

## CLINICAL STUDY

# Information-processing speed in mildly disabled relapsing-remitting multiple sclerosis patients correlates with volumetry of optic chiasma and subcortical grey matter nuclei

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**ABSTRACT**

**INTRODUCTION:** Multiple sclerosis (MS) is an inflammatory demyelinating disease leading not only to physical disability but also to cognitive dysfunction. The aim of our study was to test cognitive functions of MS patients with mild relapsing-remitting form and to find out the relationship between cognitive functions and brain volumetry.

**METHODS:** 52 patients (RRMSp) and 23 age-related healthy participants (CON) were enrolled. Mild disability was defined by mean EDSS 2.4 ( $\leq 4.0$ ), and by median of disease duration 5.2 years. Cognitive status was tested using Single Digit Modality Test (SDMT). Brain volumetry was processed in FreeSurfer 2.0.0.

**RESULTS:** RRMSp patients showed significantly lower SDMT score than CON. SDMT results correlated positively with volume of thalamus, putamen and nc. caudate, and negatively with optic chiasma volume. Compared with CON, RRMSp presented with significantly lower volume in left and right nc. accumbent, cuneus and insular GM, right putamen, total brain cortical grey matter (GM), white matters hypointensities, and 3<sup>rd</sup> ventricular widths.

**CONCLUSION:** To our best knowledge, this is the first study that presents results showing a correlation of lower SDMT with higher optic chiasma volume, due to its subclinical chronic demyelination. We confirmed that GM atrophy is involved in cognitive functions in MS (Tab. 3, Fig. 2, Ref. 73). Text in PDF [www.elis.sk](http://www.elis.sk)

**KEY WORDS:** cognitive dysfunction, SDMT, brain volumetry, optic chiasma.

**Introduction**

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) leading not only to physical disability but also to cognitive dysfunction (1, 2). Patients diagnosed with MS can develop cognitive deficits even in the early stages of the disease (2, 3). Several cognitive domains have been identified to be specific for MS, of which slowed cognitive processing was found to be the core symptom of MS (4). Processing speed is a basic cognitive function required by, and therefore influencing,

downstream processes such as learning, memory, word retrieval, and executive functions (5). Research in MS clearly supports reliability and validity of Single Digit Modality Test (SDMT) to test cognitive functions (5) due to its sensitivity to recognise slowed processing or information speed (4).

Numerous studies have tested a relationship between cognitive dysfunction (CD) in MS and Magnetic Resonance Imaging (MRI) parameters, namely brain volumetry (7–10). However, the studies have shown controversial results. Some authors presented correlation of CD with global brain atrophy (7, 9–11) while others showed superiority of subcortical grey matter atrophy in development of CD (12–16). The results indicate that the underlying processes remain unknown.

The aim of our study was to test cognitive functions of MS patients with mild relapsing-remitting form of the disease and to find out the relationship between cognitive functions and brain volumetry. We also planned to compare the results with those obtained from healthy volunteers (CON). We hypothesized that cognitive dysfunction correlates with brain atrophy, which might have a greater diagnostic value than conventional MRI in predicting overall disease progression, and segmented brain measurements would become new practical volumetric biomarkers.

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**Tab 1. Differences between relapsing-remitting multiple sclerosis patients and healthy controls.**

	RRMSp (52)	CON (23)	p
Age	34.8±1.3	37.1±1.9	0.33
EDSS	2.4 (1.0–4.0)	NA	NA
Disease duration (years)	5.2 (0.5–10)	NA	NA
SDMT	47.1±1.2	55.2±1.8	0.001
L Nc Accumbens	403.5±12.9	469.4±19.4	0.008
R Nc Accumbens	451.6±10.8	494.2±16.3	0.04
L Cuneus GM	2444.3±88.7	2875.7±133.5	0.01
R Cuneus GM	2675.8±99.8	3196.1±150.2	0.01
L Insula GM	6384.7±166.9	7111.3±250.9	0.03
R Insula GM	6359.2±174.6	7065.0±262.5	0.03
R Putamen	4343.6±65.5	4704.3±98.4	0.004
3rd Ventricle	1253.9±62.8	903.5±94.4	0.001
WM Hypointensities	29642.5±5175.4	4552.2±7781.8	0.000008
Total Cortical GM	397006.7±13496.3	461825.0±20293.3	0.009
Total GM	563424.4±14201.4	624663.5±21353.8	0.02

RRMSp = relapsing-remitting MS patients, CON = healthy controls, EDSS = Expanded Disability Status Scale, SDMT = Single Digit Modality Scale, L = Left, R = Right, GM = grey matter, WM = white matter, NA = not applicable

**Patients and methods**

Local ethics approval for this study was obtained from the Ethics Committee of Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava

*Patients and control participants*

Patients fulfilling criteria for definite MS according to McDonald 2017 (17) were randomly selected from the Multiple Sclerosis Centre in Nitra, Slovakia, and they were included in the study after signing a written consent. In total 52 patients (11 males a 41 females) with relapsing-remitting MS (RRMSp) and 23 healthy participants (2 males, 20 females) were enrolled. The inclusion criteria were the age between 18 and 65 years, the absence of clinical relapse as well as corticoids treatment within 3 months before the study entry, and EDSS ≤ 4.0. Exclusion criteria

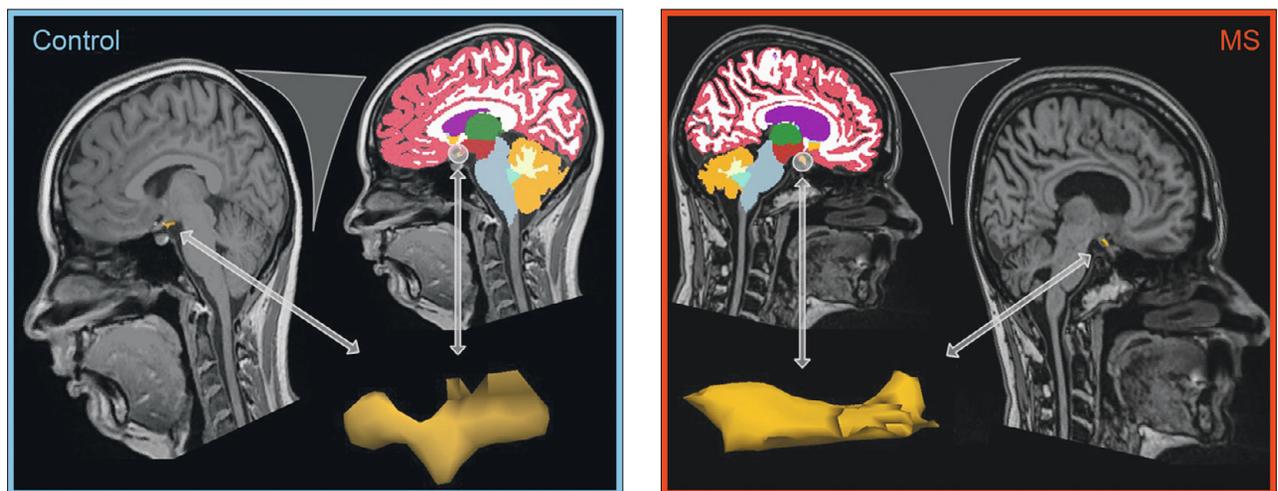
were EDSS ≥ 4.0; current or past disorders other than MS (for patients), which could affect cognitive performance at SDMT; no concomitant treatments with psychoactive drugs and no acute psychiatric disease; unwillingness to cooperate.

We collected information (Tab. 1) about the age, disease duration, immunomodulatory treatment (IMT), clinical and cognitive disability using SDMT. Out of 52 patients, 13 patients were tested before receiving any treatment and 39 were on treatment with different IMT agents (5 – teriflunomid, 2 – interferon beta 1a, 4 – glatiramer acetate, 16 – dimethyl fumarate, 3 – fingolimod, 4 – natalizumab, 2 – ocrelizumab, 3 – cladribin). The treatment (following national guidelines [www.health.gov](http://www.health.gov)) had lasted for ≥12 months before the examination and the patients remained on the same treatment. Clinical disability, assessed by Expanded Disability Status Scale (EDSS), was performed by neurologists trained in evaluating EDSS in MS patients. Cognitive status was tested using SDMT, written form, at the same time as EDSS and MRI examination were performed.

*MRI examination and volumetry using FreeSurfer*

a) Image acquisition

All subjects were scanned on a 1.5 Tesla MRI unit (MAGNETOM Avanto<sup>fit</sup>, Siemens Healthcare, GmbH, Erlangen, Germany) using a 20-channel Head/Neck coil for signal reception. The imaging protocol consisted of a head scout, 2D sagittal and axial T2-w TSE scans, a sagittal 3D FLAIR (SPACE sequence), an axial diffusion weighted scan, a sagittal 3D T1-w MPRAGE sequence and a sagittal 3D Double Inversion Recovery scan (DIR, SPACE sequence).



**Fig. 1. OPTIC CHIASMA.**

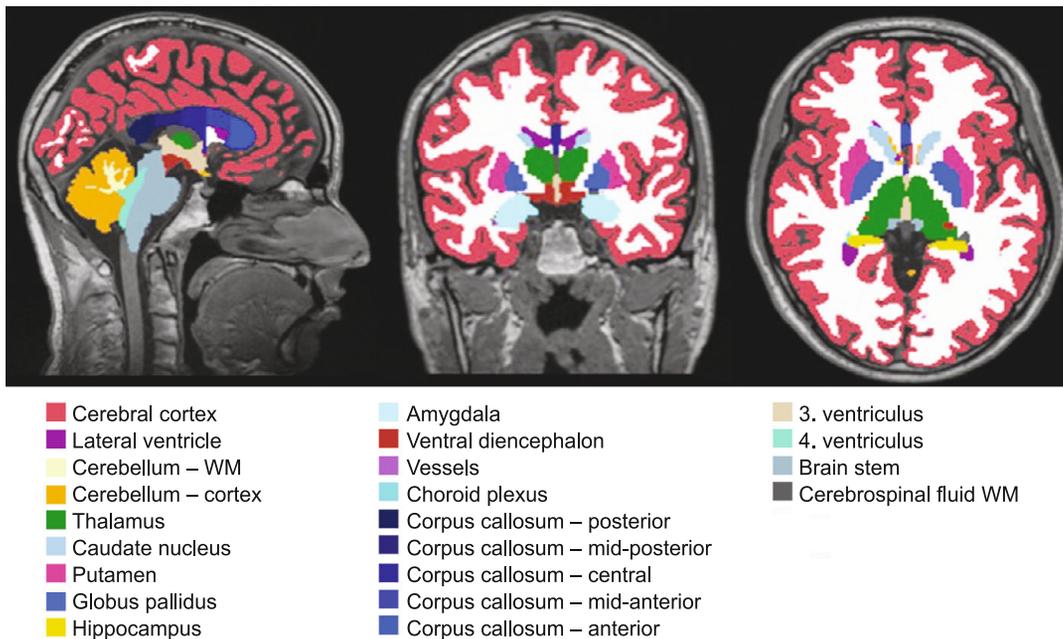


Fig. 2. Volumetry.

#### b) MR volumetry

For MR volumetry, the 3D  $T_1$ -weighted MRI (MPRAGE; Magnetization Prepared RAPid Gradient Echo) in sagittal direction was performed with following parameters: repetition time-TR/echo time-TE/inversion time-TI = 1900/2.4/900 ms, 176 slices per slab with the slice thickness of 1.2 mm and gap 0 mm, size of matrix 192x256 and pixel 1.3x1.0 mm<sup>2</sup>, flip angle 8°, one average, 2 GRAPPA-Generalized Autocalibrating Partial Parallel Acquisition factor, and scan time of 3 min 22 s.

The  $T_1$ -weighted MRI from all study participants were analyzed cross-sectionally and processed in FreeSurfer 2.0.0 (Harvard University, Boston, MA, USA). FreeSurfer enables to estimate volumes of the (i) brain structures in the right and left hemispheres (lateral ventricles, inferior lateral ventricles, cerebellum – WM and cortex, thalamus, caudate nucleus, putamen, globus pallidum, hippocampus, amygdala, nucleus accumbens, ventral diencephalon, cuneus, insula, choroid plexus, (ii) GM/WM segments with hemisphere distribution (WM-hemispherical and total, GM-cortical/subcortical/total, WM/non-WM hypointensities), (iii) specific areas of the brain such as ventricles (3<sup>rd</sup>/4<sup>th</sup>/5<sup>th</sup>), vessels-left/right, brain stem, optic chiasma, cerebrospinal fluid, corpus callosum – posterior/mid-posterior/central/mid-anterior/anterior and (iiii) brain volume (total with and without ventricles, supratentorial-total and without ventricles, estimated intracranial). (Table 2). No additional pre-processing or manual intervention was performed to avoid introducing biases in the tissue segmentations.

#### Statistical analyses

All statistical tests were performed in NCSS (version 9.0, LLC. Kaysville, Utah, USA). Differences in demographic and clinical

parameters (age, SDMT, EDSS, disease duration) as well as volumetry measures between patients and controls were evaluated using Kruskal-Wallis (ANOVA) test. The correlation of volumetry ratios with SDMT was performed using linear regression analysis. The  $p < 0.5$  was considered significant.

#### Results

##### Demographics and differences in tested parameters

RRMS patients showed significantly lower SDMT score than CON, indicating slower psychomotor speed and more intensive cognitive decline, although they did not differ in age (Tab. 1).

Volumetry measures showed in RRMSp significantly lower volume than in CON in several subcortical GM nuclei (left and right nucleus accumbent, cuneus and insular GM, and right putamen), total brain cortical and total GM. Total number of white matters hypointensities and 3<sup>rd</sup> ventricular widths were significantly higher in RRMSp than in CON. The groups did not differ in total brain volume (Tab. 1).

##### Correlation of SDMT with brain volumetry measures

In RRMSp, SDMT correlated adversely with optic chiasma (OCH) volume but not with age (Tab. 2). OCH volume significantly depended on subclinical demyelination in OCH but not with age (Tab. 3). SDMT also correlated with right putamen and thalamus, and with left caudate nucleus (Tab. 2).

In CON we did not prove correlation of SDMT with any of the volumetric measures.

Reduction of cortical grey matter was the only age-related result in RRMSp ( $R^2 = 0.09$ ,  $R = 0.31$ ,  $p = 0.006$ ).

**Tab. 2. Significant correlations of volumetric data and SDMT in RRMS patients.**

SDMT	RRMSp (52)	CON (23)
L Caudate Nc	R2=0.05 R=0.23 P=0.04	NS
R Thalamus	R2=0.05 R=0.23 P=0.03	NS
R Putamen	R2 =0.28 R=0.53 P=0.019	NS
Optic chiasma	R2=0.07 R=-0.28 P=0.014	NS

RRMSp = relapsing-remitting MS patients, CON = healthy controls, SDMT = Single Digit Modality Scale, L = Left, R = Right, nc = nucleus, NS = non-significant

**Tab. 3. Optic chiasma characteristics.**

Optic chiasma	RRMSp (52)	CON (23)
Presence of subclinical demyelination	R2=0.45 R=0.65 P=0.0001	NS
Age	R2=0.01 R=0.11 P=0.1	NS

RRMSp = relapsing-remitting MS patients, CON = healthy controls, L = Left, R = Right, NS = non-significant

## Discussion

### *Cognitive dysfunction measured by SDMT and its correlation with volumetric data*

SDMT is one of the Brief Repeatable Battery of Neuropsychological tests, which is most frequently used both in clinical practice and in research (4,18). SDMT has been proven to be the most sensitive test to evaluate sustained attention and capacity of concentration, as well as visual processing speed (19–21). This study proves significant differences in performance of SDMT between RRMSp and CON, in accordance with previous studies (4, 21, 22). In agreement with other authors and our previous research, SDMT is capable to discriminate between RRMSp and CON very well (23–26).

SDMT results of our RRMSp correlated positively with volume of thalamus, putamen and nc. caudate, and negatively with optic chiasma volume.

### *Correlation of SDMT with optic chiasma*

To our best knowledge, this is the first study that presents correlation of lower SDMT with higher optic chiasma volume. Optic chiasma is a small structure, and our results might raise suspicion of technical error. However, credibility and accuracy of MR-volumetry of optic chiasma has been confirmed in a recent large MRI study (27). The accuracy (28, 29) and scan-rescan precision (30, 31) for Free Surfer-generated surfaces and thickness estimates have been reported to be well below 1 mm.

These facts support reliability of the optic chiasma measurements in our study.

We hypothesized that the increased volume of optic chiasma could be caused by its chronic subclinical demyelination, but the lesions are not easily visible on MR imaging. Fat-suppressed T2-weighted FSE images, especially STIR T2-weighted images, is useful in detecting a signal-intensity abnormality in subclinical optic nerve and chiasma demyelination but routine T2-weighted images without fat suppression and contrast-enhanced T1-weighted FSE images do not show any signal abnormality in the affected optic nerve (32). We used T2space-dark-fluid-sag-p2-sag-MPR-tra sequence for evaluation of demyelinated lesions of optic chiasma, in agreement with published recommendations (32). We found significant positive correlation of signal-intensity abnormalities of optic chiasma with its higher volume, even though none of our RRMSp presented with acute optic neuritis or new visual relapse. We conclude that adverse correlation of SDMT with optic chiasma volume pinpoints the role of subclinical demyelination of optic chiasma in visual processing speed in RRMS patients.

The relationship between subclinical demyelination of optic chiasma in our RRMSp and lower performance of SDMT is supported by previously reported data. Generally, a decline on the SDMT has been noted during acute inflammatory phases of MS (24). SDMT performance depends on good visuospatial orientation (33), which is based on normal visual functions (34). In the latter work, the authors tested MS patients who reported normal vision. but exhibited mild decline of visual acuity that correlated with lower score of SDMT (34). Visual, oculomotor, and oral motor abilities contribute significantly to performance on the SDMT and other cognitive tests (35, 36). Therefore, these sensory and motor functions must be considered when interpreting SDMT scores (35, 36). Unfortunately, our study protocol did not include test of visual acuity, as we realised its importance when evaluating our results. More precise examination of visual functions in evaluation of cognitive processes would bring more information and we recommend to use it in future research.

### *Correlation of SDMT with subcortical grey matter nuclei*

Reduced GM volume was detected in RRMSp although the patients were not intensively disabled, and their disease duration was not long. From all subcortical GM nuclei, compared with CON, RRMSp only showed lower volume of putamen. In cortical grey matter we found reduction of nc. accumbens, insular and cuneal GM. In contrast with our research, in other study not only putamen but also other GM nuclei volume using Free Surfer software significantly differed between patients and controls: bilateral thalamus, caudate nucleus, putamen, hippocampus, amygdala (37). So far, several studies revealed diffuse cerebral and cortical atrophy in MS patients even despite their short disease duration (38–40). Calabrese and colleagues presented atrophy of frontal cortex except other structures (thalamus and cerebellum) to be an independent predictor of progression of CIS to definite MS (41).

Considering putamen, our findings of reduction of right putamen volume is in accordance with other authors comparing subcortical GM volume in MS and healthy controls. In a retrospective

study of Krämer et al, reduced volume of putamen was found at the time of appearance of first MS symptoms. Atrophy was more evident by the first year of the disease than in advanced stages of the disease (42). Atrophy of putamen was also detected in non-treated CIS patients (14, 43), and in patients with different phenotypes of MS (14, 44–46).

Atrophy of putamen strongly determined our RRMSp against CON, and it correlated with SDMT. The same results of correlation were presented by Batista et al (47). Putamen is a part of the basal ganglia. Their role in cognition is suggested by the existence of circuits connecting the basal ganglia to non-motor regions in the frontal lobe (dorsolateral prefrontal cortex, lateral orbitofrontal cortex, and anterior cingulate cortex) (48, 49). Therefore, a role of putamen in development of slowing of processing speed could be explained by demyelination of many of fronto-striatal circuits in MS (47, 49). Association of basal ganglia damage with cognitive deficits is supposed to be similar (but not identical) to those observed in focal frontal lesions. These include deficits in working memory, long-term memory retrieval, verbal fluency performance, and attention, as well as impairments in executive functions like concept formation, mental set shifting, and inhibition of responses (50). Putamen oversees proper performance not only of motor but also cognitive functions in MS (43, 47, 51).

Except putamen, caudate nucleus correlated also with SDMT in our research. The deep GM nuclei receive inputs from intralaminar nuclei of the thalamus and several cortical regions (including frontal, inferotemporal and posterior parietal cortex) to participate in parallel and partially segregated motor, oculomotor, cognitive and limbic circuits (49). We suggest that MS causes destruction of several cortico-basal ganglionic “loops”, linking the basal ganglia demyelination on MS cognitive dysfunction (53).

Atrophy of the thalamus, caudate nucleus and other DGM nuclei has been linked with clinical disease progression (12, 54, 55). Comparing our CON and RRMSp, we did not find differences in volume of the thalamus. Recent research identified thalamic volume to be a candidate MRI-based marker, associated with MS-related neurodegeneration (56), as supported by pathological studies (57, 58). Thalamus volumetric correlates of cognitive decline have been reported by many authors (12, 59, 60), as well as our study. Several authors observed that global thalamic and putamen volumes are related to SDMT scores (47, 60). Bissec et al presented thalamic atrophy as an independent and strong contributor to MS-related attention-processing speed deficit, also controlling for age and neocortical atrophy (47, 60–62). Other authors also supported the dominance of thalamus atrophy in development of cognitive decline in MS (7, 14, 63).

#### *Differences in volumetric data between RRMSp and CON*

Nc accumbens is a region in the basal forebrain rostral to the preoptic area of the hypothalamus (64). Generally, the nucleus accumbens has a significant role in the cognitive processing of motivation, aversion, reward (pleasure and positive reinforcement), and reinforcement learning (e.g. Pavlovian-instrumental transfer) (65). However, we did not prove a relationship between Nc. accumbens volume and cognitive processes in MS. We suppose that

SDMT is not sensitive enough to test behavioural abnormalities associated with Nc. accumbens atrophy.

Reduction of insular cortex in our RRMSp also did not correlate with SDMT. The insular cortex functions as an integral brain hub, connecting different functional systems underlying sensory, emotional, motivational, and cognitive processing. Insular cortex pathology could help explain complexity of cognitive and emotional problems associated with MS, as insular cortex is believed to have an impact on flexible behaviours, such as decision-making, estimation of risks, and self-awareness. So far, its role was described in psychiatric disorders including, but not limited to, anxiety disorders, addiction, depression, schizophrenia, and autism (66). Several neuropathological studies in MS revealed that the insular cortex and the temporobasal cortex are more affected than others (57, 58). However, there is no direct study confirming the role of insular cortex in MS-related cognitive problems.

Other cortical structure found reduced in our RRMSp was cuneus GM. Similar results of reduction of cortical areas in MS patients including cuneus were published by Rudko et al., who demonstrated reduction in the superior temporal and posterior cingulate cortices, as well as in the cuneus and precentral gyrus as the most prevalent along the outer cortical surface, using multi-surface magnetization transfer ratio imaging (67). The study was not targeted to test cognitive functions. Currently, it is not clear which psychological tests could correctly identify damage of cuneus GM, and which of them would be able to differentiate among damage in Nc. accumbens, insula or cuneus GM.

Atrophy of brain subcortical structures in our RRMSp was indirectly proved by increased widths of the third ventricle (3WV) that differed from CON. Value of 3WV measures in the assessment of brain atrophy has been proven (68–72). Another of our results, volume of WM hypointensities strongly discriminated RRMSp against CON but did not correlate with SDMT.

## Conclusion

To our best knowledge, this is the first study that presents results showing a correlation of lower SDMT with higher optic chiasma volume, and that optic chiasma volume, due to its subclinical demyelination in MS, is strongly associated with decline of cognitive functions measured by SDMT. We confirmed that GM atrophy is involved in cognitive functions in MS.

## References

1. Eijlers AJC, van Geest Q, Dekker I, Steenwijk MD, Meijer KA, Hulst HE et al. Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. *Brain* 2018; 141 (9): 2605–2618.
2. Schulz D, Kopp B, Kunkel A, Faiss JH. Cognition in the early stage of multiple sclerosis. *J Neurol* 2006; 253 (8): 1002–1010.
3. Khalil M, Enzinger C, Langhammer C et al. Cognitive impairment in relation to MRI metrics in patients with clinically isolated syndrome. *Multiple Sclerosis Journal* 2011; 17 (2): 173–180.
4. Benedict RH, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R. Multiple Sclerosis Outcome Assessments Consortium. Validity of the

- Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult Scler* 2017; 23 (5): 721–733.
5. **Costa SL, Genova HM, DeLuca J, Chiaravalloti ND.** Information processing speed in multiple sclerosis: past, present, and future. *Mult Scler* 2017; 23: 772–789.
  6. **Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RH.** Screening for cognitive impairment in multiple sclerosis using the Symbol digit Modalities Test. *Mult Scler* 2007; 13 (1): 52–57.
  7. **Zivadinov R, Sepcic J, Nasuelli D et al.** A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2001; 70 (6): 773–780.
  8. **Rojas JI et al.** Brain atrophy in multiple sclerosis: therapeutic, cognitive and clinical impact. *Arquivos de Neuro-Psiquiatria* 2016; 74 (3): 235–243.
  9. **Sanfilippo MP, Benedict RH, Weinstock-Guttman B, Bakshi R.** Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology* 2006; 66 (5): 685–692.
  10. **Sánchez MP, Nieto A, Barroso J, Martín V, Hernández MA.** Brain atrophy as a marker of cognitive impairment in mildly disabling relapsing-remitting multiple sclerosis. *Eur J Neurol* 2008; 15 (10): 1091–1099.
  11. **Amato MP, Portaccio E, Goretti B et al.** Association of neocortical volume changes with cognitive deterioration in relapsing-remitting multiple sclerosis. *Arch Neurol* 2007; 64 (8): 1157–1161.
  12. **Houtchens K, Benedict RH, Killiany R et al.** Thalamic atrophy and cognition in multiple sclerosis. *Neurology* 2007; 69 (12): 1213–1223.
  13. **Mineev KK, Prakhova LN, Il'ves AG et al.** Characteristics of neurological and cognitive status in patients with multiple sclerosis in relation to the location and volumes of demyelination foci and the severity of brain atrophy. *Neurosci Behav Physiol* 2009; 39 (1): 35–38.
  14. **Bergsland N, Horakova D, Dwyer MG et al.** Subcortical and Cortical Gray Matter Atrophy in a Large Sample of Patients with Clinically Isolated Syndrome and Early Relapsing-Remitting Multiple Sclerosis. *Amer J Neuroradiol* 2012; 33 (8): 1573–1578
  15. **Schoonheim MM, Popescu V, Rueda Lopes FC et al.** Subcortical atrophy and cognition. Sex effects in multiple sclerosis. *Neurology* 2012; 79 (17): 1754–1761.
  16. **Tekok-Kilic A, Benedict RH, Weinstock-Guttman B et al.** Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis. *NeuroImage* 2007; 36 (4): 1294–1300.
  17. **Thompson AJ, Banwell BL, Barkhof F et al.** Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17 (2): 162–173.
  18. **Rao SM.** The Cognitive Function Study Group. (1990). *A Manual for the Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis*. New York: National Multiple Sclerosis Society.
  19. **Nocontin U, Pasqualetti P, Bonavita S et al.** Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. *Mult Scler* 2006; 12 (1): 77–87.
  20. **Gich J, Rivero M, Puig J, Blasco G, Salavedra J, Biarnés C et al.** Cognition over the course of multiple sclerosis. *Multiple Scler J* 2016; 22: 267–268.
  21. **Benedict RH, Amato MP, DeLuca J, Geurts JG.** Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *The Lancet Neurology* 2020; 19 (10): 860–871.
  22. **Sumowski J, Benedict RH, Enzinger C et al.** Cognition in multiple sclerosis: State of the field and priorities for the future. *Neurology* 2018; 90 (6): 278–288.
  23. **Kalb R, Beier M, Benedict RH et al.** Recommendations for cognitive screening and management in multiple sclerosis care. *Mult Scler* 2018; 24 (13): 1665–1680.
  24. **Benedict RH, Morrow S, Rodgers J, Hojnacki D, Bucello MA, Zivadinov R, Weinstock-Guttman B.** Characterizing cognitive function during relapse in multiple sclerosis. *Mult Scler* 2014; 20 (13): 1745–1752.
  25. **Kantorová E, Poláček H, Bittšanský M et al.** Hypothalamic damage in multiple sclerosis correlates with disease activity, disability, depression, and fatigue. *Neurol Res* 2017; 39 (4): 323–330.
  26. **Kantorova E, Hnilicová P, Bogner W et al.** Neurocognitive performance in relapsing-remitting multiple sclerosis patients is associated with metabolic abnormalities of the thalamus but not the hippocampus-GABA-edited 1H MRS study. *Neurological Research* 2022; 44 (1): 57–64.
  27. **Knussmann GN, Anderson JS, Prigge MBD et al.** Test-retest reliability of FreeSurfer-derived volume, area and cortical thickness from MP2RAGE and MP2RAGE brain MRI images. *Neuroimage: Reports* 2022; 2 (2): 100086.
  28. **Kuperberg GR, Broome MR, McGuire PK et al.** Regionally Localized Thinning of the Cerebral Cortex in Schizophrenia. *Arch Gen Psychiatry* 2003; 60 (9): 878–888.
  29. **Rosas HD, Liu AK, Hersch S, Glessner M et al.** Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 2002; 58 (5): 695–701.
  30. **Fujimoto K, Polimeni JR, van der Kouwe AJW et al.** Quantitative comparison of cortical surface reconstructions from MP2RAGE and multi-echo MP2RAGE data at 3 and 7T. *NeuroImage* 2014; 90: 60–73.
  31. **Han X, Jovicich J, Salat D et al.** Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer. *NeuroImage* 2006; 32 (1): 180–194.
  32. **Sartoretti T, Sartoretti E, Rauch S, Binkert C, Wyss M, Czell D, Sartoretti-Schefer S.** How Common Is Signal-Intensity Increase in Optic Nerve Segments on 3D Double Inversion Recovery Sequences in Visually Asymptomatic Patients with Multiple Sclerosis? *AJNR Am J Neuroradiol* 2017; 38 (9): 1748–1753.
  33. **Oreja-Guevara C, Ayuso Blanco T, Brieva Ruiz L, Hernández Pérez MÁ, Meca-Lallana V, Ramió-Torrentà L.** Cognitive Dysfunctions and Assessments in Multiple Sclerosis. *Front Neurol* 2019; 10: 581.
  34. **Bruce JM, Bruce AS, Arnett PA.** Mild visual acuity disturbances are associated with performance on tests of complex visual attention in MS. *J Int Neuropsychol Soc* 2007; 13 (3): 544–548.
  35. **Chen MH, Chiaravalloti ND, Genova HM, Costa SL.** Visual and motor confounds on the symbol digit modalities test. *Mult Scler Relat Disord* 2020; 45: 102436.
  36. **Jakimovski D, Benedict R, Weinstock-Guttman B et al.** Visual deficits and cognitive assessment of multiple sclerosis: confounder, correlate, or both? *J Neurol* 2021; 268 (7): 2578–2588.
  37. **Popescu V, Schoonheim MM, Versteeg A et al.** Grey Matter Atrophy in Multiple Sclerosis: Clinical Interpretation Depends on Choice of Analysis Method. *PLoS One* 2016; 11 (1): e0143942.
  38. **Chard DT, Griffin SM, Parker GJM, Kapoor R, Thompson AJ, Miller DH.** Brain atrophy in clinically early relapsing-remitting multiple sclerosis. *Brain* 2002; 125 (2): 327–337.

39. Dalton CM, Chard DT, Davies GR et al. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. *Brain* 2004; 127 (5): 1101–1107.
40. De Stefano N, Matthews PM, Filippi M et al. Evidence of early cortical atrophy in MS. Relevance to white matter changes and disability. *Neurology* 2003; 60 (7): 1157–1162.
41. Calabrese M, Rinaldi F, Mattisi I, Bernardi V, Favaretto A, Perini P, Gallo P. The predictive value of gray matter atrophy in clinically isolated syndromes. *Neurology* 2011; 77 (3): 257–263.
42. Krämer J, Meuth SG, Tenberge J-G, Schiffler P, Wiendl H, Deppe M. Early and Degressive Putamen Atrophy in Multiple Sclerosis. *International Journal of Molecular Sciences* 2015; 16 (10): 23195–23209.
43. Henry RG, Shieh M, Okuda DT et al. Regional grey matter atrophy in clinically isolated syndromes at presentation. *Journal of Neurology, Neurosurgery & Psychiatry* 2008; 79: 1236–1244.
44. Jacobsen C, Hagemeyer J, Myhr KM et al. Brain atrophy and disability progression in multiple sclerosis patients: a 10-year follow-up study. *J Neurol Neurosurg Psychiatry* 2014; 85 (10): 1109–1115.
45. Sepulcre J, Sastre-Garriga J, Cercignani M, Ingle GT, Miller DH, Thompson AJ. Regional Gray Matter Atrophy in Early Primary Progressive Multiple Sclerosis: A Voxel-Based Morphometry Study. *Arch Neurol* 2006; 63 (8): 1175–1180.
46. Dolezal O, Gabelic T, Horakova D et al. Development of gray matter atrophy in relapsing-remitting multiple sclerosis is not gender dependent: results of a 5-year follow-up study. *Clin Neurol Neurosurg* 2013; 115: 42–48.
47. Batista S, Zivadinov R, Hoogs M et al. Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis. *J Neurol* 2012; 259 (1): 139–146.
48. Middleton FA, Strick PL. Basal-ganglia ‘projections’ to the prefrontal cortex of the primate. *Cereb Cortex* 2002; 12 (9): 926–935.
49. DeLuca GC, Yates RL, Beale H, Morrow SA. Cognitive impairment in multiple sclerosis: clinical, radiologic and pathologic insights. *Brain Pathol* 2015; 25 (1): 79–98.
50. Cummings JL. Frontal-Subcortical Circuits and Human Behavior. *Arch Neurol* 1993; 50 (8): 873–880.
51. Modica CM, Zivadinov R, Dwyer MG, Bergsland N, Weeks AR, Benedict R. Iron and Volume in the Deep Gray Matter: Association with Cognitive Impairment in Multiple Sclerosis. *American Journal of Neuroradiology* 2015; 36 (1): 57–62.
52. Ge Y, Jensen JH, Lu H et al. Quantitative Assessment of Iron Accumulation in the Deep Gray Matter of Multiple Sclerosis by Magnetic Field Correlation Imaging. *American Journal of Neuroradiology* 2007; 28 (9): 1639–1644.
53. Brass SD, Benedict RH, Weinstock-Guttman B, Munschauer F, Bakshi R. Cognitive impairment is associated with subcortical magnetic resonance imaging grey matter T2 hypointensity in multiple sclerosis. *Mult Scler* 2006; 12: 437–444.
54. Bakshi R, Czarnecki D, Shaikh ZA et al. Brain MRI lesions and atrophy are related to depression in multiple sclerosis. *Neuroreport* 2000; 11: 1153–1158.
55. Cifelli A, Arridge M, Jezzard P et al. Thalamic neurodegeneration in multiple sclerosis. *Ann Neurol* 2002; 52: 650–653.
56. Houtchens MK, Benedict RH, Killiany R et al. Thalamic atrophy and cognition in multiple sclerosis. *Neurology* 2007; 69: 1213–1223.
57. Azevedo CJ, Cen SY, Khadka S et al. Thalamic atrophy in multiple sclerosis: A magnetic resonance imaging marker of neurodegeneration throughout disease. *Ann Neurol* 2018; 83 (2): 223–234.
58. Haider L, Zrzavy T, Hametner S et al. The topography of demyelination and neurodegeneration in the multiple sclerosis brain. *Brain* 2016; 139 (3): 807–815.
59. Kutzelnigg A, Lassmann H. Cortical demyelination in multiple sclerosis: a substrate for cognitive deficits? *J Neurol Sci* 2006; 245 (1–2): 123–126.
60. Mahajan KR, Nakamura K, Cohen JA, Trapp BD, Ontaneda D. Intrinsic and extrinsic mechanisms of thalamic pathology in multiple sclerosis. *Ann Neurol* 2020; 88: 81–92.
61. Bisecco A, Rocca MA, Pagani E et al. Connectivity-based parcellation of the thalamus in multiple sclerosis and its implications for cognitive impairment: A multicenter study. *Hum Brain Mapp* 2015; 36 (7): 2809–2825.
62. Benedict RH, Hulst HE, Bergsland N et al. Clinical significance of atrophy and white matter mean diffusivity within the thalamus of multiple sclerosis patients. *Multiple Sclerosis J* 2013; 19 (11): 1478–1484.
63. Bergsland N, Zivadinov R, Dwyer MG et al. Localized atrophy of the thalamus and slowed cognitive processing speed in MS patients. *Mult Scler* 2016; 22: 1327–1336.
64. Uher T, Horakova D, Bergsland N et al. MRI correlates of disability progression in patients with CIS over 48 months. *Neuroimage Clin* 2014; 6: 312–319.
65. Malenka RC, Nestler EJ, Hyman SE, Sydor A, Brown RY. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*. New York: McGraw-Hill Medical 2009: 147–148, 367, 376.
66. Salamone JD, Pardo M, Yohn SE, López-Cruz L, SanMiguel N, Correa M. Mesolimbic Dopamine and the Regulation of Motivated Behavior. *Curr Topics Behavioral Neurosci* 2016; 27: 231–57.
67. Gogolla N. The insular cortex. *Curr Biology* 2017; 27 (12): 580–586.
68. Rudko DA, Derakhshan M, Maranzano J, Nakamura K, Arnold DL, Narayanan S. Delineation of cortical pathology in multiple sclerosis using multi-surface magnetization transfer ratio imaging. *NeuroImage: Clinical* 2016; 12: 858–868.
69. Simon JH, Jacobs LD, Campion MK et al. A longitudinal study of brain atrophy in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Neurology* 1999; 53: 139–148.
70. Benedict RH, Weinstock-Guttman B, Fishman I, Sharma J, Tjoa CW, Bakshi R. Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Arch Neurol* 2004; 61: 226–230.
71. Martola J, Stawiarz L, Fredrikson S et al. Rate of ventricular enlargement in multiple sclerosis: a nine-year magnetic resonance imaging followup study. *Acta Radiol* 2008; 49: 570–579.
72. Müller M, Esser R, Kötter K, Voss J, Müller A, Stellmes P. Third ventricular enlargement in early stages of multiple sclerosis is a predictor of motor and neuropsychological deficits: a cross-sectional study. *BMJ Open* 2013; 3 (9): e003582.
73. Polacek H, Kantorova E, Hnilicova P, Grendar M, Zelenak K, Kurca E. Increased glutamate and deep brain atrophy can predict the severity of multiple sclerosis. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2019; 163 (1): 45–53.

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