.02)	**<0.001**
EOT	19.26 (4.61)	17.65 (4.51)	**0.043**

Note. Scores are mean (SD).

BDI: Beck Depression Inventory, SD: standard deviation, SHAI: Short Health Anxiety Inventory, MFIS: Modified Fatigue Impact Scale, DAS: Dysfunctional Attitude Scale, EQ-i: Emotional Quotient Inventory, TAS-20: Toronto Alexithymia Scale, DIF: difficulty in identifying feelings, DDF: difficulty in describing feelings, EOT: externally oriented thinking.

The bold values indicate the P values of scales/subscales which their differences were significant.

Relationships between depression and different variables are presented in Table 13. In RRMS group, depressive symptoms were not associated with demographic and disease related variables. BDI score was strongly correlated with SHAI (r=0.512, p<0.001), MFIS (r=0.578, p<0.001), MFIS Physical subscale (r=0.541, p<0.001), TAS-20 (r=0.547, p<0.001), DIF (r=0.568, p<0.001) and DDF score (r=0.578, p<0.001). BDI score was strongly and negatively associated with EQ-i (r=-0.729, p<0.001) and the five EQ-i scales score. BDI score was negatively correlated with all EQ-i subscale score except for Problem solving. Depression was moderately associated with Cognitive fatigue

(r=0.495, p<0.001), Psychosocial fatigue (r=0.461, p<0.001), Emotion-focused coping (r=0.360, p=0.003), Emotion-centred behaviour (r=0.442, p<0.001), Love (r=0.303, p=0.012), Achievement (r=0.334, p=0.005), Autonomy (r=0.380, p=0.001) and Externally oriented thinking (r=0.377, p=0.002). Depression was moderately and negatively correlated with Problem-focused coping (r=-0.244, p=0.045) and Goal directed behaviour (r=-0.312, p=0.01). Depression didn't have any significant correlation with Problem analysing, Adaptation, Support seeking, Emotional balance seeking, Withdrawal coping styles, Approval, Perfectionism, Entitlement and Omnipotence.

In the control group, depressive symptoms were not associated with demographic variables. BDI score was strongly correlated with DDF score (r=0.613, p<0.001). BDI score was strongly and negatively associated with EQ-i (r=-0.506, p<0.001), Self-regard (r=-0.501, p<0.001), Stress Management (r=-0.556, p<0.001), Stress Tolerance (r=-0.551, p<0.001), General Mood (r=-0.533, p<0.001) and Happiness (r=-0.528, p<0.001) score. Depression was moderately associated with Health Anxiety (r=0.405, p=0.001), Fatigue (r=0.332, p=0.006) – including the three subscales – Emotion-focused coping (r=0.259, p=0.036), Approval(r=0.385, p=0.001), Perfectionism (r=0.276, p=0.025), Omnipotence (r=0.324, p=0.008), Autonomy (r=0.415, p=0.001), Alexithymia (r=0.483, p<0.001) and Difficulty in identifying feelings (r=0.351, p=0.004). BDI score was moderately and negatively correlated with Intrapersonal scale (r=-0.476, p<0.001), Assertiveness (r=-0.374, p=0.002), Dependence (r=-0.291, p=0.018), Self-actualization (r=-0.467, p<0.001), Impulse control (r=-0.386, p=0.003), Adaptability scale (r=-0.386, p=0.001), Reality testing (r=-0.366, p=0.002), Flexibility (r=-0.292, p=0.017) and Optimism (r=-0.436, p<0.001) score. Depression didn't have any significant correlation with Problem-focused coping, Problem analysing, Goal directed behaviour, Emotion-centred behaviour, Adaptation, Support seeking, Emotional balance seeking, Withdrawal coping styles, Love, Achievement, Entitlement, Emotional self-awareness, Interpersonal scale and subscales, Problem solving and Externally oriented thinking.

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Table 13 The relationship between BDI score and different variables.

	RRMS; n=68		Control; n=66	
	Correlation Coefficient	*p*-value	Correlation Coefficient	*p*-value
Gender	0.043	0.726	0.123	0.327
Age	0.09	0.465	-0.033	0.79
Education	-0.113	0.358	-0.174	0.162
Disease duration	-0.008	0.949	n.r.	n.r.
EDSS	0.003	0.982	n.r.	n.r.
SHAI	**0.512**	**<0.001**	***0.405***	***0.001***
MFIS	**0.578**	**<0.001**	***0.332***	***0.006***
Physical subscale	**0.541**	**<0.001**	***0.355***	***0.003***
Cognitive subscale	***0.495***	***<0.001***	***0.266***	***0.031***
Psychosocial subscale	***0.461***	***<0.001***	***0.284***	***0.021***
Ways of Coping				
Problem-focused strategies	***-0.244***	***0.045***	-0.049	0.695
Problem analysing	-0.087	0.481	-0.041	0.745
Goal directed behaviour	***-0.312***	***0.01***	-0.042	0.74
Emotion-focused strategies	***0.360***	***0.003***	***0.259***	***0.036***
Emotion-centred behaviour	***0.442***	***<0.001***	0.239	0.053
Adaptation	0.05	0.683	0.127	0.311
Support seeking	0.083	0.501	0.049	0.694
Emotional balance seeking	0.151	0.219	0.1	0.424
Withdrawal	0.217	0.075	0.31	0.011
DAS				
Approval	0.231	0.058	***0.385***	***0.001***

	RRMS; n=68		Control; n=66	
	Correlation Coefficient	*p*-value	Correlation Coefficient	*p*-value
Love	***0.303***	***0.012***	0.164	0.188
Achievement	***0.334***	***0.005***	0.025	0.844
Perfectionism	0.158	0.197	***0.276***	***0.025***
Entitlement	0.066	0.594	0.229	0.066
Omnipotence	0.012	0.921	***0.324***	***0.008***
Autonomy	***0.380***	***0.001***	***0.415***	***0.001***
EQ-i	**-0.729**	**<0.001**	**-0.506**	**<0.001**
1-Intrapersonal	**-0.657**	**<0.001**	***-0.476***	***<0.001***
Assertiveness	***-0.443***	***<0.001***	***-0.374***	***0.002***
Emotional self-awareness	**-0.530**	**<0.001**	-0.163	0.191
Self-regard	**-0.637**	**<0.001**	**-0.501**	**<0.001**
Dependence	***-0.331***	***0.006***	***-0.291***	***0.018***
Self-actualization	**-0.669**	**<0.001**	***-0.467***	***<0.001***
2-Interpersonal	**-0.542**	**<0.001**	-0.061	0.629
Empathy	***-0.390***	***0.001***	0.007	0.953
Social responsibility	***-0.286***	***0.018***	-0.024	0.848
Inter-personal relationship	**-0.524**	**<0.001**	-0.081	0.517
3-Stress Management	**-0.538**	**<0.001**	**-0.556**	**<0.001**
Stress tolerance	**-0.580**	**<0.001**	**-0.551**	**<0.001**
Impulse control	***-0.324***	***0.007***	***-0.364***	***0.003***
4-Adaptability	**-0.512**	**<0.001**	***-0.386***	***0.001***
Reality testing	***-0.497***	***<0.001***	***-0.366***	***0.002***
Flexibility	***-0.396***	***0.001***	***-0.292***	***0.017***
Problem solving	-0.218	0.074	-0.191	0.124
5-General Mood	**-0.712**	**<0.001**	**-0.533**	**<0.001**
Optimism	**-0.665**	**<0.001**	***-0.436***	***<0.001***
Happiness	**-0.668**	**<0.001**	**-0.528**	**<0.001**

	RRMS; n=68		Control; n=66	
	Correlation Coefficient	*p*-value	Correlation Coefficient	*p*-value
TAS-20	**0.547**	**<0.001**	***0.483***	***<0.001***
DIF	**0.568**	**<0.001**	***0.351***	***0.004***
DDF	**0.578**	**<0.001**	**0.613**	**<0.001**
EOT	***0.377***	***0.002***	0.187	0.132

Note. EDSS: expanded disability status scale, BDI: Beck Depression Inventory, SD: standard deviation, SHAI: Short Health Anxiety Inventory, MFIS: Modified Fatigue Impact Scale, DAS: Dysfunctional Attitude Scale, EQ-i: Emotional Quotient Inventory, TAS-20: Toronto Alexithymia Scale, DIF: difficulty in identifying feelings, DDF: difficulty in describing feelings, EOT: externally oriented thinking.

n.r.: not relevant.

The bold values indicate the *p* values of scales/subscales which their differences were significant.

Regression analysis showed that in MS group, 68.4 % of the variation in BDI score can be explained using EQ-i score, Cognitive subscale score of MFIS, Adaptability scale score of EQ-i, Emotion-centred behaviour score of Ways of Coping and DIF score of TAS-20 (r^2=0.684, p<0.001). In control group, 54.5 percent of the variation in BDI score can be explained using DDF score of TAS-20, Stress management scale score of EQ-i, Self-regard subscale score of EQ-i and SHAI score (r^2=0.545, p<0.001).

4.3 Integrative group therapy for people in early MS

During the three-month recruitment period, eight patients were informed about the treatment trial. One patient refused to participate because of the required time commitment and one patient who was diagnosed less than six months before was excluded. Four out of six patients were women, mean age was 31.7 years, median of disease duration was 1 year, and the Expanded Disability Status Scale (EDSS) score ranged between 0.0 and 3.0. All patients were in the early stage of MS and all of them

had RR disease course. Four patients used immunomodulatory treatment. Demographic and main clinical data of the subjects are shown in Table 14.

Table 14 Demographic and clinical characteristics of the patients.

	Intervention n=6
Gender, n (men/women)	2/4
Age, y, mean (SD)	31.7 (4.4)
Education, y, mean (SD)	16.5 (2.0)
Disease duration, y, median (IQR)	1 (0.875, 3.5)
EDSS score, median (IQR)	1.25 (0.75, 2.25)
Immunomodulatory treatment, n	4

Note. y: years, SD: standard deviation, IQR=interquartile range.

Patterns of change in the outcome measures across time are presented in Table 15. The analyses on primary outcome measures showed a decrease of the depressive symptoms according to BDI scores from a mean of 9.33 (median of eight) at baseline to a mean of 5.5 (median of six) at post-treatment, and then to a mean of 4.67 (median of 5.5) at 6-month follow-up. Results stressed that the level of health anxiety decreased over time from a mean of 22.17 (a median of 20) at inclusion to a mean of 14.17 (a median of 13) at post-treatment, and to a mean of 13.0 (a median of 12) at 6-month follow-up. Perceived fatigue tended to decline from a mean of 17.5 (a median of 17) at baseline to a mean of 15.5 (a median of 8.5) at post-treatment, and to a mean of 12.83 (a median of 15.5) at 6-month follow-up.

The analyses on secondary outcome measures showed a constant increase in EQ-i scores (from a mean of 432.83 at baseline to a mean of 453.33 at post-treatment, and to a mean of 464.33 at 6-month follow-up) across time. The frequency of problem-focused strategies tended to increase over time (from a mean of 1.74 at baseline to a mean of 1.81 at post-treatment, and to a mean of 2.16 at 6-month follow-up), while the frequency of emotion focused strategies remained stable (with a mean of 1.22 at baseline, a mean of 1.22 at post-treatment, and a mean of 1.3 at 6-month follow-up). Results stressed that the

level of alexithymia decreased over time from a mean of 44.33 at inclusion to a mean of 38.83 at post-treatment, and to a mean of 38.00 at 6-month follow-up.

Table 15 Scores on outcome measures at assessment time points.

	Intervention Group (n=6)		
	Pre-treatment	Post-treatment	6-month follow-up
Depression			
BDI	9.33 (3.56)	5.5 (4.23)	4.67 (2.5)
Health Anxiety			
SHAI	22.17 (6.18)	14.17 (2.32)	13.0 (5.76)
Fatigue			
MFIS	17.5 (12.74)	15.5 (20.12)	12.83 (10.5)
Physical subscale	8.83 (8.98)	10.67 (12.71)	7.83 (6.34)
Cognitive subscale	6.5 (6.98)	4.00 (6.29)	4.17 (4.36)
Psychosocial subscale	2.17 (1.72	1.33 (2.34)	0.83 (0.98)
Emotional-social intelligence			
EQ-i	432.83 (36.71)	453.33 (28.18)	464.33 (43.14)
EQ-i-1	126.83 (11.58)	132.67 (12.68)	137.50 (15.63)
EQ-i-2	87.17 (6.97)	90.00 (6.32)	91.17 (7.88)
EQ-i-3	59.67 (9.4)	63.00 (3.74)	64.50 (7.23)
EQ-i-4	94.33 (13.02)	98.67 (8.78)	100.33 (11.83)
EQ-i-5	64.83 (7.81)	69.00 (7.07)	70.83 (8.26)
Coping			
Problem-focused strategies	1.74 (0.65)	1.81 (0.41)	2.16 (0.46)
Problem analysing	1.89 (0.81)	2.00 (0.3)	2.28 (0.44)
Goal directed behaviour	1.58 (0.47)	1.63 (0.44)	2.04 (0.49)
Emotion-focused strategies	1.22 (0.58)	1.22 (0.58)	1.3 (0.7)
Emotion-centred behaviour	0.96 (0.58)	0.79 (0.37)	0.88 (0.61)

	Intervention Group (n=6)		
	Pre-treatment	Post-treatment	6-month follow-up
Adaptation	1.17 (0.49)	1.00 (0.45)	1.21 (0.62)
Support seeking	1.58 (0.8)	1.42 (0.66)	1.75 (0.99)
Emotional balance seeking	1.08 (0.2)	1.63 (0.45)	1.33 (0.61)
Withdrawal	1.33 (0.63)	1.28 (0.68)	1.34 (0.52)
Alexithymia			
TAS-20	44.33 (4.37)	38.83 (4.54)	38.00 (8.20)
DIF	13.50 (1.88)	11.67 (2.34)	11.00 (2.61)
DDF	13.17 (3.31)	10.17 (2.79)	10.83 (2.32)
EOT	17.67 (3.93)	17.00 (3.58)	16.17 (6.24)

Note. Scores are mean (SD).

BDI: Beck Depression Inventory, SHAI: Short Health Anxiety Inventory, MFIS: Modified Fatigue Impact Scale, EQ-i: Emotional Quotient Inventory, EQ-i-1: Intrapersonal Scale, EQ-i-2: Interpersonal Scale, EQ-i-3: Stress Management Scale, EQ-i-4: Adaptability Scale, EQ-i-5: General Mood Scale, TAS-20: Toronto Alexithymia Scale, DIF: difficulty in identifying feelings, DDF: difficulty in describing feelings, EOT: externally oriented thinking.

During the three-month recruitment period eight potential participants were approached and six patients were included, giving an average recruitment rate of two persons/month. All patients finished the intervention group, giving a completion rate of 100 %. Patients demonstrated good compliance with the treatment and the follow-up session (the attrition rate was 0%). The average number of sessions attended was 19 (range 14-20 sessions). No adverse events were reported. Results of the evaluation questionnaires are shown in Table 16. The participants were satisfied with the experience and perceived positive changes in their lives. The success of the intervention group is proven by the evolution of a peer support group.

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Table 16 Process evaluation.

Questions	Answers (n=6)
Satisfaction (5-point scale), mean	4.5
Usefulness (5-point scale), mean	4.3
Positive change, no. of responses	Yes – 6
Repetition of experience, no. of responses	Yes – 6
Recommendation, no. of responses	Yes – 6

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5. Discussion

5.1 Neuropsychological characteristics of BMS patients[4]

This study represents to our knowledge the first attempt of evaluating cognitive functions of BMS patients never treated compared to RRMS patients treated with disease modifying therapy (Hegedüs et al., 2019). We report a cohort of benign MS patients followed longitudinally for two years, with repeated disability measures and a battery of neuropsychological assessments, compared to healthy controls and RRMS patients. In our clinic the prevalence of BMS patients is in line with the occurrence rate revealed in other studies (Correale, Ysrraelit, et al., 2012). We tested the hypothesis that cognitive performance of BMS patients is similar to the capabilities of RRMS patients and both of them differ from the cognitive profile of people without MS. Furthermore, the level of depression is more elevated in both patient groups compared to healthy individuals.

Cognitive impairment is common in MS including deficits in complex attention, information processing speed, executive function and long-term memory (Chiaravalloti & DeLuca, 2008). Similar cognitive profile in BMS patients was found as in the whole MS population (Correale, Peirano, et al., 2012). We found that both BMS and RRMS patients differed from healthy controls in terms of cognitive functioning. BMS patients showed worse performance in long-term visuo-spatial memory and information processing speed, whereas, complex attention, working memory, long-term verbal memory – despite slower verbal learning – and executive function were found to be intact. RRMS patients showed significant difference in complex attention, long-term visual memory and information processing speed compared to people without MS. While working memory, long-term verbal memory – even verbal learning – and executive function were not affected. This may support the finding that executive function is a less frequently involved domain than memory and information processing speed. The most frequently affected complex attention, information processing speed and learning can

[4] Incorporated publication: Hegedüs K, Kárpáti J, Iljicsov A, Simó M. (2019) Neuropsychological characteristics of benign multiple sclerosis patients: A two-year matched cohort study. Mult Scler Relat Disord. 35: 150-155.

significantly influence the performance in other domains, meaning these functions could be targeted with cognitive rehabilitation.

As previously reported (Chiaravalloti & DeLuca, 2008), we did not find differences in cognitive functioning between BMS and RRMS patients. This result did not change after two years despite the improvement of the BMS group in verbal learning and information processing speed. Here we may consider practice effect, however, it was ferreted out by the study design, re-evaluating two patient groups. The verbal learning may improve due to intact executive function and less involved complex attention compared to RRMS group, thus, patients can generate reconstituted learning strategy in the repeated test situation. In case of information processing speed, individual cases may bias the result (two BMS subjects had a performance of 1.55 standard deviations above mean BMS value). Our findings are in line with those studies suggesting that immunomodulatory treatment may not result in significant reductions in cognitive symptoms (Haase et al., 2004; Sundgren et al., 2016) and cognitive deficits can occur independent of physical disability.

Cognitive impairment in the patient groups was in the range previously reported (BMS: 45%; RRMS: 36% at baseline) (Rao et al., 1991; Borghi et al., 2013). This aspect of cognitive performance supports the findings that information processing speed is the most involved in both MS groups, complex attention is more involved in RRMS patients than in BMS patients, working memory and executive function is less involved in both MS groups.

A high prevalence rate of depression (31%) in MS was demonstrated (Boeschoten et al., 2017). A twelve-month prevalence rate of about 20% and a lifetime prevalence rate of 50% were reported (Sa, 2008). Untreated depression is associated with suicidal ideation, impaired cognitive function and poor adherence to immunomodulatory treatment (Ziemssen, 2009). The presence of depressive disorder does not correlate well with the level of neurological disability (Goldman, 2005). However, we observed an elevated level of depression in the BMS group compared to people without MS. Herein we may consider that this patient group does not receive DMT and they do not attend regular check-up resulting in the lack of external control of the disease. It would underline the importance of involving them in the clinical routine in order to strengthen their feeling of security (Vattakatuchery et al., 2011).

Previous studies have demonstrated that the association between depression and cognitive impairment affects specific cognitive domains, such as working memory, processing speed, attention and executive functions (Arnett et al., 2008; Sundgren et al., 2013; Morrow et al., 2016). Herein, we did not find correlation between depression and the different cognitive domains in any patient groups. However, further investigation could give deeper insights into the relationship.

Our study presents some strengths. The study design allowed a detailed neuropsychological assessment of matched cohorts followed longitudinally. The inclusion criteria of BMS group involved the natural course of the disease enabling the examination of the effect of disease modifying therapy on cognitive functioning. The presented cognitive profile provided implication for cognitive rehabilitation apart from DMT. It outlined the higher level of depression in BMS patients.

We need to mention some limitations that may have an impact on the findings of present study. Our design was clinic-based instead of population-based with relatively low sample size. However, all registered patients were involved, including those not necessarily returning to the clinic for regular check-ups. The two-year follow-up and the low number of patients involved allowed us to present preliminary data and tendency. Paraclinical factors, such as fatigue, were not investigated, which could have an impact on cognition itself. Further limitation of our study could be the absence of MRI data, however, our aim included the focus on clinical – more precisely – on neuropsychological status. Further study should include the MRI parameters of the patient groups in order to have a better understanding of cognitive functioning.

5.2 Psychological characteristics of MS patients

In the study we aimed at investigating psychological characteristics of MS patients compared to healthy population, determining the correlates of depression and clarifying the relationship between depression and the factors associated with it. By identifying risk and protective factors, we intended to design an adequate intervention program to prevent an eventual depression and the associated risk of suicide.

We did not find a relationship between depression and demographic factors (age, gender, education) nor between depression and illness related factors (disease duration,

functional status). This underlines the hypothesis that psychological factors play an important role in the emergence of depression in RRMS patients (Lynch et al., 2001).

With regards to psychological characteristics, more than half of MS patients presented depressive symptoms that is a much higher prevalence rate compared to general population, being in line with previous results (Feinstein et al., 2014). It can be as high as the lifetime prevalence rate of major depressive disorder (Solaro et al., 2016) because we used the cut-off score/threshold for mild depression in order to include those patients who have clinically significant level of mood disorder.

One-fifth of the participants showed health anxiety, thus demonstrating twice as high prevalence rate as the general population did. It is equal to the one of generalized anxiety disorder (Korostil & Feinstein, 2007) and it is unrelated to physical status.

We found that the prevalence rate of fatigue (38.2%) was as high as the incidence of fatigue over 2 years in the study of Fiest et al. (2016). Compared to general population physical and psychosocial fatigue was significantly higher while cognitive fatigue was not more elevated. Four times more MS people present fatigue compared to healthy people, making it the most debilitating symptom.

Our result did not show a preference for the use of a specific coping method, MS patients had a normal and diversified use of these strategies. However, they tended to use less support seeking strategy and were more prone to use withdrawal strategy compared to general population. These coping strategies would be important for adjusting to the adaptive demands of the disease (Goretti et al., 2010). While depression was associated with emotion-centred behaviour and had an inverse link with goal-directed behaviour. In our control sample there were no relationships between depression and different coping strategies. Our results confirm the traditional link between emotion-focused coping and depression in MS population (Gay et al., 2010; Lynch et al., 2001).

It is well-supported that dysfunctional attitudes are a stable marker of cognitive vulnerability to depression and do not react according to changes in mood (Fresco et al., 2006). In our study, RRMS patients exhibited different pattern of dysfunctional attitudes compared to general population, they more frequently used cognitive distortion in the value systems of love, entitlement and autonomy. Depression was linked with love, achievement and autonomy, while in general population it is associated with approval,

perfectionism, omnipotence and autonomy. Cognitive distortions and dysfunctional attitudes related to love and autonomy could be addressed in psychological interventions.

Although alexithymia, a difficulty in identifying, describing feelings and an externally oriented cognitive style, cannot be considered a psychopathological feature, it is a personality construct that can lead to misinterpretation of emotional arousal as symptoms of physical illness (Taylor, 1984). Moreover, alexithymia might influence the way in which patients perceive and experience disease-related somatic symptoms (Lumley et al., 1997). We found that RRMS patients showed a significantly higher level of alexithymia, had significantly more difficulties to identify and describe emotions and used more frequently externally oriented thinking compared to general population. More than one-third of the participants had alexithymia or borderline alexithymia while this proportion was only one-tenth in healthy control, which is consistent with the results of other research (Bodini et al., 2008). There was a strong positive correlation of alexithymia with depression and with fatigue in patients with RRMS in line with the findings by other authors (Chahraoui et al., 2014; Eboni et al., 2018). Scores on different subscales of TAS-20 (DIF, DDF, EOT) showed that all three subscales correlated with depression as found by Stojanov and Stojanov (2020). It means that alexithymia, namely difficulty in identifying and communicating emotions and externally oriented thinking, might play a role in the development and the severity of depression.

Regarding the relationship between alexithymia and fatigue, we found that alexithymia was associated with fatigue which might support the hypothesis that MS patients with alexithymia may tend to amplify somatic sensations such as fatigue (Bodini et al., 2008).

Considering the wide range of difficulties in physical, emotional, cognitive and social part of MS patients' lives, emotional-social intelligence could play an important role in adjustment. Since being emotionally and socially intelligent means to effectively manage personal, social and environmental change by realistically and flexibly coping with the immediate situation, solving problems and making decisions. The competences of emotional-social intelligence are significantly related to physical and psychological health (Bar-On, 2006).

Our results showed that total EQ-i score and its subscales except four items (empathy, social responsibility, impulse control and problem solving) were significantly

lower in MS patients than in controls. It means that RRMS patients have lower competencies in the following fields:

- to accurately perceive, understand and accept themselves,
- to be aware of and understand their emotions,
- to express their emotions and themselves effectively and constructively,
- to be self-reliant and free of emotional dependency on others,
- to strive to achieve personal goals and actualize their potential,
- to establish mutually satisfying relationships and relate well with others,
- to effectively and constructively manage emotions,
- to objectively validate their feelings and thinking with external reality,
- to adapt and adjust their feelings and thinking to new situations,
- to be positive and look at the brighter side of life, and
- to feel content with themselves, others and life in general.

It confirms previous findings (Ghajarzadeh et al., 2014), however, we did not find differences in impulse control and problem solving but did find differences in interpersonal relationship.

As hypothesised based on the findings in general population (Bar-On, 2006), in RRMS patients, depression was strongly and negatively associated with emotional-social intelligence and the competencies of (a) the ability to recognize, understand and express emotions and feelings; (b) the ability to understand how others feel and relate with them; (c) the ability to manage and control emotions; (d) the ability to manage change, adapt and solve problems of a personal and interpersonal nature; and (e) the ability to generate positive affect and be self-motivated except for problem solving. It means that emotional social intelligence could be identified as a protective factor.

In sum, RRMS patients present lower emotional and social intelligence, alexithymic characteristics, use less problem-focused coping strategies and support seeking, and tend to withdraw. Their attitude is driven by the desire for love, entitlement and less autonomy compared to general public. In RRMS patients, depression was associated with health anxiety, fatigue, emotion-focused coping, cognitive distortions in the value systems of love, achievement and autonomy, alexithymia and emotional-social intelligence.

Among these factors we wanted to determine the main predictors for vulnerability to depression. We found that a combination of lower level of global emotional-social intelligence, cognitive fatigue, lack of competencies in change management (adaptability), emotion-centred coping and difficulty in identifying emotions allow the prediction of the appearance of depression. While in general public, difficulty in describing emotions, lack of competencies in stress management, lower self-regard and higher level of health anxiety influence the appearance of depression. These results support that different therapeutic approach is necessary in prevention and treatment of depression in MS.

In conclusion, these psychological features should be addressed in the prevention and treatment process of depression given priority to emotional-social competencies, change management, adaptive coping mechanism and identifying emotions. Furthermore, a successful treatment of depression can in turn decrease fatigue (Solaro et al., 2018) and health anxiety by targeting cognitive biases (Hayter et al., 2016).

5.3 Integrative group therapy for people in early MS

In the past two decades several new immunomodulatory therapies were introduced which reduce relapse rate and slow progression of the disease. Patients' QoL has significantly improved, however, acceptance of a chronic illness still causes difficulties. People with MS frequently report low mood, anxiety problems (Hanna & Strober, 2020) and adjustment difficulties (Giovannetti et al., 2017) that impact individuals' perceived health and well-being. Significant distress is often experienced in the early stage of MS as during this period people start learning about MS and its consequences and developing management strategies.

As there is growing evidence that psychosocial interventions are effective in improving psychological well-being (Sesel et al., 2018), our aim was to develop an integrative intervention group protocol for people in the early stage of MS to support the adaptation process and to prevent the development of severe psychological consequences. The program could be included in the routine clinical practice as part of the multidisciplinary management of MS. Although we cannot draw a conclusion regarding

treatment effects, we may note that the levels of both depression and health anxiety decreased over time.

Regarding fatigue, clinically significant difference (Rooney, McFadyen, et al., 2019) could be experienced in response to the intervention. Cognitive fatigue could be decreased that was identified as predictor for susceptibility for depression. Our result confirms the findings of a recent review that the use of psychological interventions for MS-related fatigue management may reduce fatigue in people with MS (Phyo et al., 2018).

Concerning protective and risk factors for depression, emotional-social intelligence – including the competencies and skills in self-awareness, self-expression, social awareness, interpersonal relationship, stress and change management, and self-motivation – could improve over time. The use of problem-focused strategies and the coping mechanism of support seeking tended to increase, while the frequency of emotion focused strategies remained stable. However, a priori the group members used these types of coping style only occasionally. The level of alexithymia decreased over time, the participants could improve in identifying and describing feelings.

During the recruitment procedure we tried to imitate current clinical practice by involving patients who reported psychological problem. However, the recruitment rate should be improved. Implementing a screening process from the onset of the disease would be an option. Once patients had been included, the intervention seemed to be feasible. There was no attrition during the study that can be explained by voluntarism in seeking treatment. The participants reported satisfaction and positive personal change due to the group experience. These findings were independent of the severity of the disease (some patients had mild, others more active disease course). The patients generally appreciated the opportunity to learn adjustment strategies, to share experiences, and to meet people who had a similar condition. After the intervention they established a monthly peer support group meeting (still functioning at 12-month follow-up) which indicates the importance of social interactions and peer support (Salminen et al., 2014). The intervention program was accepted by the participants who were in the early stage of MS, which implies that the psychological service was sensitive and supportive for them (Dennison et al., 2010). Despite the promising results and feedback, the number of cancellations could be decreased by considering flexibility in treatment schedule.

Further investigation is needed to determine the effectiveness of our protocol. Future studies should have a randomized controlled design with a larger sample size using a screening process for inclusion and including outcome measure for QoL. Cognitive impairment and psychological dysfunction are well-known phenomena in MS. It could be investigated whether improving emotional well-being by using this intervention protocol has any influence on cognitive functioning.

In conclusion, this integrative group intervention program might be beneficial for and accepted by people in the early stage of MS, it might reduce depressive symptoms, health anxiety and fatigue. It may reinforce social support, protective factors such as emotional-social intelligence, change management, promote adaptive coping mechanism and reduce risk factors such as alexithymia. Including the program in the management of recently diagnosed MS patients could play an important role in the prevention of developing depression or adjustment difficulty and as a result in improving their QoL.

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6. Conclusions

In our study we used a multidimensional approach to understand the cognitive and psychobehavioural dimensions of multiple sclerosis, to reveal their complex interplay with the intention of designing a psychological preventive intervention program to be included in the routine clinical practice.

The results of our study confirm that cognitive functions and mood can be affected in MS independent of disease course. Therefore the "benign" label should be treated only as a reference to the physical status. Cognitive and psychological status should be assessed and managed irrespectively to MS subtype, meaning the need for routine monitoring of non-motor symptoms in MS in order to detect clinically meaningful changes and to start a timely and effective treatment. Thus a younger patient age could be targeted, when compensatory abilities, brain plasticity, and cognitive reserve may be better exploited.

Although the clinical relevance of BMS is said to be limited (Reynders et al., 2017) we consider this patient group with longstanding minimal disability without DMT as an existing entity. Prognostic factors of BMS status still need to be identified. The ability to predict clinical course would be important in order to optimize patient management and to select the most appropriate therapeutic interventions.

As previously reported, the prevalence of depression, anxiety, and fatigue is high in the MS population. Left untreated, they do not seem to improve spontaneously. With respect to the pathogenesis of depression in MS, a multifactorial aetiology can be supposed. Studying different psychological characteristics of MS patients, we can conclude that lower emotional and social intelligence, alexithymia, emotion-focused coping strategies are present in this population. Their attitude is driven by the desire for love, entitlement and less autonomy compared to general public. Therefore a different therapeutic approach is necessary in psychological interventions in MS.

We have identified lower level of emotional-social intelligence, cognitive fatigue, lack of competencies in change management, emotion-centred coping and difficulty in identifying emotions as predictors for the susceptibility of depression in MS. Therefore we can conclude that these psychological features might play an important role in the

vulnerability to depression and they should be addressed in psychological intervention programs.

Implementing the findings of previous studies and our results, we aimed to design an integrative intervention group protocol for people at the early stage of MS to support the adjustment process and to avoid severe psychological complications. Preliminary findings show that our program might be beneficial for and accepted by MS patients, and it might reduce depressive symptoms, health anxiety and fatigue. Furthermore, it may reinforce social support, protective factors – such as emotional-social intelligence, change management – promote adaptive coping mechanism and reduce risk factors, i.e. alexithymia. A future effectiveness study could include outcome measures for cognitive functioning as well.

As stated in the introduction, considering the challenges imposed by MS in the early stage, delivering care and early interventions for this group can substantially reduce disease burden. These support strategies may improve cognitive, emotional, and social functioning, and enhance the adjustment process resulting in a positive spill-over effect on family and economic burdens.

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7. Summary

Multiple sclerosis, the most common neurological disease that causes disability in early life, does not only influence physical functioning but is also related to cognitive impairment, fatigue, depression, and anxiety and can significantly impact quality of life. Disease burden may manifest at individual, family, community and economic levels. Understanding the complex interplay between various factors concerning the nature of MS is of utmost importance in the management of the disease. Adjustment to disease in different life domains creates challenges for both patients and their family members. The need for MS specific psychological interventions cannot be called into question.

Therefore we studied different still interacting aspects of MS. First, we aimed to investigate the pattern of cognitive functioning and depression in benign MS and relapsing remitting MS patients following them for two years. Second, we intended to explore the differences in psychological characteristics between MS patients and healthy population. Third, we aimed to design an integrative intervention group protocol for MS patients in the early stage to support the adjustment process and to prevent the development of severe psychological consequences.

The results of our study confirm that cognitive functions and mood can be affected in MS independent of disease course. Therefore the “benign” label should be treated only as a reference to the physical status and cognitive and psychological status should be assessed and managed irrespectively to MS subtype. Regarding different psychological characteristics of MS patients, we can conclude that lower emotional and social intelligence, alexithymia, emotion-focused coping strategies are present in this population. Our preliminary findings show that the designed integrative intervention group program might reduce depressive symptoms, health anxiety and fatigue. It may reinforce social support, protective factors, promote adaptive coping mechanism and reduce risk factors.

Considering the challenges imposed by MS in the early stage, delivering care and early interventions for this group can substantially reduce disease burden. These support strategies may improve cognitive, emotional, and social functioning, and enhance the adjustment process resulting in a positive spill-over effect on family and economic burdens.

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8. Összefoglalás

A sclerosis multiplex a leggyakoribb, általában fiatal felnőttkorban kezdődő, neuroimmunológiai megbetegedés. A betegség szomatikus tünetei mellett gyakran észlelhető kognitív funkciócsökkenés, fáradékonyság, hangulatzavar vagy szorongás, ami jelentős befolyással bír az életminőségre. A betegségteher nemcsak egyéni szinten, hanem családi, társadalmi és gazdasági szinten is megnyilvánulhat. A betegség kezelésében ezért fontos szerepe van a különböző tényezők közötti összefüggések megértésének. A betegséghez való alkalmazkodás az élet különböző területein kihívást jelent mind a páciensek, mind a családtagok számára.

Így célul tűztük ki az SM különböző aspektusból való megvizsgálását. Először benignus és relapszáló-remittáló SM betegek kognitív működését és hangulatát követtük két évig. Másodszor SM betegek pszichés jellemzőinek feltárását kíséreltük meg, hogy előkészítsük harmadik célunk megvalósítását: egy olyan integratív csoportterápiás program kidolgozását a betegség korai szakaszában lévők számára, amely segítheti az alkalmazkodás folyamatát, illetve prevenciós hatása lehet a különböző pszichés zavarok kialakulásában.

Az eredményeink azt mutatják, hogy mind a kognitív funkciók, mind a hangulat érintett lehet függetlenül a betegség lefolyásától. Tehát a benignus megjelölés leginkább a fizikai állapotra vonatkoztatható, illetve a kognitív és pszichés státuszt is célszerű folyamatosan követni, szükség esetén pedig a megfelelő beavatkozást beilleszteni a kezelésbe. A pszichés jellemzőket tekintve megállapítható, hogy az SM betegeket alacsonyabb szociális-érzelmi intelligencia, alexitímia és érzelem-fókuszú megküzdési stratégiák jellemzik. A tervezés során ezen tényezőket is figyelembe véve, a kidolgozott integratív csoportterápia javíthatja a hangulatot, csökkentheti az egészségszorongást és a fáradékonyságot. Megerősítheti a társas támogatást, a protektív tényezőket, segíthet adaptív megküzdési módok elsajátításában és csökkentheti a hangulatzavar kockázati tényezőit.

Az SM kezelésében a korai intervenciók jelentősen csökkenthetik a betegségterhet a kognitív, az érzelmi és a szociális működésmód javításával, illetve az alkalmazkodás elősegítésével. Mindez pedig továbbgyűrűzve pozitív hatással lehet a családi és gazdasági terhek tekintetében.

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Appendix – List of Tables