Staging and stratifying cognitive dysfunction in multiple sclerosis

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ABSTRACT

Background: The sequence in which cognitive domains become impaired in MS has not yet been shown. It is unclear whether processing speed dysfunction temporally precedes other cognitive impairments, such as memory and executive function.

Objective: Determine the order in which different cognitive domains become impaired in MS and validate these using clinical and vocational outcomes.

Methods: In a longitudinal sample of 1073 MS patients and 306 healthy controls with a mean 1.6 visits, we measured performance on multiple neurocognitive tests. We used a novel event-based staging approach to estimate the sequence in which cognitive domains become impaired. Each model stage represented a point in the sequence when an additional domain became impaired.

Results: Our model suggested that the order of impairments was as follows: processing speed, visual learning, verbal learning, working memory/attention, and executive function. Stage of cognitive impairment predicted greater disability (β=0.16, p<0.001) and unemployment (β=1.14, p<0.001).

Conclusion: Our findings suggest that processing speed is the first domain to show cognitive impairment, followed by memory and attention. Executive functioning is affected last. This is the first study to introduce a cognitive staging and stratification system for MS. Findings underscore the importance of using the Symbol Digit Modalities Test in routine screening for cognitive impairment and memory testing to assess patients later in disease evolution.

INTRODUCTION

During the evolution of MS different cognitive domains are not affected randomly. Slowed cognitive processing speed (CPS) is the most common cognitive impairment observed in people with Multiple Sclerosis (PwMS).[1] The Symbol Digit Modalities Test (SDMT)[2] is regarded as the most sensitive measure of CPS impairment in MS[3] and is recommended by the MS Outcome Assessments Consortium (MSOAC) for screening of general cognitive impairment in MS clinical care.[4] Disease-related impairment is also frequently seen on tests of other cognitive domains, such as verbal and visuospatial memory,[5,6] with poor performance on these other tests often statistically explained by severity of CPS impairment.[7, 8,9] This suggests—and it is widely assumed—that CPS impairment temporally precedes other impairments as MS progresses, signifying the predictive utility of the SDMT as a screening measure. However, despite its clinical importance, the tenets of this assumption have yet to be examined empirically. The sequence of decline across cognitive domains is still unclear and, to date, no previous study has examined the order in which various cognitive functions become impaired. It has not been established whether the onset of individual impairments follows a common pattern among PwMS as the disease progresses.

Event-based modelling (EBM)[10] is a novel analysis technique that can address the lack of evidence on the evolution of cognitive dysfunction. It estimates the most likely order of occurrence for disease-related events and has been used in previous studies to stage cognition on the timeline of Alzheimer's disease.[11,12] While EBM has been used previously in MS to elucidate the progression of regional atrophy,[13] it has yet to be applied to MS cognitive changes. We believe it is suitable for describing the potential pattern of cognitive impairment in PwMS using both cross-sectional and longitudinal data.

In this study we conducted a retrospective analysis of a uniquely large longitudinal database (n=1073 PwMS) which contained multiple measurements of several cognitive outcomes. We sought to

determine the likeliest order of occurrence for cognitive test deficits in PwMS. We employed well-established metrics [4, 14,15] and hypothesized that SDMT impairment preceded impairments in memory and executive function. We also aimed to explore the clinical relevance of staging cognitive decline by relating it to EDSS-based neurologic disability and unemployment. To our knowledge, this is the first study to examine the order of onset for various cognitive impairments in MS.

METHODS

Subjects

The longitudinal sample comprised 1073 PwMS and 306 healthy controls (HCs) at the Jacobs Multiple Sclerosis Center at the University at Buffalo. All data were taken from a large, multi-study database aggregated over 18 years. Subjects provided written consent and study protocols were approved by the University at Buffalo Institutional Review Board. Inclusion and exclusion criteria were as follows: (a) diagnosis of clinically definite relapsing or secondary progressive MS; (b) no relapse or steroid treatment within the previous 90 days; (c) age 18+ years; (d) English fluency; (e) no neurologic disorder other than MS; (f) no history of substance abuse, developmental disorder, or psychiatric disorder other than mood or behavior change following onset of MS; and (g) no motor or sensory defect that might interfere with cognitive test performance (e.g. corrected near vision of at least 20/70). HCs had the same inclusion and exclusion criteria with the exception of (a-b) above. Individual time-points for each subject were considered for use if all cognitive tests under investigation were available.

While t-tests and chi-squared analyses (Table 1) showed the MS and HC groups were not significantly different on age and race ($p>0.05$), the HC group had 6% more males (29.1%) than the MS group (23.1%), $X^2(1, 1379)=4.6$, $p=0.032$, and longer years of education ($M=15.4$, $SD=2.2$) than the MS group ($M=14.5$, $SD=2.4$) at baseline, $t(1377)=6.23$, $p<0.001$. To control for this disparity, all test scores were converted to age-, sex-, and education-corrected *z*-scores based on published norms.[16]

Measures and Procedure

Neuropsychological examinations were administered by trained technicians, neurology or neuropsychology trainees, or a neuropsychologist. CPS was assessed with the SDMT, oral response. Visual/spatial memory and verbal memory were assessed with the Brief Visuospatial Memory Test-Revised (BVMTR)[17] and the California Verbal Learning Test, 2nd Edition (CVLT2)[18] respectively. As

recommended for the Brief International Cognitive Assessment for MS (BICAMS), the total learning subscores were used for each.[15] Attention/working memory was assessed with the Paced Auditory Serial Addition Test (PASAT).[19] Executive function was assessed with the Delis–Kaplan Executive Function System[20] card sorting task, and the description (DKEFS-ds) and total correct sorts (DKEFS-cs) scores were used in the final analyses.

Three secondary outcomes were used for predictive validation analyses, but were not included in the staging model itself. These outcomes were the Expanded Disability Status Scale (EDSS)[21] score, employment status, and negative work events (e.g., employer criticism/reprimand for errors, reduction in paid hours) as measured by the Buffalo Vocational Monitoring Survey (BVMS).[22]

Statistical Analysis

We used an event-based model (EBM), as described previously,[13] to estimate the sequence in which cognitive tests are likely to show impairment in MS. An impairment 'event' was defined as an abnormal score in comparison with the expected score based on a healthy sample. There are three primary steps to the EBM approach.

The first step is fitting Gaussian mixture models to the data. The EBM makes no suppositions about what defines 'impairment', in that it is not determined by establishing discrete score cutoffs a priori (e.g., a z-score≤-1.5). Instead, the model incorporates the *likelihood* of impairment and the *likelihood* of unimpairment on a measure into its estimation of the sequence of progression. This is done by fitting Gaussian mixture models to the data for a particular measure, which includes both MS patients and controls. Once these mixture models have been fitted to the data for each cognitive test, the likelihood of impairment and the likelihood of unimpairment for a subject on a particular test at a particular timepoint is determined based on where their individual score falls on each of these two distributions. The likelihood of impairment is the probability density function calculated at where that

score falls on the 'normal' or healthy distribution, while the likelihood of unimpairment is the probability density function estimated at where that score falls on the 'abnormal' distribution of the mixture model.

The second step of the EBM is to find the most likely sequence of impairment events (with six total events corresponding to our six outcome measures). For this step, 10 randomly chosen sequences are selected for a "greedy ascent" search, which is a procedure that makes multiple comparisons of individual sequences and takes the more optimal sequence from each comparison. For our greedy ascent search, two elements in each starting sequence were randomly "flipped," choosing the new "flipped" sequence only if it has a greater likelihood. This procedure is repeated 10,000 times for each of the 10 starting sequences until convergence upon a single most likely sequence is achieved. See the Supplementary Material for the full formula of our EBM.

The third step of the EBM is a final k-fold cross-validation. This was done by dividing the data into 10 equally-sized folds (i.e., subsets). The uncertainty of an event's position in the sequence was estimated by repeating the procedures described above 10 times, each time using nine of the folds to train the model and leaving out one as a test fold. We used Markov Chain Monte Carlo (MCMC) sampling from the posterior distribution, ultimately generating 1,000,000 MCMC sampled sequences (10 folds with 10 starting sequences for each fold, and 10,000 samples from each starting sequence). Each of these sampled sequences was overlaid on a positional variance diagram, which shows the uncertainty of each event at each stage of the sequence with the highest likelihood. For this diagram, darker boxes indicate that a particular event appeared more frequently at that particular stage among the total number of MCMC sampled sequences, whereas lighter boxes indicate that a particular event appeared at that stage less frequently. As such, darker boxes show greater certainty of that event occurring at that stage in the sequence. Following the EBM, we extracted each subject's most likely stage of cognitive impairment at each timepoint, as described in the Supplementary Material.

Disease course groups and HCs were then compared on baseline EBM stage with a three-way Analysis of Variance (ANOVA) model. Change in EBM stage over time was modeled using linear mixed effects analysis with fixed effects for study group and time (from study entry), and with time also nested within subjects as random effects, to adjust for repeated-measures.

For subsequent examination of the EBM's predictive value regarding clinical outcomes, subjects' estimated stage of impairment was included as a fixed effect predictor in four linear mixed effects models predicting disability (EDSS) and negative work events. Two mixed effects logistic regression analyses were also performed on the binary outcome of work status (employed vs. unemployed). For each outcome, one model was run with a fixed effect for baseline EBM stage and another with a fixed effect for the EBM stage concurrent with the measurement of work status. For both the linear and logistic mixed effects analyses, time was again included as both a fixed and random effect. For the models predicting employment status, EDSS was included as a covariate.

RESULTS

Sample characteristics

Data from 1379 subjects were included in the final models, 1073 PwMS (900 relapsing remitting and 173 secondary progressive) and 306 HCs (Table 1). The average time (*SD*) from the first to the last visit was 4.5 (3.6) years. The average time (*SD*) between each individual visit was 1.8 (3.2) years. A mean (*SD*) of 1.6 (1.0) visits were completed for each subject.

Estimated sequence of impairment progression

For the first step of the EBM (Figure 1a), mixture models were fitted for each cognitive variable. For the second step of the EBM (Figure 1b), the greedy-ascent search, after 10,000 iterations, the log-likelihood of the 10 randomly-chosen starting sequences (range: -10750 to -9,750) all converged to -7500 establishing the primary sequence of events. Following the third step of the EBM, the MCMC cross-validation procedure, the final positional variance diagram for the full sample of PwMS was created, as shown in Figure 1c. As hypothesized, the model estimated that SDMT impairment occurred first, prior to impairment in any other cognitive function. Our model suggested that BVMTR was next to become impaired, followed by (3) CVLT2; there was uncertainty in the positions of these two impairment events, indicating that they were essentially interchangeable at either stage 2 or 3. These were followed by (4) PASAT, and finally (5-6) DKEFS card sorting.

Change in EBM Stage over Time

The ANOVA comparing disease groups on EBM stage at baseline was significant, $F(2)=67.30$, $p<0.001$. LSD post-hoc comparisons found SPMS patients ($M=3.03$, $SD=0.17$) had a significantly higher EBM stage ($p<0.001$) than both RRMS patients ($M=2.25$, $SD=0.07$), and HCs ($M=0.92$, $SD=0.12$). RRMS also had a significantly higher EBM stage than HCs ($p<0.001$).

In the linear mixed effects model predicting EBM stage over time, there was weak evidence for the interaction of study group and time (β=0.17, *p*=0.055). This showed that, for MS patients, more cognitive domains became impaired earlier, compared to HCs.

Event-based model staging predicting clinical outcomes

In the linear mixed effects model predicting EDSS (Figure 2) that included fixed effects for EBM stage and time (with time also defined as random subjects-level effect), EBM stage showed a significant positive association with EDSS (β=0.16, *p*<0.001). In a separate model, higher baseline EBM stage also significantly predicted EDSS longitudinally (β=0.16, *p*<0.001). In a similar model predicting negative work events (Figure 3), EBM stage was also positively associated with number of negative work events (β=0.05, *p*=0.04), such that those with a higher EBM cognitive stage (i.e. more impairments) were more likely to experience negative work events. However, baseline EBM stage did not significantly predict negative work events longitudinally (β=0.05, *p*=0.14). In the logistic mixed effects model that again also included time as a main effect and nested within subjects and with EDSS as a covariate, higher EBM stage was associated with a greater probability of unemployment (β=1.14, *p*<0.001). In a separate model, higher baseline EBM stage also predicted greater probability of unemployment longitudinally (β=2.01, *p*<0.001); with each increase in baseline stage, the log-odds of unemployment increased by two.

DISCUSSION

In the present study, we examined for the first time the sequence in which various cognitive domains become impaired in PwMS over the course of the disease. We developed a cognitive staging and stratification system in a large and unique MS cohort with longitudinal cognitive assessments. When we used clinical and vocational outcomes to validate our model, baseline cognitive stage from our model predicted later disability accumulation and probability of later job loss.

As hypothesized, the event-based model showed that PwMS tend to exhibit impairment on SDMT prior to other impairments. This provide novel insights by introducing a discrete series of cognitive changes that begins with CPS decline. It also aligns with previous findings, which until now only showed that memory and executive function tests are rarely impaired independently of CPS[1,23,24] and that CPS often is the only observed impairment early in the disease.[25, 26] We also found that visual and verbal memory impairments precede impairments of executive function. This sequence of onset is particularly informative; prior studies have only reported proportions of these impairments co-occurring cross-sectionally, without placing them on the timeline of MS progression. Our results establish a new expectation that verbal and visual memory will decline following initial CPS deficiency, with working memory and executive dysfunction likely to occur only after verbal and visual memory become defective.

Interestingly PASAT appeared later in the sequence of impairments than SDMT and the learning or memory tests. While PASAT is, in part, a test of processing speed, it also draws on working memory and attention to a large extent, with a growing consensus that the SDMT is a much more reliable test of CPS.[3,27, 28] Importantly, PASAT is a test of calculation and flexibility too, which relies heavily on executive functions. This is likely why impairment on PASAT immediately precedes the DKEFS card sorting in our model, rather than earlier in the sequence.

It is of potential clinical relevance to determine a patient's stage of cognitive impairment. For one, differences in stage correspond to differences on the EDSS when controlling for time, suggesting cognitive impairment quite frequently worsens along with other symptoms of the disease. However, the cerebral function subscore of the EDSS on its own does not give a reliable metric of cognitive impairment[29] and cannot adequately replace more sensitive neuropsychological testing such as with the SDMT. Echoing the MSOAC recommendations,[4] we reaffirm that patients should be routinely screened with at least the SDMT, and that those with an identified initial impairment be monitored with more comprehensive neuropsychological testing on a regular basis. This is vital, given that patients with a lone impairment on the SDMT (corresponding to EBM stage 1) are more likely to develop other subsequent cognitive impairments.

The clinical utility of cognitive stratification was also exemplified by the relationship between cognitive stage and work status. Given previous findings,[30,31] it is unsurprising that the higher a patient's cognitive stage (i.e., the more impairments they have), the more likely they are to be currently unemployed or at-risk for job loss. We also showed that *baseline* cognitive stage predicts longitudinal employment changes; those with higher baseline stages are more likely to lose their jobs later on. This again argues strongly for routine screening of patients to determine their cognitive stage and that proactive measures be taken for those at higher stages to prevent work problems and future job loss.

As shown in Figure 1c, the positions of visuospatial memory and verbal memory impairments in the sequence are interchangeable. One potential explanation is that there is virtually simultaneous onset of these impairments for individual subjects, in that general learning and memory (irrespective of the subtype) becomes impaired following severe processing speed deficits. This is especially likely given the observed role of CPS in performance on both verbal and visual memory tests.[32,33] Another possible explanation is that there are actually two distinct courses of memory impairment progression in PwMS.

Future work will explore this possibility and the neurological factors that distinguish patients who first experience onset of one type of memory deficit over the other.

One limitation of this particular EBM is its assumption that stages progress monotonically. As has been shown previously in PwMS, recovery of cognitive function is possible, especially following steroid treatment for an acute relapse[34,35] and there are potential practice effects with each test that could affect the perception of deterioration; i.e., patients can potentially revert to earlier stages on occasion. However, we do not believe our studied population of PwMS violates this assumption, given that (a) observed recoveries from relapse are not usually a full return to baseline functioning, [35, 36] (b) we did not include subjects tested during periods of acute relapse, and (c) alternate test forms were usually used for repeat testing to limit practice effects. Our follow-up analysis showed only a small proportion of MS subjects (7.3%) ever reverted to an earlier stage. Even so, newer staging approaches do not rely upon the assumption of monotonicity and can also parse separate courses of progression, with potential for future application to cognition.[37,38]

Future work may also wish to focus on specific biomarkers that precede or coincide with the cognitive impairment events outlined here. It would be especially relevant to explore how our cognitive model fits with previous models of grey matter atrophy progression in MS.[13] Additional biomarkers yet to be sequenced with cognition in this way, such as T2 lesion load or serum neurofilament light chain, may also shed light on the relationship between disease progression and cognitive decline.

CONCLUSION

Our work introduced a cognitive staging and stratification system for MS. We showed that slowed processing speed, as measured by the SDMT, tends to precede other cognitive impairments in MS.

Memory and attention tend to become impaired secondarily, with executive function being the last domain to show deficits and only after all others have declined. Our findings demonstrate that different cognitive tests have varying values to assess cognition as patients progress. PwMS at advanced stages in this process are at a higher risk of disability and job loss, requiring vigilant screening and intervention to mitigate these negative outcomes.

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