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ABSTRACTS

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ORAL PRESENTATIONS

O1: Feasibility of detecting atrophy relevant for cognition on 3D-FLAIR

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Aim
Cognitive impairment is known to be related to brain atrophy in multiple sclerosis (MS), but high resolution 3D-T1 imaging required for brain volumetrics is often unavailable in clinical protocols, unlike 3D-FLAIR. This study investigated the feasibility of detecting atrophy relevant for cognition on 3D-FLAIR.
Method
This study included 3T-MRI data of 173 MS patients and 48 controls. Cognitive assessments were based on an expanded BRB-N. Brain segmentation was performed on 3D-FLAIR with SynthSeg and SAMSEG and compared to segmentation performance in the same subjects on 3D-T1 (FreeSurfer, SynthSeg and SAMSEG).
Results
Volumes derived from 3D-FLAIR showed good relative agreement with those derived from 3D-T1 for brain and grey matter volumes (ICC>0.8). Cognitively impaired (CI) patients showed more atrophy compared to cognitively preserved (CP) patients using all methods. Effect sizes for 3D-FLAIR assessments were comparable to FreeSurfer for brain, ventricle and deep gray matter volumes. On 3D-FLAIR, SynthSeg had a higher effect size for thalamus compared to SAMSEG (d=0.83 vs. d=0.60), but lower for cortical volumes (d=0.40 vs. d=0.67).
Conclusion
3D-FLAIR can be used to detect global and regional atrophy relevant for cognitive dysfunction, which could enable monitoring of neurodegeneration in a clinical setting.*Disclosures*: the authors did not disclose any links of interest.

O2: Brain age as a surrogate marker for IPS in MS

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Background Data from neuro-imaging techniques allow us to estimate a brain's age. Brain age is easily interpretable as "how old the brain looks", and could therefore be an attractive communication tool for brain health in clinical practice. This study aimed to investigate its clinical utility by investigating the relationship between brain age and the main cognitive deficit in MS, i.e. information processing speed.

Methods A linear regression model was trained to predict age from brain MRI volumetric features and sex in a healthy control dataset (HC_train, n=1690). This model was used to predict brain age in two test sets: HC_test (n=50) and MS_test (n=201). Brain-Predicted Age Difference (BPAD) was calculated as BPAD=brain age minus chronological age. Information processing speed was assessed by the Symbol Digit Modalities Test (SDMT).
Results] Brain age was significantly related to SDMT scores in the MS_test dataset (r=-0.45, p<.001), and contributed uniquely to variance in SDMT beyond chronological age, reflected by a significant correlation between BPAD and SDMT (r=-0.23, p=0.001) and a significant weight (-0.23, p=0.004) in a multivariate regression equation with age.
Conclusions Brain age is a candidate biomarker for information processing speed in MS and an easy to grasp metric for brain health.
This abstract has been presented previously at: COMPAGE 2020; MSVirtual 2020; ACTRIMS Forum 2021
Disclosures: the authors did not disclose any links of interest.

O3: Distribution of cortical lesions across functional networks is non-random and related to cognitive impairment

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AIM To characterize the localization and extent of cortical lesions (CLs) across functional networks in MS and their relation with cognitive impairment.
METHODS 176 MS patients (age 54±9 years, disease duration 16.7±5.7 years) from the Amsterdam MS cohort underwent neuropsychological testing (expanded BRB-N) and structural MRI, including double inversion recovery. Patients were categorized as cognitively preserved (CP; n=83) and impaired (CI; z−1.5 on ≥2 cognitive tests, n=93) compared to 48 matched healthy-controls. The Brainnetome atlas was used to parcellate the brain into 7 functional networks: visual, sensorimotor (SMN), ventral attention (VAN), dorsal attention (DAN), default mode (DMN), frontoparietal (FPN) and limbic. CLs volumes/fractions within each network were compared between groups.
RESULTS In the total MS group, largest lesion volumes were found in DMN (median[IQR] mm3; 50.4[169.8]), limbic (48.2[149.9]) and VAN (45.5[143.0]). Looking at CI versus CP, a higher total lesion volume and fraction ($p<0.001$) was seen in all networks, with highest effect sizes in the DMN (Eta squared $\eta2=0.1$; CP 19.8[78.4]; CI 68.6[176.3]), limbic ($\eta2=0.08$; CP 19.8[78.4]; CI 68.6[176.3]) and SMN ($\eta2=0.08$; CP 21.9[85.0]; CI 89.6[218.8]).
CONCLUSION: Cortical lesion volume is higher in the DMN, limbic and VAN, while cognitive relations are strongest in the DMN, SMN and limbic network.
Disclosures: the authors did not disclose any links of interest.

O4: Associations of White Matter and Basal Ganglia Microstructure to Cognitive Fatigue Rate in Multiple Sclerosis

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Objective: Cognitive fatigue is one of the mot debilitating symptoms reported by persons with multiple sclerosis (pwMS). Cognitive fatigue has been associated with disruptions in striato-thalamo-cortical and frontal networks, but what remains unknown is how the *rate* in which pwMS become fatigued relates to microstructural properties within the brain.
Methods: Sixty-two persons with relapsing-remitting MS completed diffusional kurtosis imaging (DKI), and behavioral and neuropsychological measures. The slope of eight fatigue ratings during a within-scanner fatigue inducing task was designated as 'cognitive fatigue rate' (CFR). Microstructural integrity of white matter and basal ganglia was quantified using tract-based spatial statistics and regional analyses.
Results: Results showed CFR to be related to seven white matter tracts associated with basal ganglia connectivity or previously proposed fatigue networks. In addition, CFR was associated with putamen microstructure, though this did not survive multiple comparisons correction. Lastly, CFR was associated with trait cognitive fatigue, but not behavioral or neuropsychological outcomes.
Conclusion: Our approach of using rate, rather than trait fatigue, brings us closer to understanding how brain pathology may be impacting the experience of fatigue in pwMS, which is crucial for developing interventions. These results hold promise for continuing to unpack the complex construct that is fatigue.
Disclosures: the authors did not disclose any links of interest.

O5: Multilingualism as a protective factor against cognitive impairment in multiple sclerosis

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Background: Multilingualism is known to be a protective factor (cognitive reserve) against cognitive impairment (CI) in Alzheimer's disease.
Objective: To explore if multilingualism is protective against CI in relapsing MS.
Methods: A retrospective study of relapsing MS aged 18-59 who completed the Minimal Assessment of Cognitive Function in MS. We used one-way ANOVA to compare scores on the Brief Visuospatial Memory Test (BVMTR) and Symbol Digit Modalities Test (SDMT) between groups (uni- vs. multillingual). Chi-square was used to compare impairment on BVMTR and SDMT between groups.
Results: We identified 678 subjects: 73.9% female, mean age 39.6 (±9.6) years, mean education 13.9 (±2.2) years. 563 subjects were unilingual and 114 were multilingual (102 bilingual).
There was no significant difference on the BVMTR-IR (p=0.195) or BMVTR-DR (p=0.100) between groups and no difference in the number of subjects impaired on the BVMTR-IR (*X2* (1, N=678) = 3.167, p=0.057) or BVMTR-DR between groups (*X2* (1, N=678) = 2.996, p=0.083).
There was no significant difference on the SDMT (p=0.502) between groups, or in number of subjects impaired on the SDMT between groups (*X2* (1, N=678) = 1.023, p=0.312).
Conclusion: This study demonstrates that multilingualism does not has a protective effect against CI in MS.
Disclosures: the authors did not disclose any links of interest.

O6: A Taxonomy of Cognitive Phenotypes in MS

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Background. Characterization of cognitive impairment (CI) in MS into distinct phenotypes holds promise for individualized treatments and biomarker exploration. Here we applied a diagnostic algorithm to identify a taxonomy of the nature and distribution of diagnostic phenotypes in MS.
Methods. Using a procedure designed to derive cognitive diagnoses in other neurological disease, a six-domain model composed of two neuropsychological tests per domain was applied via retrospective review of 232 PwMS. A domain was impaired if both measures were at least -1.0z (and then -1.5z) below controls. The distribution and nature of PwMS meeting criteria for single-domain, bi-domain, multi-domain impairment, or no impairment, were computed.
Results. At -1SD threshold: 38.8% were intact, 29.3% had single-domain, 8.6% bi-domain, and 23.3% multi-domain impairment. At -1.5SD threshold: 64.8% were intact, 12.2% had single-domain, 11.7% bi-domain, and 11.3% multi-domain impairment. Across thresholds, attention/processing speed was the most frequent single domain impairment, followed by immediate memory, delayed memory, and executive function.
Conclusions. These findings provide new information regarding the taxonomy of cognitive phenotypes in MS and advances understanding of their distribution in MS. This paves the way for further investigation of associated clinical biomarkers and provides clinically meaningful information to guide clinical treatment and rehabilitation.
Disclosures: the authors did not disclose any links of interest.

O7: Cognitive performance is related to GABA-receptor density in multiple sclerosis

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Objective: To explore how GABA-receptor density relates to cognitive functioning in persons with MS (PwMS).

Methods: Twenty-two PwMS (age 43.8±10.3 years, 17 females, disease duration 9.9±8.3 years) and 10 healthy controls (HCs, age 45.2±13.5 years, 7 females) underwent neuropsychological testing (expanded BRB-N). Ten PwMS were classified as cognitively impaired (CI, scoring <-1.5SD below norms on ≥30% of tests). The other 12 PwMS were cognitively preserved (CP). Volume of distribution (i.e. an estimate of GABA-receptor density) was assessed using [11C]flumazenil positron emission tomography.

Results: PwMS and HCs did not differ on age and sex. However, volume of distribution of deep grey matter (GM) was higher in PwMS than in HCs (p=0.03). When comparing CP and CI PwMS to HCs, CP showed higher volume of distribution on total GM (p=0.02), deep GM (p=0.04) and hippocampus (p=0.04). Volume of distribution was strongly associated with information processing speed (IPS) in the MS group only (r=0.56, p=0.007).

Discussion: Increased GABA-receptor density was primarily observed in CP PwMS which was related to better cognitive functioning, specifically with IPS. We hypothesize that GABA receptors are upregulated in CP PwMS to regulate neurotransmission in the presence of pathology which may, temporarily, preserve cognitive functioning.
Disclosures: the authors did not disclose any links of interest.

O8: Cognitive decline in early RRMS is linked to altered sodium MRI in functional brain networks

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Cognitive impairment in multiple sclerosis (MS) is associated with abnormalities in functional brain networks identified with resting state fMRI (rs-fMRI). The mechanisms of functional connectivity abnormalities are poorly understood, but it has been suggested that network 'hub' regions are susceptible to energy failure due to their high metabolic demands. In this pilot study we carried out a longitudinal assessment of cognition in a group of 23 people with early relapsing-remitting MS (assessed over a mean of 2 years). We then acquired rs-fMRI combined with sodium MRI to assess total sodium concentration (TSC), a marker of axonal energy state, in functional network regions in the same patients and in 10 non-MS controls. We examined whether 1) TSC levels differ between network regions and the rest of the brain; 2) TSC is altered in network regions in RRMS patients relative to controls; and 3) TSC correlates with cognitive performance in RRMS patients. We found that TSC was higher in resting state network regions than in the rest of the brain. People with MS showed lower TSC within these regions and, furthermore, lower TSC correlated with worse cognitive performance. Our findings point to higher sodium levels in functional network hub regions, possibly reflecting greater energy demand than other brain regions. Evidence of altered TSC within these network regions in early MS may reflect a regional vulnerability to pathology, which relates to cognitive outcomes. *Disclosures*: the authors did not disclose any links of interest.

O9: Altered diffusion in lesional and normal-appearing cortex is related to cognitive impairment in multiple sclerosis.

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AIM To evaluate the relationship between cognitive impairment and grey matter (GM) integrity in MS quantified by diffusivity within regions with cortical lesions (CL) and normal-appearing GM (NAGM).
METHODS 176 MS patients and 48 healthy controls (HC) underwent MRI (3D-FLAIR, 3D-T1, 3D-DIR and diffusion) and neuropsychological assessment (expanded BRB-N). GM integrity based on fractional anisotropy (FA) and mean diffusivity (MD) was assessed within CL and NAGM, which were spatially divided into seven networks of functionally related regions. Integrity was compared between cognitive groups: cognitively preserved (CP), mildly cognitively impaired (MCI), or cognitively impaired (CI).
RESULTS Mean cortical MD was increased in MS versus HC ($p<0.001$), FA showed no change. CI showed higher cortical MD compared to CP in both CL and NAGM. Within-subject differences between CL and NAGM showed diffusivity increases in CL in CI ($p=0.01$), but not in MCI and CP. Regionally, MD was increased in CI compared to CP in ventral attention, frontoparietal, sensorimotor and default-mode networks (p-range=0.001-0.03), with largest effect sizes in sensorimotor and default-mode networks.
CONCLUSION Cortical diffusion increases are most pronounced in cognitively impaired MS patients and seen in both lesional GM and NAGM. GM integrity was most severely reduced in sensorimotor and default-mode networks.
Disclosures: the authors did not disclose any links of interest.

P1: Cerebellar grey matter volume loss is associated with clinically meaningful deterioration in SDMT performance, in people with active PPMS under ocrelizumab treatment.

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Introduction
Ocrelizumab is the only approved Disease Modifying Treatment (DMT) for active primary progressive multiple sclerosis (aPPMS).
Aim
To investigate potential correlations of changes in SDMT performance with cerebellar volumetric measures, in ocrelizumab treated aPPMS, over a 12-month period.
Methods
Twenty-two people with aPPMS (12 males, mean age 48.5 ± 1.69, mean disease duration 9.05 ±0.92, mean EDSS 4.91 ± 0.3) were included in this study. Cerebellar volumetric analysis -using the CERES automated pipeline- and SDMT examination were performed, in baseline and after 12 months. Statistical analysis included comparison of volumetric measurements between groups.
Results
Participants (n:8) with clinically meaningful deterioration in SDMT performance (≥4 points) exhibited greater absolute and normalized cerebellar grey matter volume loss (-10.79 ± 5.88 vs. -0.7 ± 1.74, p = 0.041; -9.14 ± 3.88 vs. -0.84 ± 1.97, p = 0.048 respectively), as compared to those without clinically meaningful deterioration in SDMT performance (n: 14) at 12 months.
Conclusion
Several studies have demonstrated the relation of SDMT performance with cerebellar pathology. A recent sub analysis of the ORATORIO study, demonstrated that ocrelizumab may reduce cerebellar atrophy rates. Whether cognitive and volumetric outcomes may be used as measures of response to DMTs, warrants further investigation.
Disclosures: the authors did not disclose any links of interest.

P3: Focal cortical and periventricular damage alters global brain network properties in multiple sclerosis patients hereby affecting information processing speed

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Brain network properties relate to cognition; focal cortical and white matter damage in patients with multiple sclerosis (pwMS) might lead to network alterations associated with cognitive impairment. We applied microstructure-weighted connectomes to investigate global network metrics and information processing speed (IPS) and whether disruption by focal lesions is associated with IPS.
PwMS (n=68) and healthy controls (n=92) underwent neuropsychological examination and 3T brain MRI. Whole-brain deterministic tractography and connectometry were performed using dMRI. Connectomes were obtained using the Spherical Mean Technique and weighted for the intracellular fraction. 3D FLAIR images identified white matter lesions (WML), MP2RAGE images detected cortical lesions (CL). PwMS were subdivided into cognitive preserved (CPMS) and cognitive impaired (CIMS) using the Symbol Digit Modalities Test (SDMT) z-score at cut-off of -1.5 standard deviations. Statistical analyses were performed using robust linear models with age, sex, years of education, and network density as covariates.
Of 68 pwMS, 18 were CIMS and 50 were CPMS. We found significant changes in all global network metrics except for modularity. Global network metrics were correlated with SDMT (r=0.24-0.27), except for modularity (inverse correlation (r=-0.27)). Leukocortical and periventricular volume significantly influenced density and IPS (leukocortical white matter p=0.026, periventricular p=0.004) and modularity and IPS (leukocortical white matter p=0.013, leukocortical grey matter p=0.02, periventricular p= 0.018). MS-lesions and their interaction with global network metrics influenced IPS. These results provide new knowledge about mechanisms leading to increased cognitive disabilities in pwMS.
Part of this abstract has been presented previously at ECTRIMS 2021 Congress and at the Swiss Neurological Society Conference in Interlaken
Disclosures: the authors did not disclose any links of interest.

P4: Impact of information processing speed (IPS) on episodic memory (EM) in multiple sclerosis (MS): a survival analysis.

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In learning assessment, time limits or fixed number of trials make it difficult to distinguish between the effect of reduced cognitive ability and lack of time to complete the task.
Our study proposes to use time-to-event data approach to address this issue. Survival analysis focuses on the time until a particular event occurs (recall the total word's list) and appears appropriate to characterize the progression of learning in EM task (*SRT*, requiring to recall a 15 words list twice consecutively) in RRMS- and PPMS-patients compared to controls.
We examined recall performances on the SRT in 157 MS-patients and 157 controls. 31% of patients manage to recall the entire list of words, twice consecutively, compared to 79% of controls. The median survival times decreased from 9-trials in patients to 8-trials in controls, indicating that controls achieved the recall on two consecutive trials sooner than patients. Learning curves analysis showed an increasing linear trend for patients, suggesting that more and more patients completed the task as trials progress.
Survival analysis provides a complementary assessment of EM to the traditional paradigm, and an innovative way to address slow-learning in MS. This study underlines a possible beneficial effect of extra-time on learning performance.
Disclosures: the authors did not disclose any links of interest.

P5: NICARA: Clinically feasible detection of structural connectivity changes in individual MS patients

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Introduction
Quantifying structural tract damage yields important information beyond individual lesions. However, it is currently not feasible to visualize such pathology in a clinical setting in individual patients. To tackle this issue, we propose NICARA™, a novel connectome software to run automated processing pipelines and reports for individual patients.
Method
12 patients and 10 age matched healthy controls were included. We used NICARATM (nicara.eu) to assess structural connectomes running an automated processing pipeline using MrTrix3 and FreeSurfer/Cat12 on fiber tracts with known associations to cognitive and motor performance.
Results
Patients with medium severe EDSS, increased lesion load and/or long disease duration, showed profound reductions in structural connectivity of both thalamo-cortical and interhemispheric sensorimotor projections. NICARA even detected light reductions in tract integrity in individual patients with an EDSS of 0 and few lesions. The automatically detected structural connectivity reductions were plausible as visibly co-localized with manually detected WM lesions.
Discussion
Using the NICARA pipeline connectome changes were detectable in this preliminary sample of patients, as well as in individual patients compared to controls. Structural connectivity changes closely mimicked clinical profiles, which might indicate that NICARA could be a valuable contribution beyond classical MRI techniques in the clinic.

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Disclosures: Yong Li and Markus Butz-Ostendorf are employed with Biomax and therefore will be affected by any commercial implications caused by this manuscript. All other author declare the absence of any conflict of interest.

P6: Is age an aggravating factor of cognitive impairment in multiple sclerosis (MS)?

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If cognitive disorders in MS are now well documented, few studies examined the impact of age on cognitive impairment. This study investigates the potentially differential impact of age on cognition in MS patients compared to matched healthy participants and according to the clinical form of the disease. 321 MS-patients (192 relapsing-remitting, 99 secondary-progressive, 30 primary-progressive), matched to 258 controls, underwent cognitive assessment: episodic memory (*Selective Reminding Test*), working memory (forward and backward digit spans), processing speed (code), cognitive flexibility (categorical and phonemic fluencies). Moderation analyses via hierarchical linear regressions tested the moderating effects of group on the relationship between age and cognition (with education level as a co-variate). For all cognitive variables, age and MS negatively predicted cognitive performances. No interaction effects between age and group (MS *vs* controls) were observed on all cognitive variables. Regarding the effect of clinical form (relapsing-remitting vs. progressive), the progressive form negatively impacted processing speed and cognitive flexibility. However, no interaction effects were observed between age and clinical form of MS. While age had a negative impact on cognitive functioning, no differential effect of age was observed, either between patients and healthy participants or among the different clinical forms of the disease. MS represents a risk factor for the occurrence of cognitive impairment. Nevertheless, age does not seem to be an aggravating factor on the importance of this impairment. *Disclosures*: the authors did not disclose any links of interest.

P7: Altered functional brain states predict cognitive decline 5 years after a clinically isolated syndrome

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Background
Cognitive impairment occurs in the earliest stages of multiple sclerosis (MS) and is related to altered functional connectivity (FC).
Objective
Investigate the evolution of dynamic FC states in early MS and their role in shaping cognitive decline.
Methods
Thirty-two patients were enrolled after their first neurological episode suggestive of MS and underwent cognitive evaluation and resting-state functional MRI (fMRI) over 5 years. Twenty-eight healthy controls were also included at baseline.
Results
Cognitive performance was stable during the first year and declined after 5 years.
At baseline, the number of transitions between states was lower in MS compared to controls ($p < 0.05$). Over time, frequency of high FC states decreased in patients, while it increased in state with low FC ($p < 0.05$). Cognitive performance at year 5 was best predicted by the mean connectivity of high FC state at year 1.
Conclusion
Patients with early MS showed reduced functional network dynamics at baseline. Longitudinal changes showed longer time spent in a state of low FC, but less time spent and more connectivity disturbance in more integrative states with high within and between network FC. Disturbed FC within this more integrative state was especially predictive of future cognitive decline. *Disclosures*: the authors did not disclose any links of interest.

P9: Does brain networks represent cognition in MS?

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Graph-theoretical analysis is a novel tool to understand the organisation of the brain. When applied in MS, the network parameters are altered in MS compared to healthy subjects (HS) for functional and structural imaging, and correlations with cognition are small (<0.5) or not significant. Yet the question remains whether altered graph theoretical parameters reflect real pathology-induced network reorganization of the brain's structure and functioning or if the current used network construction methodology are not suitable for the MS pathology. In functional imaging we found a reduced signal quality (possibly linked to hypoperfusion) to significantly explain the differences observed in GTA parameters in fMRI. While in structural imaging we found a general decline in diffusivity (which is linked to the demyelination), to reflect more the overall central nervous system damage caused by MS rather than being specific for cognition. In conclusion our studies suggest that differences in network parameters between MS and HS do not reflect a functional or structural reorganisation of the brain for cognition, but that MS pathophysiological mechanisms alter the network construction.
Disclosures: the authors did not disclose any links of interest.

P10: The seasonal fluctuation of fatigue in multiple sclerosis

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Background: Fatigue is a common symptom in patients with multiple sclerosis. Several studies suggest that heat can impact fatigue severity, but we lack a systematic investigation of seasonal fluctuations.
Methods: Fatigue was assessed with the Fatigue Score for Motor and Cognition (FSMC). This study included 258 patients with multiple sclerosis from 572 visits temporally distributed over the year. The data were adjusted for age, sex, cognition, depression, disease severity, and follow-up time. Linear regression models were performed to determine whether the temporal course of fatigue was time-independent, linearly time dependent, or non-linearly time dependent.
Results: Fatigue was lowest during January (mean FSMC: 49.84) and highest during August (mean FSMC: 53.88). The regression analysis showed the best fit with a model that included months + months^2, which was a non-linear time dependency.
Conclusion: In multiple sclerosis, fatigue showed a natural temporal fluctuation. Fatigue was higher during summer compared to winter. This finding should be carefully taken into account when monitoring multiple sclerosis.
Disclosures: the authors did not disclose any links of interest.

P11: Alpha power as an independent marker of reduced information processing speed in multiple sclerosis

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Objective: Cognitive impairment is common in multiple sclerosis (MS), significantly impacts daily functioning and is difficult to assess. We examined whether the alpha band power measured with magnetoencephalography (MEG) is associated with cognitive scores in MS.
Methods: A total of 68 MS patients and 47 healthy controls underwent MEG, T1-and FLAIR weighted magnetic resonance imaging (MRI) and neuropsychological testing. Alpha power in the occipital cortex was quantified in alpha1 (8-10Hz) and alpha2 (10-12Hz). Next, we performed best subset regression to assess the added value of neurophysiological measures with respect to commonly available MRI measures.
Results: Alpha2 power significantly correlated with information processing speed ($p<0,001$) and was always retained in all multilinear models, whereas thalamic volume was retained in 80% of all models. Alpha1 power was correlated with visual memory ($p<0,01$) but only retained in 16% of all models.
Conclusions: Alpha2 (10-12Hz) power in rest is associated with information processing speed, independent of standard MRI parameters. Significance: This study stresses that a multimodal assessment, including both structural and functional biomarkers, is likely required to capture cognitive impairment in MS.
Disclosures: the authors did not disclose any links of interest.

P13: French validation of the work difficulties questionnaire in Multiple Sclerosis: Preliminary data.

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Work difficulties is a recent highlight in Multiple Sclerosis (MS). The present study aims to validate into French the MS Work Difficulties Questionnaire (MSWDQ) and evaluate the psychological and cognitive factors that may induce it. 45 MS patients (31 recurrent remittent and 14 Progressive forms) filled a cognitive evaluation including the BICAMS and the following questionnaires: MSWDQ French adaptation, DEX for cognitive complaint, Fast BDI for depression, GAD 7 for anxiety, and EMIF for fatigue. The score of handicap on EDSS correlated only with the Physical Barriers factor measured at the MSWDQ, r.37, p=.01. The cognitive complaint at the DEX strongly correlated with all three factors of MSWDQ, but mainly with the Psychological and Cognitive Barriers (PCB) factor, r=.61, p<.00001. When taking into account depression and anxiety, only the level of anxiety significantly impacted the total score and mainly on the PCB, β.35, p<.05. Physical, cognitive and social fatigues strongly correlated with all scores at the MSWDQ. Among the cognitive scores, only processing speed measured at the SDMT impacted PCB scores, F=6, p=.01. The French validation of the MSWDQ is in progress. Further research will aim at reducing work difficulties by proposing cognitive rehabilitation.
Héloise Joly received a grant from the ARSEP foundation.
Disclosures: the authors did not disclose any links of interest.

P14: The role of estimated premorbid cognitive abilities in differences between selfreported cognitive difficulties and formal cognitive assessment in people with multiple sclerosis

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Background: Cognitive difficulties are reported in up to 60% of people with MS (pwMS). There can often be a discrepancy between self-reported cognitive difficulties in daily life reported by pwMS and performance on formal cognitive assessments in clinic. Some of this discrepancy can be explained by depression and fatigue. Additional variance may be accounted for by estimated premorbid cognitive abilities (PCAs), which protect against formally assessed cognitive impairment. Specifically, pwMS with higher estimated PCAs may notice cognitive difficulties in everyday life whilst still performing within the norm on formal assessments, which can negatively impact mood and quality of life.
Objectives: We explore whether estimated PCAs predict self-reported cognitive difficulties. We hypothesise that controlling for depression and fatigue, estimated PCAs will contribute to (1) performance on formal cognitive assessments and (2) differences between self-reported and assessed cognitive ability.
Method: PwMS completed the Test of Premorbid Functioning, the Brief International Cognitive Assessment for MS (BICAMS), and measures of self-reported cognitive difficulties (MS Neuropsychological Questionnaire), fatigue (MS Fatigue Impact Scale), and depression (Hospital Anxiety and Depression Scale).
Results and Discussion: Data collection is ongoing, with n=60 collected to date. We will present preliminary results. Findings may have important implications for clinical practice. *Disclosures*: the authors did not disclose any links of interest.

P17: Reduced network dynamics in cognitively impaired MS patients might be explained by more energetically costly state transitions

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Aim MS patients frequently develop cognitive impairment (CI), where a disorganization of the functional brain network plays a vital role. This study investigates dynamic network behavior in CI-MS by looking at functional brain states.
Methods Resting-state functional MRI and diffusion tensor imaging were included from 332 patients with MS and 96 healthy controls (HCs). Cognition was assessed with an expanded BRB-N, from which cognitive groups were defined (87 CI, 65 mild CI and 180 cognitively preserved [CP]). Functional connectivity was determined using edge time-series and four connectivity states were identified using K-means clustering, characterizing how the brain transitions between network configurations. Finally, the minimum input energy needed for these functional state switches was calculated using subject-specific structural connectivity and network control theory.
Results MS patients with CI showed an overall loss of dynamic network behavior compared to CP ($p=0.002$). More specifically, these patients spent more time in a lowly connected internally oriented state ($p=0.004$), but less in a state featuring more between-network connectivity ($p=0.001$). Additionally, patients with CI required more input energy to transition to and dwell in this between-network connected state ($p<0.001$).
Conclusion MS patients with CI show reduced functional network dynamics that might be explained by more energetically costly state transitions.
Disclosures T.A.A.B., L.D. & V.M.R. report no conflicts of interest. J.J.G.G. is an editor of Multiple Sclerosis Journal. He serves on the editorial boards of Neurology and Frontiers in Neurology and is president of the Netherlands organization for health research and innovation. He has served as a consultant for or received research support from Biogen, Celgene, Genzyme, MedDay, Merck, Novartis and Teva. M.M.S. serves on the editorial boards of Neurology and Frontiers in Neurology, receives research support from the Dutch MS Research Foundation and has served as a consultant for or received research support from Atara Biotherapeutics, Biogen, Celgene, Genzyme, MedDay and Merck.

P18: Cognitive impairment and brain network organisation in MS patients

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In this study, we aimed to examine the relationship between EEG-based connectivity measures and cognitive impairment in a large cohort of MS patients. EEG recordings were obtained from 250 persons with MS, in conjunction with cognitive data. Cognitive functioning was assessed with the Neuropsychological Screening Battery for MS. A patient was classified as cognitively impaired when scoring below the 5th percentile of a normal population on two or more tests. Weighted EEG-based connectivity (i.e., imaginary coherence and phase locking values) matrices were obtained by within 4 frequency bands: delta (1-4Hz), theta (4-8Hz) alpha (8-12Hz) and beta (13-30Hz). We used machine learning to assess the predictive value of functional connectivity for cognitive status. We used 2 (edge detection methods) x 4 (frequency bands) types of feature sets to predict cognitive impairment in our MS sample. The machine learning analysis using a random forest classifier showed no relationship between connectivity and cognitive status across the feature sets. Given the large sample size, this suggests that while in rest with eyes closed, the (non-linear) relation between connectivity and cognition is likely small.
Disclosure: This study has been funded by Merck N.V.-S.A., Overijse, Belgium, an affiliate of Merck KGaA (CrossRef Funder ID: 10.13039/100009945).

P21: Effects of Cognitive Reserve and biological sex on cognitive changes in people with Multiple Sclerosis: a longitudinal study

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Introduction. Longitudinal studies on the effect of cognitive reserve (CR) on cognition in people with Multiple Sclerosis (pwMS) are inconsistent (Amato et al., 2013; Sumowski et al., 2014), and the interaction effect between sex and CR on cognition was not evaluated. The aim of the study was to evaluate the effect of CR, sex, and their interaction on cognitive changes in a sample of newly diagnosed pwMS.
Materials and methods. 74 pwMS (41 women, 33 men) according to 2018 McDonalds criteria underwent the following assessment at baseline (T0) and follow-up (T1; 20.2 ±4.9 months): neurological evaluation, neuropsychological battery (BRB-N) and Cognitive Reserve Scale (Altieri et al., 2018). A MANOVA for repeated measures with correction for multiple comparison was performed. P values ≥ 0.05 were considered statistically significant.
Results. The MANOVA revealed a significant main effect of i) time on SRT-LTS, SRT-D, SPART, SPART-D, SDMT, PASAT 3'', WLG, STROOP scores (T1>T0), and ii) sex on SRT-CLTR, SRT-D scores (women>men). The interaction between time, sex and CR on SPART, SPART-D, WLG, STROOP was also significant.
Discussion. Only men with high CR showed an improvement on cognition at T1, revealing a combined role of CR and sex on cognitive changes in MS.
Disclosures: the authors did not disclose any links of interest.

P23: Comparison of cognitive functions in relapsing and progressive multiple sclerosis patients on ocrelizumab treatment

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Background Ocrelizumab has been shown to be an effective treatment for both relapsing multiple sclerosis (RMS) and progressive multiple sclerosis (PMS). We aid to evaluate cognitive function changes with ocrelizumab as a part of treatment effectiveness using BICAMS tool.
Methods The data of 28 RMS and 100 PMS was investigated in this prospective study. Cognitive performance was assessed using Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS- SDMT; Symbol Digit Modalities Test; CVLT-II; California Verbal Learning Test second edition; BVMT-R; Brief Visuospatial Memory Test-Revised). Each test was done twice; before ocrelizumab initiation and in the sixth month.
Results CVLT-II scores were significantly increased in the progressive form at month 6, compared to baseline assessment ($p<0,05$), but no significant difference was observed in the relapsing form.
Conclusions Our data confirms the abscence of cognitive function worsening at the early stages of ocrelizumab treatment in RMS.
This abstract has been presented previously at ECTRIMS 2021.
Disclosures: the authors did not disclose any links of interest.

P25: Influence of emotional valence on episodic autobiographical memory

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Introduction: Autobiographical memory (AM) has been poorly studied in MS with inconsistent results. Strong links have been demonstrated between the quality of memory recall and their emotional valence (EV). Our study aimed to evaluate the influence of EV on the recall of episodic autobiographical memories.
Method: 37 RRMS patients and 30 healthy-controls (HC) (similar by age, gender and level of education) had an original AM test (emotional TEMPau) evaluating quality recall (QR) for three periods of life (0-17 years, 18-30 years, last 12 months), by varying the EV and a battery of executive tests. Inter/intra-group comparisons were conducted using adapted statistical tests.
Results: Patients performed worse than HC in all time periods and for the two first periods, QR is better for non-neutral memories than neutral ones. For the last period, this difference only appeared between positive and neutral memories. Correlations were found between working memory, verbal fluency and QR of neutral memories (1st and last periods) in patients. Significant differences were observed for verbal fluency, flexibility and inhibition tests between patients and HC.
Conclusion: Compared to HC, patients have difficulties in recovering autobiographical memories whatever the life period. However, recall is enhanced by the EV. Working on the EV may facilitate recall and compensate executive difficulties.
Disclosures: the authors did not disclose any links of interest.

P26: Assessment of executive disorders in multiple sclerosis using virtual reality tool

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Introduction: In MS, executive dysfunction is not always identified by traditional psychometric tests although patients may complain about it. Many studies suggest the interest of virtual reality (VR) techniques to evaluate cognitive functions as close as possible to daily life of patients. We investigate the value of VR tool in the assessment of executive disorders in MS compared to traditional tests.
Method: 30 patients RRMS and 30 healthy-controls (HC) similar by age, gender and level of education, have performed a VR task (shopping in a supermarket; main cues: total duration and travelled distance) with a familiarization phase followed by a test phase. Finally, traditional tests assessing executive functions were proposed. Inter/intra-group comparisons were conducted using adapted statistical tests.
Results: No significant differences were found between two groups in traditional tests. However, in VR, significant differences were found during the familiarization phase with all the cues. In the VR test phase, differences were not found.
Conclusion: VR test seems to be more sensitive than our traditional tests in detecting executive difficulties in patients. On the other hand, we noticed a learning effect during the test phase, which allows us to envisage rehabilitation with VR for a transfer into daily life.
Disclosures: the authors did not disclose any links of interest.

P27: Icognition – towards telemonitoring of cognitive performance in multiple sclerosis

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Introduction: Monitoring cognitive impairment in multiple sclerosis (MS) with cognitive tests is hampered by practice effects, lack of trained personnel and suboptimal testing conditions during clinical visits.
Methods: We developed a smartphone-based cognitive assessment tool, which can be used independently at home. One test, the Symbol test, assesses information processing speed, and a second test, the Dot Memory test, assesses visuospatial short-term memory and learning. Practice effects are reduced by randomly generated exercises, that change with every trial. We assessed performance on these tests and two comparable paper-pencil tests, the Symbol Digit Modalities Test (SDMT) and the 10/36 Spatial Recall test (SPART), in 76 patients with MS.
Results: The Symbol test significantly and positively correlated with the SDMT ($r = 0.69$, $p < 0.001$, $n = 76$). The Dot Memory test showed no correlation with the SPART ($r = 0.09$, $p = 0.444$, $n = 70$).

Discussion: While the Dot Memory test shows no correlation with its paper-pencil equivalent, the Symbol test has a moderate concurrent validity with the traditional paper-pencil SDMT. Since this smartphone-based test reduces issues of practice effects, personnel and testing conditions, it could be a good alternative for more frequent and reliable cognitive monitoring in MS.
This abstract will also be presented at the European Multiple Sclerosis Platform (EMSP) 2022
Disclosures: the authors did not disclose any links of interest.

P28: Don't be late! Timely Identification of Cognitive Impairment in Multiple Sclerosis: A study protocol

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Background: Cognitive deficits frequently occur in people with multiple sclerosis (pwMS), negatively affecting quality of life. Currently, neuropsychological testing is no consistent part of standard care due to lack of time and trained personnel, hampering early identification of cognitive decline and change within a person over time. Therefore, the BICAMS-based Multiple Screener©, a self-explanatory digital screening tool, has recently been developed to assess cognitive performance in MS time-efficiently without the need of a test-leader.
Objectives: To validate the Multiple Screener© in a representative Dutch sample of pwMS and to investigate the relationship between cognition, psychological factors, work-and societal participation in MS.
Methods/Design: In this cross-sectional multicentre study, we will include 750 pwMS (aged 18-67 years). Patients will be recruited across 10 hospitals in the Netherlands and will be assessed with the MACFIMS (gold-standard) and Multiple Screener©. Sensitivity, specificity, and predictive values for identifying (mild) cognitive impairment will be determined. Test-retest reliability for the Multiple Screener© will be determined in a subset of participants. Information on psychological and work-related factors will be assessed with questionnaires.
Conclusion: Validating the Multiple Screener© in pwMS and investigating cognition and its determinants will further facilitate early identification and adequate monitoring of cognitive decline in MS.
Disclosures: the authors did not disclose any links of interest.

P30: Decreased functional dynamics of thalamocortical states in cognitively impaired multiple sclerosis patients

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Aim: Thalamic atrophy in MS has been consistently associated with cognitive impairment (CI), but thalamic connectivity remains understudied. This study investigates whether the thalamus exhibits altered thalamocortical connectivity dynamics in MS patients with CI.
Methods: 332 MS patients and 96 healthy controls (HC) underwent (f)MRI scanning and neuropsychological testing. Patients were classified as cognitively preserved (CP-MS; n=180), cognitively impaired (CI-MS; n=87, z≤−2 on ≥2 domains), or mildly cognitively impaired (MCI-MS; n=65,

z≤−1.5 on ≥2 cognitive domains). A sliding window approach was used to determine meta-states, i.e. thalamocortical functional connectivity per window. Five states were determined using k-means clustering.
Results: Compared to HC, CI-MS showed fewer meta-states (39.8 vs 36.2; p=0.034) and a smaller state span (11.2 vs 10.5; p=0.05). Compared to CP-MS, CI-MS showed fewer meta-states (39.5 vs 36.2; p=0.022) and a shorter distance travelled (122.5 vs 113.3; p=0.03). MS patients occupied a state of generalized low thalamocortical connectivity significantly more than HC (p<0.001). More dwell time in this thalamocortical state correlated with cortical grey matter volume (r=−0.18, p=0.007) and cognition (r=−0.23, p<0.001).
Conclusion: The thalamus shows reduced state dynamics in MS, indicating a more rigid thalamic network. These thalamic changes were most prominent in patients with CI. *Disclosures*: the authors did not disclose any links of interest.

P31: Evaluating No Evidence of Disease Activity (NEDA) in Patients With Relapsing Multiple Sclerosis: Post Hoc Analysis of the Phase 3 RADIANCE and Open-Label Extension Studies of Ozanimod

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Introduction: NEDA is a composite efficacy outcome and treatment target for multiple sclerosis.
Methods: Data are from a randomized phase 3 trial (RADIANCE–NCT02047734) of oral ozanimod 0.92mg/d vs intramuscular interferon β-1a (IFN) 30µg/wk and an open-label extension trial (DAYBREAK–NCT02576717) of ozanimod 0.92mg/d. NEDA-3 (no gadolinium-enhancing lesions, new/enlarging T2 lesions, relapses, and EDSS score progression) and NEDA-4 (NEDA-3 plus whole brain volume loss ≤0.4%/year) were calculated from RADIANCE baseline and rebaselined to RADIANCE month 12.
Results: NEDA-3 rates at RADIANCE month 24 and DAYBREAK month 36 were 24.6%* and 10.7% with continuous ozanimod and 17.0% and 7.4% for those on/transitioned from IFN (IFN→ozanimod), respectively. NEDA-4 rates were 14.0%* and 10.3% for continuous ozanimod and 7.8% and 6.3% for IFN→ozanimod. After rebaselining to month 12, NEDA-3 rates at RADIANCE month 24 and DAYBREAK month 36 were 52.6%* and 21.3% with continuous ozanimod and 33.4% and 14.8% for IFN→ozanimod. Rebaselined rates of NEDA-4 were 33.5%* and 14.1% for continuous ozanimod and 19.7% and 11.0% for IFN→ozanimod.
Conclusion: More patients achieved NEDA-3 and NEDA-4 at month 24 with ozanimod vs IFN. Rebaselining to month 12 resulted in more patients on continuous ozanimod vs IFN→ozanimod achieving NEDA-3 and NEDA-4 in DAYBREAK. *P<0.05 vs IFN.
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P34: Evaluation of a Self-administered, IPad-based Processing Speed Test for People with Multiple Sclerosis

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Introduction: Even though cognitive impairment is a prominent feature in people with MS (pwMS), standard clinical care in pwMS does not always include neuropsychological assessment mainly due to limited clinical resources. The aim of this study was to evaluate the feasibility of a self-administered, IPad-based cognitive screening tool (Processing Speed Test, PST) Furthermore, sensitivity compared to the Symbol Digit Modalities Test (SDMT) was assessed.
Methods: We included 160 pwMS (61% female, mean age=38.63±9.24) and performed the Brief International Cognitive Assessment in MS (BICAMS). Afterwards, pwMS were asked to perform the PST in a quiet or waiting room setting.
Results: SDMT scores were highly correlated with the PST in both settings (quiet: r=0.78, p<0.001; waiting room: r=0.78, p<0.001). Regarding cognitive impairment (defined by a zvalue

£-1.5), 48 pwMS (30%) were cognitively impaired in a single BICAMS domain, thereof 43 pwMS (27%) in the SDMT compared to 9 pwMS (6%) in the PST.
Conclusion: Our results show high correlations between the SDMT and the IPad-based PST. However, the SDMT proved to be more sensitive than the PST. In routine clinical care, the PST could be a helpful cognitive screening, if no formal neuropsychological assessment is available.
Disclosures: the authors did not disclose any links of interest.

P35: Relation between MEG oddball connectivity and cognitive evolution in MS

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Background: Half of PwMS suffer from cognitive deterioration, causing increased burden of disease, but we currently do not have sufficiently strong biomarkers to predict cognitive evolution in MS.
Goal: To examine the predictive value of inter- and intrahemispheric coherence connectivity based on source-reconstructed, parcellated magnetoencephalographic (MEG) measurements during an oddball task in relation to cognitive evolution in MS.
Results: In total, 100 PwMS were included. Seven were excluded from the analysis because of movement artefacts in the MEG. 81 consented to cognitive retesting after three years. PwMS with worsening cognition after three years showed significant differences in baseline connectivity compared to stable or improving PwMS.
Four edges showed a significant difference in coherence at the group level between the cog+ and cog- groups. One of these was intrahemispheric, between the left dorsolateral prefrontal cortex and the left superior frontal cortex. The other three were interhemispheric: between the left superior parietal cortex and the right temporal gyrus, between the left medial occipital and right inferior parietal cortex, and between the left precuneus and right lateral occipital cortex.
Conclusion: Inter- and intrahemispheric coherence assessed on source reconstructed and parcellated MEG oddball data is a promising biomarker for cognitive evolution in multiple sclerosis.
Disclosures: the authors did not disclose any links of interest.

P37: Volumetric MRI markers and their relation to cognitive and physical impairment in MS at age 53: Descriptions from a birth cohort

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Aim: To study how cognitive impairment and disability are related to volumetric measures on MRI, avoiding the confounding effect of age by using a birth cohort of MS-patients (pwMS) and healthy controls of the same age: Project Y.
Methods: Thalamic, deep- (DGMV), cortical- (CGMV) and cerebellar grey matter, as well as white matter lesion volumes (LV) and mean upper spinal-cord area (MUCCA) were quantified on 3T-MRI from 234 pwMS and 113 HC (mean age 53 years). Correlations (Spearman's rank/ Pearson's r) were explored with symbol digit modalities test (SDMT), EDSS, nine hole peg test (9HPT) and timed 25 foot walking test (T25FWT), corrected for sex and MS-subtype. Z<-1.5 vs. HC was considered atrophic or impaired.
Results: SDMT was impaired in 26% of pwMS. All volumes were lower in pwMS and worst in the DGMV, where 24% showed atrophy. Strongest correlations with SDMT were seen with lesion volume and CGMV, MUCCA showed no correlation. EDSS showed strongest correlations with MUCCA, and 9HPT with all volumes except MUCCA. TWT only correlated with MUCCA.

Conclusion: At a median age of 53, 26% MS patients suffered from SDMT impairment. Cortical volume was the most important correlate of cognition independent of the effect of ageing.
Disclosure:.R.J. de Ruiter and F.C. Loonstra, I.C.E. Van Leeuwen, J.R. Jelgerhuis, E.M.E. Coerver, A. A. Toorop, B. Moraal, E.M. Strijbis report no disclosures. M.M. Schoonheim serves on the editorial board of Frontiers in Neurology, receives research support from the Dutch MS Research Foundation and has served as a consultant for or received research support from Atara Biotherapeutics, Biogen, Celgene, Genzyme, MedDay and Merck. B.M.J. Uitdehaag received consultancy fees from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, and Teva.
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P38: Impact of ozanimod treatment on cortical grey matter volume (CGMV): up to 5 years' experience in phase 3 and extension trials

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Introduction: Accelerated early CGMV loss occurs in interferon-treated RMS patients.
Methods: CGMV was quantified in randomized phase 3 (SUNBEAM–NCT02294058, RADIANCE–NCT02047734) trials comparing oral ozanimod 0.92 and 0.46mg/day with intramuscular interferon 30µg/week and an ongoing, open-label extension trial (DAYBREAK–NCT02576717) of ozanimod 0.92mg/day in RMS. MRI was performed at months 6 (SUNBEAM), 12 (RADIANCE/SUNBEAM), and 24 (RADIANCE), then every 12 months (DAYBREAK). CGMV was analyzed through DAYBREAK month 36.
Results: The rate of CGMV loss was greater ($P<0.001$) with interferon than ozanimod 0.92mg during SUNBEAM/RADIANCE: LS mean percentage change from baseline was -0.67% vs -0.02%, respectively, at month 6 and -1.04% vs -0.16% at month 12 in SUNBEAM, and -0.80% vs -0.13% at month 12 and -1.26% vs -0.53% at month 24 in RADIANCE. Switching from interferon to ozanimod reversed CGMV loss in year 1 of DAYBREAK. Thereafter, annualized rates of CGMV loss were similar among participants who switched from interferon and those continuously treated with ozanimod. Patients continuously treated with ozanimod lost less CGMV in DAYBREAK relative to RADIANCE/SUNBEAM baseline than patients initially treated with interferon.
Conclusion: Switching from interferon to ozanimod reversed CGMV loss. Earlier treatment with ozanimod led to less CGMV loss over 4–5 years, supporting early ozanimod use.
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grant support from Genentech. LK: Institutional research support: steering committee, advisory board, consultancy fees: Actelion, Bayer HealthCare, Biogen, Bristol Myers Squibb, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, Shionogi, and TG therapeutics, speaker fees: Bayer HealthCare, Biogen, Merck, Novartis, Roche, and Sanofi; support of educational activities: Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, and Teva; license fees for Neurostatus products; and grants: Bayer HealthCare, Biogen, European Union, Innosuisse, Merck, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation. GC: compensation for consulting and/or speaking activities from Almirall, Biogen, Celgene, EXCEMED, Forward Pharma, Genzyme, Merck, Novartis, Roche, Sanofi, and Teva. HPH: personal fees for consulting, serving on steering committees, and speaking from Bayer Healthcare, Biogen, Celgene, GeNeuro, Genzyme, Merck, MedImmune, Novartis, Octapharma, Roche, Sanofi, and Teva. CYC: employee and shareholder of Bristol Myers Squibb. DS: employee and shareholder of Bristol Myers Squibb. JAC: personal compensation for consulting for Biogen, Bristol Myers Squibb, Convelo, Genentech, Janssen, NervGen, Novartis, and PSI; and serving as an Editor of Multiple Sclerosis Journal. DLA: personal fees for consulting and/or grants from Albert Charitable Trust, Alexion Pharma, Biogen, Celgene, Frequency Therapeutics, Genentech, Med-Ex Learning, Merck Serono, Novartis, Population Council, Roche, and Sanofi-Aventis; grants from Biogen, Immunotec, and Novartis; and an equity interest in NeuroRx.

P39: Sustained attention during prolonged walking in persons with multiple sclerosis

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Background: Growing evidence demonstrates that walking requires cognitive control. It is also known that there is a decrease in walking speed during long-distance walking in persons with multiple sclerosis (pwMS). However, it is unknown whether pwMS can retain sustained attention while performing simultaneous motor tasks (i.e., walking) in long-distance tests. This study investigated cognitive attention during prolonged walking in pwMS and compared it with healthy controls (HC).
Methods: Thirty-seven pwMS and 14 age-gender matched HC performed the 6-Minute Walk Test (6MWT) with an auditory vigilance task. Participants were provided a letter every 2.5s and were instructed to say "yes" as fast as possible when they heard the two selected letters through the application to assess vigilance. The number of errors, average reaction time, and distance per minute were calculated.
Results: A significant time and group∗time interaction effect were found for reactions times, represented by a significant increase in pwMS during the 6 mins. Time or group∗time interaction was not found for the number of errors. There was a minute-by-minute decrease in walking distance in both groups, but there was no group*time interaction.
Conclusion: Our findings suggest that sustained attention deteriorated overtime during the six minutes of walking in pwMS.
Disclosures: the authors did not disclose any links of interest.

P40: Differences on accuracy estimating cognitive performance between multiple sclerosis phenotypes and healthy controls.

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Aim: To compare the accuracy estimating cognitive performance in patients with different multiple sclerosis (MS) phenotypes and healthy controls (HC).
Methods: 54 HC and 112 MS patients (relapsing-remitting MS -RRMS-; n=65 and progressive MS -PMS-; n=47) underwent neuropsychological evaluation and completed the Perceived Deficits Questionnaire (PDQ). Participants were classified as objectively preserved (OP) or impaired (OI) and subjectively preserved (SP) or impaired (SI) according to results on neuropsychological tests and PDQ, respectively. Accurate estimators were those OP and SP or OI and SI. OP but SI patients were considered under estimators and OI but SP over estimators.
Results: Differences in the proportion of OI were found (63.8% in the PMS group versus 32.3% of RRMS and 11.1% of HC, $p<0.001$) but not in the proportion of SI ($p=0.075$). Regarding accuracy, statistically significant ($p<0.001$) differences were found: PMS had higher ratios of over estimators (34.8% versus 17.2% of RRMS and 3.7% of HC) while the RRMS had more under estimators (20.3% versus 10.9% of PMS and 11.1% of HC).
Conclusion: The progressive group has a greater proportion of cognitive impairment but not of subjective impairment, also has a greater proportion of over estimators. Presence of anosognosia in progressive MS could explain these results.
Disclosures: the authors did not disclose any links of interest.

P42: Remote Cognitive Testing in Multiple Sclerosis during the COVID-19 Pandemic

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Approximately 43-70% of people living with multiple sclerosis (MS) experience cognitive impairment. This study-within-a-trial (SWAT) takes place within a host trial investigating the feasibility of the Cognitive-Occupation-Based programme for people with MS (COB-MS), a holistic therapy on the management of cognitive symptoms in MS. Reliable remote cognitive testing could provide safer and more convenient care for MS patients, during the COVID-19 pandemic and thereafter. The SWAT examines the reliability of delivering the Brief International Cognitive Assessment for MS (BICAMS) and the Trail-Making Test (TMT) remotely to people to 68 people with MS experiencing cognitive difficulties. Group 1 (N=34) were tested in-person pre-pandemic. Group 2 were tested remotely. No significant differences between virtual and in-person administrations of the CVLT-II and SDMT were detected. BVMT-R scores were significantly higher for virtual administrations, possibly indicating inter-rater differences. Strong positive correlations were found for in-person and virtual scores within Group 1 on the CVLT-II. The findings support the reliability of remote administration of BICAMS and the TMT in people living with MS. Future research with larger samples could investigate performance on BVMT-R with regards to screen size of device used.
Disclosures: the authors did not disclose any links of interest.

P43: Predicting cognitive impairment in multiple sclerosis: between cognitive reserve and brain volume

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Introduction Cognitive reserve (CR) theory posits that baseline differences in lifetime intellectual enrichment affect cognitive performance in neurodegenerative disease. The aim of this study was to identify which MRI measures of disease burden and/or CR proxies best predict cognitive decline in MS.
Methods Fifty MS patients underwent 3Tesla brain MRI to estimate disease burden (T2 lesion load; T1 lesion load; atrophy of gray matter [GM] and white matter). CR was assessed with the 'Cognitive Reserve Questionnaire'(QRC) (Rami et al, 2011) and education level. We measured cognitive status with MACFIMS. An overall cognitive status composite was calculated as the mean of the z-scores derived from the battery's tests.
Results In the linear regression analyses investigating the effect of MRI measures of structural damage, QRC score and education on overall cognitive composite, subcortical GM was the only MRI measure retained (R2=0.407, p=0.001), after controlling for age and sex. Additionally, QRC score was an independent predictor of overall cognitive status ((R2=0.479, p=0.020), such that patients with higher QRC score had better cognitive status.
Conclusion Our study provides evidence of CR in MS, namely, supports the QRC as a meaningful proxy. These results corroborate previous work that support that subcortical GM correlates with cognitive deficits.
Disclosures: the authors did not disclose any links of interest.

P44: Determinants of fatigue and cognition in different MS phenotypes

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Aim: To look for the factors influencing cognitive decline and fatigue according to the MS phenotype.
Material and methods: 66 MS persons (40 with RRMS and 26 –with SPMS) and 70 healthy controls were examined. Fatigue (MIFS), depression (BDI) and cognition (computer system Rila Cogni Soft) were tested.
Results: The most vulnerable cognitive domain in patients was the speed of information processing (SIP) and it was significantly worse in SPMS ($p < 0.01$). The majority of people with SPMS suffered from moderate to severe depression, while those with RRMS experienced mild depression ($p < 001$). We found a moderate negative correlation between BDI and SDMT results, i.e. the slow SIP was partly determined by increased depression. SDMT scores were moderately affected by age, education and EDSS, and weakly - by disease duration. Patients reported a higher fatigue than controls. We did not find a significant difference in the fatigue level between the patients groups, but the higher fatigue score (MIFS) correlated with higher EDSS. We found a moderate positive correlation between the fatigue severity and depression. Fatigue was weakly affected by age and does not depend on the disease duration.
Conclusion: We confirm that the nature of fatigue and cognitive changes in people with MS is complex and needs further in-depth research.
Disclosures: the authors did not disclose any links of interest.

P45: Konectom™ cognitive processing speed testing and the influence of reaction time

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Smartphone-based Konectom cognitive processing speed test (CPST) includes a symbol-to-digit (S2D) substitution task followed by a digit-to-digit (D2D) matching test. Assessing the S2D substitution time (ST), by subtracting mean D2D reaction time (RT) from mean S2D RT for each test, may limit the influence of visuomotor impairment on scores. The objective of this analysis was to explore the reliability and convergent validity of these Konectom CPST features against standard measures of cognition and disability in PwMS.
The DigiToms study (NCT04756700) is enrolling people with multiple sclerosis (PwMS) aged 18-64 years, with Expanded Disability Status Scale (EDSS) score ≤ 6.0. Baseline in-clinic assessments include Konectom CPST, EDSS, and symbol digit modalities test (SDMT). Konectom CPST is subsequently self-administered remotely over 14 consecutive days.
40 PwMS completed testing at interim data cut (mean age=41.9, 82.5% female, median EDSS=2.0). Remote test–retest reliability [ICC] for CPST ST testing was good (0.74). CPS ST correlated with SDMT (ρ= -.72, $p<0.0001$) and EDSS scores (ρ=.41, $p<0.0001$). D2D RT correlated with SDMT (ρ=-.65, $p<0.0001$) and EDSS scores (ρ=.48, $p<0.0001$).
Cognitive processing speed can reliably be self-assessed remotely by PwMS using Konectom. Potential non-redundancy between S2D ST and D2D RT will be further elucidated.
*Disclosure: **
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P46: Cerebellar atrophy and cognitive function in multiple sclerosis: does it matter?

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Introduction: Cerebellum has been disregarded in cognitive functioning to the detriment of its classic association with motor function. However, cerebellum is involved in cognition and emotion, and increasing evidence indicates that cerebellar damage is important in a range of cognitive disorders.
Objective: To investigate the association of cerebellar atrophy with cognitive impairment in multiple sclerosis (MS) patients.
Methods: Sixty MS patients and 60 healthy controls (HC) demographically-matched were enrolled. All participants underwent cognitive testing (MACFIMS) and 3Tesla Brain-MRI. Using Freesurfer software,

white-matter (WM), cortical and subcortical gray-matter volumes were calculated, including cerebellum-WM and cerebellum-cortex volumes.
Results: Compared to HC, MS patients had lower scores on all cognitive domains and decreased volumes of cerebellum-WM and cerebellum-cortex ($p<0.05$). Moreover, cerebellum WM and cortex volumes were significantly reduced in patients with cognitive impairment compared to those with normal cognitive performance($p<0.05$).
In the MS group, cerebellum-WM volume correlated positively and was the main predictor of information-processing speed (SDMT and PASAT) while cerebellum-cortex volume correlated positively and was the main predictor of visual-learning (BVMT-R).
Conclusions: This study suggests that cerebellar atrophy contributes for cognitive impairment in MS patients, particularly in the information-processing speed and visual learning domains, reflecting a probable disruption of the cortico-cerebellar pathways.
Disclosures: the authors did not disclose any links of interest.

P48: Frequency of isolated cognitive impairment, MRI patterns and its development over time

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Objectives: to study the frequency of single-domain cognitive impairments, domain-specific MRI correlates in people with MS (PwMS), and its development over time.
Methods: 348 PwMS (mean age 48±11yrs, 67% female) underwent neuropsychological testing (expanded BRB-N) at with 5-yr follow-up and baseline structural MRI. Cognitive impairment was classified as Z-scores ≤-1.5 below normative data. PwMS with single-domain impairment were appointed to the eponymous phenotype groups. MRI correlates per phenotype were explored using regression models. Progression of isolated cognitive impairment was evaluated over time.
Results: At baseline, 31% of PwMS suffered from isolated cognitive impairment. Most PwMS were impaired on executive functioning or working memory (EF/WM;N=37), followed by processing speed (IPS;N=25), memory (N=23), and attention (N=23). Of PwMS with IPS impairment at baseline, 69% became impaired in ≥2 domains at follow-up, versus 18-31% of PwMS with other isolated cognitive problems at baseline. Isolated IPS impairment correlated to cortical volume (ß=0.405,p=0.04) and fractional anisotropy (ß=0.429,p=0.05; R2=0.539, p<0.001); memory correlated to cortical (ß=-0.749,p<0.001) and hippocampal volume (ß=0.428,p=0.027; R2=0.497, p=0.002). EF/WM and attention did not correlate to the included MRI measures.
Conclusion: Isolated cognitive impairment is frequently present in PwMS. Compared to other deficits, twice as many PwMS with isolated IPS deficits deteriorated further.
Disclosures: the authors did not disclose any links of interest.

P49: The role of serum and CSF levels of NfL and GFAP in predicting cognitive functioning in people with multiple sclerosis

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Objective: To investigate the potential of neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) in both serum and CSF independently and on top of MRI as markers of cognitive functioning in people with MS (PwMS).
Methods: Eighty-six PwMS (51 females, age:47±10 years, disease duration:13±9 years) underwent neuropsychological (MACFIMS) and neurological examination, structural MRI, blood sampling and lumbar puncture. PwMS were classified as cognitively impaired (CI) if scoring ≥1.5SD below normative scores on ≥20% of test scores. Otherwise they were defined as cognitively preserved (CP). Binary logistic regressions were used to predict cognitive status, and diagnostic accuracy was assessed by ROC-curves.
Results: Higher levels of serum NfL (sNfL) and sGFAP were found in CI (N=46) compared to CP PwMS (N=36; p=0.010 and p=0.035). Only higher sNfL and CSF NfL were correlated with worse processing speed (r=-0.586, p=0.012 and r=-0.364, p=0.007, respectively). sNfL added unique variance in the prediction of cognitive status on top of matter volume. A combination of MRI and sNfL resulted in an area under the curve of 0.751 (sensitivity=85%, specificity=58%).
Conclusion: sNfL may serve as a marker for cognitive impairment, yet its combination with grey matter volume seems most promising for detecting cognitive deficits in MS.
Disclosures: the authors did not disclose any links of interest.

P50: The effects of ketone-based diets on neuropsychiatric outcomes in Multiple Sclerosis – an exploratory approach

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Introduction: Multiple sclerosis (MS) is the most common non-traumatic debilitating disease of the central nervous system in young adults and neuropsychiatric symptoms belong to the most disabling symptoms. Ketone-based diets such as ketogenic diets (KD) and fasting (FD) were shown to improve neuropsychiatric symptoms in some neurodegenerative diseases.

Methods: This is an exploratory sub-cohort analysis of the NAMS study (NCT03508414), a randomized, controlled study, investigating data of 71 patients over 9 months. Patients were randomized to a KD with a restricted carbohydrate intake, a FD with 7-day fasts every 6 months or a standard healthy diet (SD).
Results: Mild depressive symptoms improved by 17% in the FD group and deteriorated by 31% in the SD group (higher baseline values in the FD group must be considered). There was an increase of 2.52 points in the cognition score in the FD and an increase by 3.9 points in the KD group, but only in KD patients who had a relevant ketosis. The diets did not have a relevant effect on fatigue symptoms.
Conclusion: A healthy diet combined with fasting interventions may be a low-risk multi-target approach that could be recommended to MS patients to improve mild depressive symptoms and cognitive impairment.
Disclosures: the authors did not disclose any links of interest.

P51: Validation of the MS-IADL-Q to measure cognitive functioning in daily life: an update

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Objective: To provide an update on the validation of the MS Instrumental Activities of Daily Living Questionnaire (MS-IADL-Q) to measure cognitive functioning in daily life.
Methods: MS patients and their proxies filled out the MS-IADL-Q twice with a two-week interval. The MS-IADL-Q consists of eight categories with a total of 51 items. Inter-rater agreement and test-retest reliability was assessed using the intra-class correlation coefficient (ICC).
Results: Hundred MS patients (73 RRMS) and their proxies (N=100) filled out the questionnaire. The total score on the MS-IADL-Q at T0 was 19.70±17.55 for patients and 22.94±17.37 for proxies. At T1, the total score for patients was 20.02±17.36. We found poor agreement between patients and proxies (ICC<0.5) for three items (“Being responsible for own medication”, “Operating other devices”, “Taking care of others”), moderate agreement (ICC=0.5-0.75) for 27 items and excellent agreement (ICC>0.75) for 21 items. For patients, the test-retest reliability ranged between 0.5-0.75 for six items (moderate reliability), whereas excellent reliability (ICC > 0.75) was found for the other items (N=45).
Discussion: This interim analysis shows favorable test-retest reliability for the patient version of the MS-IADL-Q. A few items (N=3) need reconsideration as a consequence of low inter-rater agreement between patients and proxies.
Disclosures: the authors did not disclose any links of interest.

P52: Assessing cognitive impairment in Multiple Sclerosis by smartphone-based training games: Results of a feasibility study

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Background: Cognitive impairment occurs in up to 70% of MS-patients severely impacting quality of life. Comprehensive neuropsychological assessment is time consuming and frequently not well accepted. As part of a smartphone-app for monitoring MS disease-activity and progression (dreaMS) we evaluated feasibility and acceptance of using cognitive games as an assessment tool for cognition.
Methods: Ten smartphone-based games were included in the dreaMS-App. At baseline, participants underwent a neuropsychological test-battery and were asked to play all games twice per week for 5 weeks. Mean game-performance was correlated with established reference tests (Spearman's rho) and acceptance was assessed via questionnaire (5-point Likert-scales) at week 6.
Results: We included 31 PwMS (mean age of 43.4; 68% female; median Expanded Disability Status Scale score 3.0) and 31 age- and sex-matched HC. All except one game showed significant correlations with their predefined reference tests (rho= 0.332-0.751). Mean overall impression for all games was 4.6, perceived MS-relevance 4.69 points.
Conclusion: Correlations with predefined established tests suggest that cognitive games might allow assessment of cognitive functions and are well accepted, which is a necessary condition for long-term adherence. Studies of longer duration in larger populations, to further validate such games as monitoring tool for MS-patients, are ongoing.
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P53: Daily Cognitive Activities Questionnaire: A PATIENT-REPORTED OUTCOMES QUESTIONNAIRE ABOUT ATTENTIONAL DEFICITS IN MULTIPLE SCLEROSIS.

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Background: Cognitive impairment affect daily life and is detected in about half of the persons with multiple sclerosis (PwMS) including several domains as information processing speed (IPS) or attention. Questionnaire specific for a given cognitive domain is promising to detect attention impairment or cognitive changes.
Objective: To appreciate the potential of a new self-report questionnaire about attentional deficits, the Daily Cognitive Activities Questionnaire (DCAQ)
Method: 35 P wMS with CI and 21 healthy subjects (HS) were matched for age, gender and education. The cognitive assessment included paper-and-pencil tests concerning 4 cognitive domains, subtests of the Test of Attentional Performances, the Urban DailyCog and the DCAQ. All PwMS answered fatigue, depression, and anxiety assessment.
Results :The clinical data of PwMS were: disease duration [6.6 ± 4.3 years] and median EDSS [2.5 (0-8)]. All NP scores, except two, and score of all questions of the DACQ short version were significantly different between PwMS and HS. Significant correlations between NP scores, mainly scores of attentional tests, and DCAQ questions were found. In addition a few other correlations were observed with working memory tests.
Conclusion: The DACQ shows a great potential for diagnostic value, for referral to a full assessment or the monitoring post-rehabilitation.
Disclosures: the authors did not disclose any links of interest.

P54: Cognitive and motor fatigue is associated with increased excitation/inhibition (E/I) balance

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Introduction
Recent research combining neurocomputational modelling with measurements of local field potentials indicates that the slope with which the spectrum of neuronal activity rolls off (i.e. the exponent a in ( ) is a non-invasive marker of the excitation/inhibition balance and has been successfully linked to arousal level and cognitive load. We hypothesized that fatigue in MS is associated with increased E/I ratio (see Bachinger et al.2019).
Methods
MEG datasets were acquired of 46 MS patients during resting-state eyes-closed condition. Fatigue was assessed by the Fatigue Scale for Motor and Cognitive Function (FSMC) test on the same day. MEG data were preprocessed using the OSL library and parceled into 42 brain parcels. We used the fitting oscillations and one over f (FOOOF) algorithm to estimate the 1/f exponent. Next, we calculated the Pearson correlations between 1/f slopes and FSMC scores and corrected for multiple comparison using Benjamini-Hochberg's procedure.
Results
We observed a significant correlation between the 1/f slope – averaged across the full brain - and FSMC scores: motor fatigue ($r = 0.42$, p-value = 0.004), cognitive fatigue ($r = 0.33$, p-value = 0.02) and FSMC sum score ($r = 0.39$, p-value = 0.007). An increased Excitation/Inhibition balance is associated with higher levels of fatigue.
Disclosures: the authors did not disclose any links of interest.

P55: Sex differences in brain reserve and cognitive reserve in MS

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Sex differences in regional and whole brain atrophy and cognitive performance have been reported in MS. We tested the hypothesis of sex differences in brain reserve and cognitive, whereby women and men are differentially affected by the extent to which disease burden predicts neurocognitive test performance. **METHODS:** Patients were scanned using 3T MRI. Normalized brain volumes were calculated using Sienax and FIRST. A comprehensive neuropsychological battery was administered. Sex differences were evaluated using ANOVA controlling for age and disease duration; sex differences in reserve were tested using stepwise linear regression predicting each outcome, entering age, sex, disease duration, whole brain volume (WBV), and each sex x brain metric interaction term. **RESULTS:** In 245 patients (170 women), women had larger grey matter (GMV) and WBV; and larger left and right amygdala, and right caudate (all $p<.001$). Women performed better than men on SDMT, SRT (learning, recall), BVMT (learning), and Nine Hole Peg Test (NHPT; all $p<.01$). Linear regression showed significant contribution of sex x WBV, GMV, and WMV over and above age, sex, disease duration, and WBV for predicting NHPT. These results suggest that women are better able to withstand brain atrophy to maintain performance on neurocognitive tasks than men with MS.
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