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Research Article Open Access

Impairment of Visual Cognition in Progressive Multiple Sclerosis

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Abstract

Background: Impairment of visual cognition occurs in up to 25% of patients with MS, however data on progressive disease is limited and the neural basis remains unknown.

Objective: To evaluate the influence of multifocal inflammatory CNS white matter demyelination burden on visual cognition in equivalent SPMS and PPMS cohorts.

Methods: 59 SPMS and 27 PPMS patients matched for demographic and disease characteristics were evaluated using visuospatial and visuoperceptual components of the Addenbrooke's cognitive examination-revised (ACE-R) battery. Factors influencing performance were then identified by logistic regression. Exploratory logistic models were also used to determine the predictive value of deficits in attention, working memory, and arithmetic abilities. Finally, comparison of deficits between equivalent primary (PPMS) and secondary (SPMS) progressive disease groups was used to evaluate a potential dose-response for cumulative multifocal inflammatory CNS white matter demyelination.

Results: The overall prevalence of impairment in visual cognition was 14.0% (95%CI=6.4 to 21.4%) with no difference between disease groups. Qualitatively, the observed deficits in visual cognition were subtle, and patients were not able to predict them. Impairment was more common in women (OR 3.2; 95% CI=0.8 to 13.2), and subjects with a Beck depression inventory II score ≥ 25 (OR 5.2; 95% CI=1.1 to 24.2). No effect was seen for: age, years in full-time education, disease duration, clinical evidence of anterior visual pathway dysfunction, or motor disability. Exploratory analyses showed no predictive association with deficits in attention or working memory, however impairment of basic arithmetic skills was a highly significant predictor of impaired visual cognition (OR 29.4, 95% CI 3.0 to 291.9). Allowing for all significant predictors, secondary and primary progressive disease groups had equivalent rates of impairment (OR 1.6, 95% CI 0.4 to 7.1; p=0.538).

Conclusions: Impairment of visual cognition in progressive MS is more common in women and patients with high levels of depressive symptomatology, but occurs independently from anterior visual pathway dysfunction and the cumulative burden of inflammatory CNS white matter demyelination. These findings suggest that the site rather than the absolute quantity of brain pathology is crucial, with the strong association observed to impairment of basic arithmetic skills implicating possible localization to the intraparietal sulcus.

Keywords: Brain diseases; Demyelinating diseases; Multiple sclerosis, Chronic progressive; Multiple sclerosis, Secondary progressive; Multiple sclerosis, Primary progressive; Cognition; cognition disorders; Cognitive science; Visual pathways; Parietal lobe

Introduction

Cognitive impairment occurs in 42-70% of people with multiple sclerosis (pwMS), with deficits most frequently described, in complex attention, efficiency of information processing, executive functioning, processing speed, and long-term memory [1]. Although impairment of visual cognition in pwMS has received comparatively less attention, it is present in up to 25% of subjects [2]. Moreover, deficits in visual cognition are not secondary phenomena due to disease involving the anterior visual pathways and associated (simple) perceptual impairment [3], nor explained as part of a universal impairment of cognitive abilities in MS [4].The real-world consequence of such deficits can be highly significant, as demonstrated by the observation that impaired visual learning and memory in pwMS is the strongest predictor of traffic violations and collisions [5]. Crucially, these deficits may be under-recognised in clinical practice as they occur independently to more commonly evaluated frontal-executive abilities [6].

Despite awareness that visual cognitive functions are frequently impaired in MS, the neural basis of clinical deficits remains unknown [4]. Increasing recognition of both inflammatory and neurodegenerative components in MS pathology [7]-the latter of particular salience in progressive disease-raises the question to what

extent clinical deficits reflect archetypal multifocal inflammatory demyelination in CNS white matter, or alternative pathogenic processes such as grey matter inflammatory demyelination and/or neuroaxonal loss [8]. Determining the role of these pathogenic processes is particularly challenging given that imaging biomarkers are currently able to offer only general insights; measures of brain atrophy or white matter T2 hyperintense lesions lack pathological specificity [9], and less than 20% of grey matter lesions are detectable by the most sensitive contemporary (double-inversion recovery) MR techniques [10]. An alternative strategy to evaluate the effects of pathological processes on cognitive impairment is the comparison of MS patient groups who differ in their dominant brain pathology. Patients with primary progressive MS (PPMS) are characterized by the steady accumulation of fixed disability from onset and have minimal levels of multifocal inflammatory CNS white matter demyelination [11]. In contrast, patients with secondary progressive MS have high levels throughout their disease course [12,13]. Detailed clinical phenotyping of patients with a well-established disease course therefore allows evaluation of a potential "dose-response" between multifocal inflammatory CNS white matter demyelinating pathology and clinical features.

Like other cognitive functions, the evaluation of visual cognition in MS is challenging due to a wide range of potentially confounding factors. Weakness, ataxia, spasticity, and other physical manifestations limit performance on tasks involving copying or drawing (Figure 1). In addition, reduced information processing speed affects performance on timed tasks [14]; dysarthria on tasks requiring verbal responses; and deficits of memory, attention, and executive functions have the potential to impact on any complex task. Components of the Addenbrooke's Cognitive Examination (ACE-R) that have been adapted from the Visual Object and Space Perception (VOSP) battery offer an opportunity to minimize the contribution of these factors [15,16]. Furthermore, the dot counting and incomplete letter recognition tasks in the ACE-R provide a differential assessment of function in the dorsal and ventral visual processing streams respectively [17]. We therefore used these simple visual cognition tasks that are robust to motor and other physical deficits, and compared performance between MS patient groups with high (SPMS) and low (PPMS) levels of multifocal inflammatory CNS white matter demyelination. Our aim was to test a prediction that the rate of impairment in visual cognition would be equivalent between SPMS and PPMS groups, indicating that the cumulative burden of multifocal inflammatory demyelination in the CNS white matter did not play a pathogenically significant role.

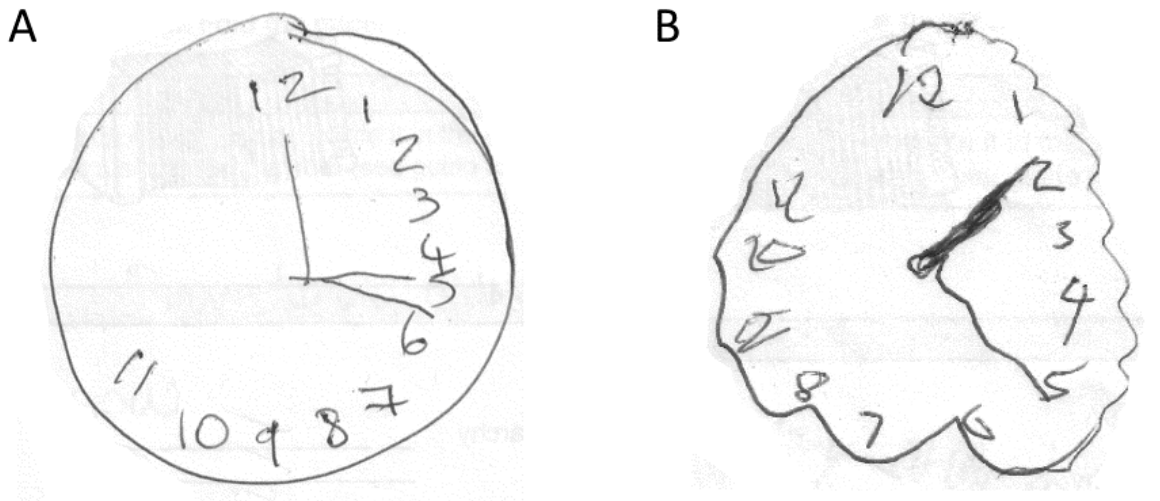

Figure 1: Clock drawing test impairment with and without motor disability of dominant hand. Clock drawing test impairment is shown for two patients with progressive MS. Patients were instructed to "draw a clockface with both numbers and hands, showing the time as ten past five". Panel A shows a patient with normal dominant hand motor function. Panel B shows a patient with impairment of dominant hand motor function.

Methods

Participants

Participants were recruited from a UK hospital-based MS clinic. Eligibility criteria were: revised (2010) McDonald Criteria MS [18]; progressive disease course; logMAR visual acuity <0.2 in at least one eye (equivalent to 6/9 or better on Snellen); and the absence of an additional major affective, psychiatric, or neurological disorder. Approval was obtained from the local ethics committee, and all patients gave written informed consent.

Tests and procedures

Patients were assessed at a single visit in a hospital setting through neurological history and examination including: multiple sclerosis impact scale-29 (MSIS-29), expanded disability status scale (EDSS), the multiple sclerosis functional composite (MSFC), Beck depression inventory–II (BDI-II), Addenbrooke's cognitive examination

(Revised) (ACE-R) and the 3-second paced auditory serial additions test (PASAT). Subjects were asked if they thought they had cognitive impairment by the question "do you suffer from problems with your memory or concentration". Clinical evidence of disease involving the anterior visual pathway was defined as the presence of one or more of the following: clinical history consistent with optic neuritis, optic atrophy, an afferent pupillary defect, or an abnormality of visual evoked responses consistent with demyelination. Visual assessment tasks were performed binocularly using the subject's optimum refractive correction. All assessments were administered by a single observer (PC) who was blinded to the patient's disease course. Two ACE-R tasks that are robust to confounding by motor or other cognitive deficits were used to evaluate visual cognition: dot counting and incomplete letters [16]. Both tasks comprise four elements. For the dot counting task, two odd-number and two even-number elements were presented, and the subject instructed to count and report the total number of dots in each element. For the incomplete letters task, the letters K, M, A, & T were presented in a sans-serif font with multiple edge segments missing. Subjects were asked to report the letters shown. Both tasks are untimed and do not require a motor response.

Statistical analysis

Cognitive impairment for the PASAT, ACE-R, and visual cognition tasks was defined by scores less than two standard deviations from the mean of published age-matched norms [2,15,16]. Potential explanatory/confounding factors were assessed by logistic regression. The sum of ACE-R dot counting and incomplete letters test scores was used to provide a composite assessment of function in the post-primary visual cortex pathways. Model selection was achieved through a forward stepwise selection procedure with initial covariates of: age, sex, years of education, MS disease duration, clinical evidence of anterior visual pathway dysfunction, motor function in the dominant hand-assessed by time in minutes to complete the nine-hole peg test (NHPT), and depression (defined as a BDI-II score ≥ 25). Covariates were retained if significant at the 20% level. This model was then compared to a second model that included an indicator variable for disease group (SPMS vs. PPMS). Improvement in model fit (model two over model one) was assessed by the likelihood ratio test. The 95% confidence interval for the odds ratio of cognitive impairment due to SPMS in the second model was then used to evaluate equivalence between groups. An upper limit for δ (OR) of 8.9 was pre-defined as this represents the observed ratio of white matter lesions in SPMS compared to PPMS [19].

Results

Recruitment, data completeness, and participant characteristics

Ninety-two patients were screened for eligibility. After evaluation, six patients were excluded due to lack of a definite progressive disease course. Fifty-nine patients with SPMS and twenty-seven with PPMS were therefore recruited. Seven patients were unable to perform the nine-hole peg test due to severe motor disability in their dominant upper limb and ten patients declined to perform the PASAT. Timing for disease onset could not be defined for two patients with PPMS, and seven patients did not provide a response to the question regarding subjective cognitive impairment (3/59 [5.1%] SPMS group vs. 4/27 [14.8%] PPMS group; p=0.1257). Data ascertainment was complete for all other assessments.

Clinical evidence of disease involving the anterior visual pathway was seen in both disease groups, although more frequently in the SPMS group (25/59 [42.4%] SPMS vs. 2/27 [7.4%] PPMS; p=0.001). No other differences were seen between groups in demographic or disease characteristics (Table 1). Ten SPMS patients were classified as cognitively impaired on PASAT (10/59 [17.0%] of the total SPMS group; 10/53 [18.9%] of those who performed the task), and fifteen on the ACE-R (15/59 [25.4%]). Six PPMS patients were classified as cognitively impaired on the PASAT (6/27 [22.2%] of the total PPMS group; 6/23 [26.1%] of those who performed the task), and three on the ACE-R (3/27 [11.1%]).

	Patient group		
	SPMS	PPMS	p
n	59	27	-
Age (mean, SD)	50.4 (8.6)	53.6 (9.7)	0.127
Male sex (%)	55.9	59.3	0.773*
Years of education (mean, SD)	13.3 (3.2)	12.6 (2.7)	0.319
Disease duration (mean, SD)	13.2 (7.7)	10.3 (5.9)	0.094
EDSS (mean, SD)	5.9 (1.1)	5.5 (1.5)	0.188
MSIS-29 – total (mean, SD)	87.1 (20.9)	78.7 (20.6)	0.088
MSIS-29 – physical (mean, SD)	63.9 (16.1)	58.4 (14.9)	0.139
MSIS-29 – psychological (mean, SD)	22.8 (7.7)	20.2 (8.0)	0.163
BDI-II score (mean, SD)	14.7 (9.6)	12.6 (8.7)	0.284
Clinical evidence of disease involving the anterior visual pathway (%)	42.4	7.4	0.001*
Subjective cognitive impairment (%)	66.1	43.5	0.063*
PASAT score (mean, SD)	38.4 (11.9)	37.6 (14.2)	0.802
Total ACE-R score (mean, SD)	91.5 (7.8)	92.1 (4.0)	0.435

Table 1: Subject characteristics by disease course. SPMS: Secondary Progressive MS; PPMS: Primary Progressive MS; MSIS-29: Multiple Sclerosis Impact Scale 29; EDSS: Expanded (Kurtzke) Disability Status Scale; BDI-II: Beck Depression Inventory (II); PASAT: Paced Auditory Serial Additions Test. Significance tests by Student's t-test or (*) Fisher's exact test.

Performance on visual cognition tasks

The overall prevalence of visual cognition dysfunction assessed by the combined score for dot counting and incomplete letter tests was 14.0% (95% CI=6.5 to 21.4%), with no difference between SPMS (9/59 [15.3%]) and PPMS (3/27 [11.1%]) groups (p=0.607). Impairment on the dot counting test was seen in 12.9% (95% CI=6.6% to 22.0%) of the total cohort, whereas impairment on the incomplete letters test was seen less frequently (1.1%; 95% CI=0.03% to 6.4%; p=0.003). The severity of impairment on either task was subtle: one sixty-two year

old female with PPMS and no evidence of anterior visual pathway dysfunction responded incorrectly in two (2/4) dot counting elements, the remainder of patients who made errors failed on only one element. All patients who made errors on the incomplete letters test failed only one (1/4) element. The absolute magnitude of errors on the dot counting tasks was also small, with all erroneous responses within one integer of the correct score.

Predictors of performance on visual cognition tasks

Logistic regression was then used to evaluate the influence of demographic and disease characteristics on visual cognition performance. Forward stepwise selection established a best-fit model that included: female sex (OR 3.2; 95% CI=0.8 to 13.2) and BDI-II score ≥ 25 (OR 5.2; 95% CI=1.4 to 36.8). No effect was seen for: age, years of education, MS disease duration, clinical evidence of anterior visual pathway dysfunction, or motor function in the dominant hand assessed by time in minutes to complete the nine-hole peg test (NHPT). When asked about memory or concentration difficulties, patients were unable to predict their visual cognition performance (expected agreement 43.4%, observed agreement 43.0%, κ=- 0.01). Moreover, this question also resulted in poor prediction of impaired performance on the two "global" measures of cognition: PASAT (expected agreement 44.1%, observed agreement 54.4%, κ=0.18) and total ACE-R score (expected agreement 44.8%, observed agreement 55.7%, κ=0.20).

To investigate a potential confounding effect of attentional deficits on visual cognition task performance, subjects with possible impairment of attention (defined as any score below ceiling [<18/18] on the ACE-R attention domain) were identified (n=20). Of the twelve patients with visual cognition impairment, four (4/12) also had attentional performance below ceiling. Agreement between attentional and visual cognition impairment was poor (expected agreement 69.3%, observed agreement 72.1%, κ=0.09). Then, in order to examine the possibility that attentional deficits might alter the influence on visual cognition task performance of significant covariates (female sex and BDI-II scores ≥ 25), regression analysis was repeated following the addition of an indicator term for possible impairment of attention. No significant effect of possible impairment of attention was seen (OR 1.4; 95% CI 0.3 to 5.8) and the best-fit model was unchanged. Finally, a sensitivity analysis was performed by repeating the primary regression model after exclusion of subjects with possible impairment of attention (resultant n=66). Using this approach, two covariates were retained with significance at the 20% level, although neither was significant at the 5% level: years of education (OR 1.2 [per year] 95% CI 0.9 to 1.5) and BDI-II score ≥ 25 (OR 5.4, 95% CI 0.9 to 31.9).

To investigate a potential confounding effect of working memory deficits on visual cognition performance, subjects with possible impairment of working memory (defined as performance below ceiling [<5/5] on a 5-letter reverse word spelling task) were identified (n=13). Of the twelve patients with visual cognition impairment, one (1/12) also had working memory performance below ceiling. Agreement between working memory and visual cognition impairment was poor (expected agreement 72.5%, observed agreement 69.7%, κ=- 0.10). Repetition of the regression analysis with an indicator term for impaired working memory showed no significant effect (OR 0.4, 95% CI 0.0 to 3.3) and the best-fit model was unchanged). Effects of working memory impairment on the dot counting and incomplete letter recognition test scores were also differentially examined because of the potential for a greater impact on the dot counting performance. One patient (1/11) had impairment of working memory in addition to impairment on the dot counting test; agreement was again therefore poor (expected agreement 73.4%, observed agreement 71.1%, κ=- 0.09). The single patient with impairment on the incomplete letter recognition test had no evidence of impaired working memory.

Two principle strategies were observed during performance of the dot-counting task (Figure 2). Namely, progressive visual inspection of the test area with sequential addition of dots as they were encountered (ie. 1,2,3,4… x), or visual inspection of the test area by sub-sections that contain clusters of dots with subsequent addition of the cluster scores (e.g. 2+3 +4). Subjects who have poor basic arithmetic skills may have therefore experienced difficulty with either strategy. The presence of acalculia was therefore explored by performance on a serial subtraction test (five subtractions of seven from an initial value of 100). Although frequently viewed as a test of concentration, performance on the familiar "serial sevens test" is almost entirely determined by arithmetic skills [20]. Subjects with possible acalculia (n=29) were identified by scores below ceiling (<5/5). Using this definition, nine (9/11) patients with impaired performance on the dot counting test also had possible acalculia. Despite the significant proportion of patients with dot counting impairment who had concomitant acalculia, the large number of patients with possible acalculia but no impairment of dot counting (20/75) was reflected by only modest agreement (expected agreement 62.1%, observed agreement 74.4%, κ=0.33). A more stringent definition for possible acalculia (<4/5) was therefore explored. Using this definition, five (5/11) subjects with impairment of dot counting also had possible acalculia

However, the number of patients with possible acalculia but normal dot counting remained high (10/75) and agreement was therefore lower than with the original definition (expected agreement 74.2%, observed agreement 81.4%, κ=0.28). Repetition of the regression analysis for total visual cognition performance (dot counting and letter recognition) following addition of an indicator term for possible acalculia (defined as performance below ceiling on the serial subtraction test), showed a highly significant effect of possible acalculia (OR 29.4, 95% CI 3.0 to 291.9) with a new best-fit model that also included the two covariates previously identified: female sex (OR 3.4, 95% CI 0.7 to 17.4) and BDI-II score ≥ 25 (OR 20.1, 95% CI 1.9 to 217.7).

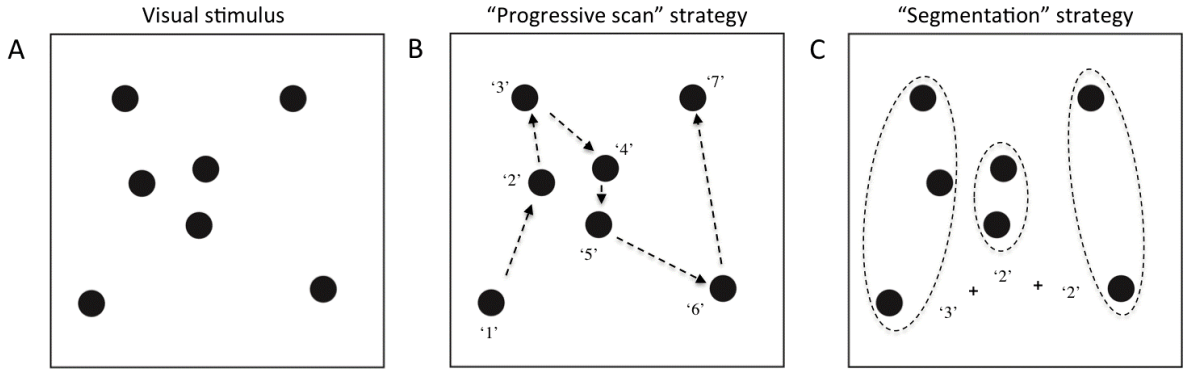

Figure 2: Principal strategies for dot counting task performance. The two principal strategies observed for performing the dot counting test are shown. Patients were asked to count the number of dots in the box without pointing to them. Panel A shows the visual stimulus. Panel B shows a strategy of progressive visual inspection of the test area with sequential addition of dots as they were encountered (patients choosing a "route" of visual scanning according to personal preference). Panel C shows a strategy of visual inspection of the test area by sub-sections that contain clusters of dots (patients defining clusters according to personal preference) with subsequent requirement for addition of the segment totals.

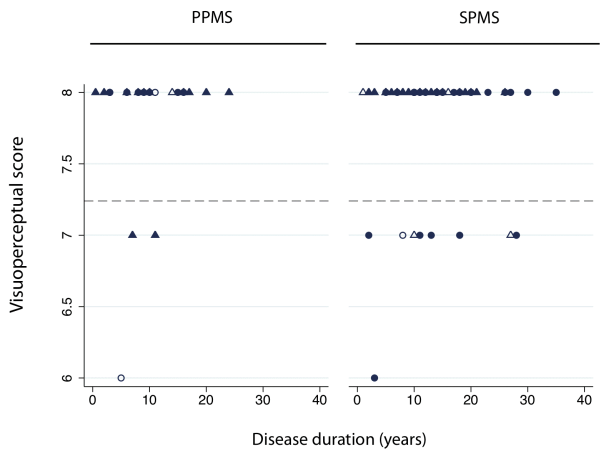

Figure 3: Performance on visual cognition tasks by disease group. Individual subject performance on visual cognition tasks (sum of incomplete letter test and dot counting scores) are shown by disease group and disease duration, with the lower limit of normal (2 standard deviations below the control mean) indicated by dashed lines. Males are shown as triangles, females as circles. Subjects with a Beck depression inventory-II score ≥ 25 are shown as hollow-markers. PPMS: Primary Progressive MS; SPMS: Secondary Progressive MS. Impairment in seen in both SPMS and PPMS groups, affecting individuals from both sexes, with or without significant levels of depression.

The influence of disease group on visual cognition performance

Impairment on visual cognition tasks was seen in both disease groups at all stages of disease (Figure 3). Addition of an indicator term for SPMS/PPMS status to the best-fit logistic regression model showed no improvement in model fit (δ McFadden's r^2=0.009; p=0.80). The 95% confidence interval upper-bound estimated for the odds ratio reflecting SPMS (ie. compared to PPMS and adjusted for sex, BDI-II score ≥ 25, and acalculia) was within the pre-defined limit to demonstrate equivalence (OR 1.6, 95% CI 0.4 to 7.1; p=0.538) (Figure 4).

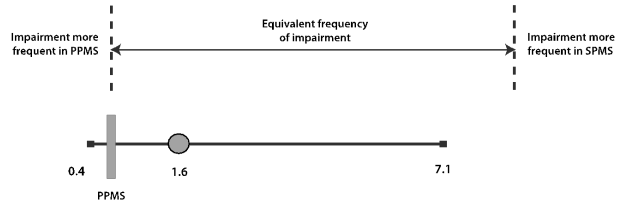

Figure 4: Difference in odds of impaired visual cognition by disease group. The odds ratio and 95% confidence interval (CI) is shown for impaired visual cognition in the SPMS group (referenced to the PPMS group). Pre-defined equivalence bounds are also shown by the dashed lines (see text). The odds ratio 95% CI upper bound did not cross the limit for equivalence, indicating that impairment of visual cognition was not more frequent in the SPMS group.

Discussion

We found that deficits of visual cognition were present in 14% of subjects, with assessment of dorsal visual stream ("where") functions identifying a significantly higher proportion of impairment (12.9%) than assessment of ventral visual stream ("what") functions (1.1%). Clinical deficits of the anterior visual pathways were seen in 31.4% of subjects, comparable to descriptions in recent targeted epidemiological studies [21], however these did not predict impairment of visual cognition. In contrast, impairment of visual cognition was strongly

associated with acalculia and high self-reported depressive symptomatology; female-sex was a possible further independent risk factor. Finally, risk of visual cognitive impairment was not influenced by the overall quantity of CNS white matter pathology-as indicated by the absence of a dose response comparing SPMS to PPMS groups.

Few prior studies have compared cognitive impairment across MS patient subgroups. In the largest, Huijbregts et al. used the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) to examine 71 patients with SPMS and 55 with PPMS [23]. Patients with SPMS performed significantly more poorly than those with PPMS on the 10/36 spatial recall test (SRT) for both immediate and delayed recall tasks. However, this finding cannot be confidently attributed to a differential rate of impairment in visual cognition. Although intact visual cognition is necessary for success in the 10/36 SRT, a wide range of specific cognitive deficits may also cause impaired performance; these include deficits in attention, visual perception, visuospatial (dorsal stream) function, working memory, visual learning (encoding), and visual recall (memory). Indeed, the application of cognitive tests requiring complex and multi-domain cognitive integration has consistently been demonstrated to detect higher rates of impairment in SPMS cohorts compared to PPMS and relapsing remitting MS (RRMS). This is unsurprising given that the cumulative burden of brain pathology is highest in SPMS, and provides support for the case to consider using cognitively complex-albeit simple to administer-tasks as metrics of cumulative disease burden in pwMS, avoiding the limitations of predominantly motor metrics, or the practical challenges of imaging based approaches. However, such cognitively complex tasks are of more limited value in cognitive psychology and cognitive neuroscience due to difficulties with isolating the specific cognitive deficit under investigation. This issue led Huijbregts et al. to conclude that it would be useful to pursue the strategy of comparing MS patient subgroups "with simpler tasks measuring for example only information processing speed or visuospatial processing".

Despite the simplicity of visual cognition tests used in our study, potential confounding by other cognitive deficits remained possible. Exploratory regression modeling showed no significant predictive value of attentional or working-memory deficits on visual cognition performance. However, the presence of acalculia was a strong predictor of impairment. Given that the majority of visual cognition deficits present were seen on the dot counting test, it is possible that this observation either represents a causal association based on inability to perform dot counting due to acalculia, or codependence mediated by an external factor (e.g. parietal lobe pathology) with effects on both arithmetic ability and dorsal visual stream functions. The modest agreement seen between acalculia and visual cognition impairment confirms functional dissociation, however only two (2/12) subjects with visual cognition impairment did not have concomitant acalculia and the negative predictive value of acalculia with respect to visual cogniton impairment was therefore high (96.5%). The possibility of codependence in MS due to pathology involving brain regions that mediate both functions-in particular the intraparietal sulcus [24] is further supported by the recently described association between dorsal visual stream dysfunction and developmental dyscalculia [25,26].

In addition to impaired arithmetic performance, two further covariates were predictors of impaired visual cognition: female sex and a high level of depressive symptomatology reported on the Beck depression inventory II (BDI-II ≥ 25). Sex-based differences in visual cognition task performance are a frequently reported finding, although the method of test administration may have an impact on the magnitude of differences observed [27]. In contrast, the relationship between depression and impaired visual cognition is less clear. Our findings are notably different from those seen in patients with "pure" affective disorder (ie. subjects without MS) where ACE-R visuospatial domain scores did not differ from healthy controls [28]. This observation argues against an interpretation that impaired visual cognition in our cohort can be causally attributed to comorbid depression. Given that the BDI-II has been validated as an appropriate marker of depression in pwMS [29], possible explanations for the strong association in our study therefore include a causal link in the reverse direction (ie. impairment of visual cognition resulting in increased depressive symptomatology), or shared variance due to the influence of an external factor. Although the latter is at face value more likely, no plausible candidates currently exist for a shared neuroanatomical or functional locus encompassing both visual cognition and affective functions. Regional atrophy imaging studies of MS patients with and without depression have reported conflicting results, however frontal and temporal lobe pathology appear as the most consistent associations [30–32]. The possibility that impairment of visual cognition may have predisposed to depression in our cohort is therefore worthy of consideration, and would be consistent with previous reports of an interaction between cognitive impairments and either high levels of avoidance coping or low levels of active coping [33]. Finally, no effect on visual cognition task performance was seen in our study for disease involving the anterior visual pathways, disease duration, motor disability, or years of education. Moreover, patients were unable to predict their performance when a generic "cognitive impairment" question from the 29-Item Multiple Sclerosis Impact Scale (MSIS-29) was used. It is possible that this question lacked specificity for symptoms relevant to visual cognition, or that insight into clinical deficits is limited-a phenomenon recently described with high prevalence in patients with MS [34].

To evaluate the relationship between visual cognition and multifocal inflammatory CNS white matter disease, a dose response was hypothesized: if pathogenically relevant, a higher frequency of impairment in subjects with SPMS ("high dose") than those with PPMS ("low dose") would be predicted. This relationship was not found, suggesting that the site of MS brain pathology may be crucial rather than the total quantitative burden of pathology. This interpretation would reconcile our findings with those of Stankiewicz et al. who recently reported strong correlation (r=-0.70) in patients (n=24) with predominantly (>80%) relapsing-remitting disease between impairment on the JLO task and total fluid-attenuated inversion-recovery (FLAIR) brain lesion volume on MR imaging [35]. Further research combining neuroimaging with comprehensive assessment of visual cognition to test this hypothesis is therefore supported.

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