ABSTRACT

OBJECTIVE

To assess whether a videogame-like digital treatment is superior to a control in improving processing speed in adults with multiple sclerosis (MS).

METHODS

Adults with MS and baseline Symbol Digit Modalities Test (SDMT) z-scores between -2 and 0 were enrolled in a double-blind randomized controlled clinical trial. After completing a baseline in-clinic evaluation (Visit 1) they were randomized to complete an in-home, tablet-based videogame-like digital treatment (AKL-T03) or control word game (AKL-T09) for up to 25 minutes/day, 5 days/week, for 6 weeks. A repeat in-clinic evaluation occurred at 6 weeks (Visit 2), and again 8 weeks later to determine persistence of effects (Visit 3). The pre-specified primary outcome was change in SDMT score between Visit 1 and 2.

RESULTS

SDMT increased at Visit 2 for participants randomized to both AKL-T03 ($p < 0.001$) and AKL-T09 ($p=0.024$). These respective mean improvements were +6.10 and +3.55 (comparison $p=0.21$). At Visit 3, 70% of participants randomized to AKL-T03 maintained a clinically meaningful 4+-point increase in SDMT above their baseline, compared with 37% for AKL-T09 ($p=0.038$).

CONCLUSION

This in-home digital intervention resulted in substantial and durable improvements in processing speed. A larger randomized controlled clinical trial is planned.

This trial is registered on ClinicalTrials.gov under “NCT03569618”, https://clinicaltrials.gov/ct2/show/NCT03569618.

INTRODUCTION

Multiple sclerosis (MS) typically first manifests during an individual's most productive years; almost half of affected individuals eventually experience cognitive impairment (CI).[1] Worsening CI predicts loss of employment and of quality of life.[2] The landmark MEMREHAB cognitive remediation trial first showed efficacy in treating CI (specifically, verbal memory) in MS.[3, 4] Subsequent studies have targeted—and improved—specific cognitive domains impacted by MS.[5] However, accessible tools are urgently needed to overcome the many barriers to screening for and treating CI – barriers including accessibility, transportation, time, and limited availability of skilled therapists. Digital technologies, especially when deployed remotely, may play a substantial role in bridging these unmet needs, including a number of interventions reported to improve processing speed,[6-12] as previously reviewed.[5] Many of these studies did not include an active comparator.[5]

The Symbol Digit Modalities Test (SDMT) has emerged as the most sensitive test for detection of cognitive decline even early in the MS disease course.[13] Consequently, SDMT is included as a component of several widely used cognitive batteries for MS.[14, 15] In an open-label study, we previously reported strong patient enthusiasm for and feasibility of using a tablet-based, videogame-like digital treatment to improve processing speed in patients with MS, as well as an average 3.6 point improvement in the SDMT over 4 weeks of treatment.[16] However, we could not exclude practice effects. Here, we compare the efficacy of this treatment approach to an active comparator. We aimed to evaluate: improvement in processing speed, predictors of study retention, and predictors of response to intervention.

Materials and Methods

Participants and study setting. A total of 60 participants with a diagnosis of clinically isolated syndrome (CIS) or MS by 2010 Revised McDonald criteria[17] were recruited from the UCSF Multiple Sclerosis and Neuroinflammation Center between March and September 2018. Participants were either referred by their primary MS clinician, or identified through review of their clinician's notes for mention of either patient subjective cognitive complaints or of observed abnormalities on testing. They were included if they were adults with written SDMT z-scores between -2 and 1 (per Kiely et al., 2014[18]), had WiFi at home, and visual acuity was 20/50 OU or better. Exclusion criteria included moderate to severe depression based on self- or clinician-report, and clinical relapse within prior 30 days. Regarding cognitive performance, for the efficacy analyses, we aimed to enroll 44 participants with SDMT z-scores of 0 to -2 for final n=40, assuming 10% dropout. We also included several other subgroups to allow feasibility and future hypothesis-testing: 4 participants with greater visual or dexterity impairment; and 12 participants with no cognitive impairment (SDMT z-score>0 at screen) (CONSORT Figure).

Study activities. Participants completed a baseline neurological and cognitive evaluation (Visit 1). Then, unblinded study staff followed a simple randomization scheme to allocate participants to an in-home, tablet-based, videogame-like digital treatment (AKL-T03) or an active tablet-based placebo control (AKL-T09). Study activities were designed to be consistent with other blinded, randomized and controlled trials of digital cognitive rehabilitation tools in MS.[11] Participants were asked to complete 25 minutes daily, 5 days weekly, for 6 weeks. After 6 weeks, they returned for a second evaluation (Visit 2) to determine efficacy. To evaluate the persistence of effects, after another 8 weeks, and without further treatments, participants returned for a third evaluation and provided feedback about the study (Visit 3). Both participants and study staff completing the evaluations were blinded to treatment assignation.

Standard clinical and cognitive measures.

- Demographic (age, sex, ancestry, education, employment) variables were obtained from all participants, and MS type, duration since first symptoms, Neurostatus Expanded Disability Status Scale (EDSS) within 6 months [19] and MS treatment were obtained from the medical record for MS participants. When a recent EDSS was not available, this was completed at Visit 1 by an MS clinician (RB).
- The in-clinic evaluation was performed by a trained, blinded examiner and included:
- MS Functional Composite 4 (MSFC4) components, as outlined by Cohen et al[20]
    - Walking speed: T25FW Timed 25 Foot Walk (T25FW).
    - Dexterity: Nine-hole peg test (9HPT).
    - Sloan low-contrast letter acuity test (LCLA).
    - Paced Auditory Serial Addition Task (PASAT - 3" version): processing speed and working memory.
- Paper-and-pencil cognitive tests: Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)[14], a standardized, internationally validated battery requiring 15 minutes or less. Serial versions of all tests were used to minimize practice effects.[21]
    - Information processing speed: Symbol Digit Modalities Test (SDMT). The written version was administered to allow adequate comparison with the digital tools.
    - Verbal memory (immediate recall): California Verbal Learning Test Second Edition (CVLT-II), first five recall trials.
    - Visual memory (immediate recall): Brief Visuospatial Memory Test Revised (BVMT-R), first three recall trials.
- Patient-reported symptoms

- Depression: Center for Epidemiologic Studies Depression Scale (CESD). This 20-item self-report questionnaire is designed to measure depressive symptomatology and retains high sensitivity and specificity for depression within the MS population. [22]
- Anxiety: State Trait Anxiety Inventory (STAI). A 40-item self-report questionnaire scored on a Likert-scale, designed to assess both transient/situational (state) and dispositional (trait) anxiety, which has been validated and used extensively in MS.[23]
- Fatigue: Modified Fatigue Impact Scale (MFIS). A 21-item self-report questionnaire designed to assess the physical, cognitive, and psychosocial impact of fatigue in people living with MS.[24]

Clinically-acquired MRI measures

Participants provided images from the clinically- or research-acquired brain MRI performed closest to the evaluation. In our Intend to Treat (ITT) group, isotropic T1 and T2 FLAIR images from 32 participants were available, 34.4% on 1.5T MRI and 65.6% on 3T MRI, at a median (IQR) of 19.1 (0-138) weeks from study entry.

Lesion segmentation was performed using the LST-LPA 2.0 DICOM v1.4 segmentation pipeline, which creates lesion probably maps, masks, and labels. These were then manually validated by an expert radiologist (SS).

Volumetric analysis was performed from T1 anatomical images using three complementary tools: FreeSurfer 5.3 and ANTs Morphology 2.1.0.,[25] used to segment tissue into CSF, cortical grey matter, subcortical grey matter, white matter, brainstem and cerebellum, and Mindboggle 1.0.,[26] which combines the morphology outputs of FreeSurfer and ANTs to generate volume images and tabular information for further analysis.

Digital treatment (full details, including screenshots, are available in Supplement 1).

- AKL-T03. AKL-T03 is an investigational medical device software developed by Akili Interactive. It is designed using a Selective Stimulus Management Engine (SSME^{TM}) that engages the patient in two simultaneous sensory and motor tasks and is designed to engage frontal neural networks.[27] In a closed-loop system, the algorithms adapt in both real-time (during game play), and between treatment sessions to automatically adjust the level – or dose – for a personalized treatment experience that is adapted to the needs of each individual patient. This enables real-time monitoring of patient progress and continuously challenges each patient so that the test is never too easy or too difficult, encouraging patients to improve their performance. The treatment locked out at 6 weeks, regardless of adherence over this time period.
- AKL-T09. Administered on a digital platform similar to AKL-T03, AKL-T09 is a game in which the aim is to connect letters on a grid to spell as many words as possible. Points are earned by tracing words with two or more letters, in any direction, based on number of words formed, word length, and use of uncommon letters; with progressive letter grid difficulty. The active placebo control was used to provide similar time on task and engagement.

Protocol Approval and Consent

All study procedures were in accordance with the ethical standards of the UCSF Institutional Review Board (#16-19891) and with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all participants.

Statistical analyses.

Adherence. We defined adherence as completion of 50% or more of prescribed sessions of training, i.e. 75 sessions (~375 minutes) for AKL-T03 and 375 minutes for AKL-T09. We defined strong acceptability as ≥ 75% participants adhering to the study.

Predictors of Adherence. To evaluate the predictors of adherence throughout the 6-week intervention period we performed a least absolute shrinkage and selection operator (LASSO) analysis. From the full list of demographic (i.e., age, sex and education), MS clinical (disease duration, EDSS, vision, walking, dexterity), comorbidity (depression, anxiety, fatigue) and cognitive variables, salient predictors of adherence identified via LASSO were further assessed for effect size by Bayesian logistic regression.

Efficacy. Our pre-specified primary outcome was change in SDMT (# correct) between Visits 1 and 2, and secondary outcome was PASAT. Exploratory outcomes included mood (depression, anxiety) and fatigue scores, as well as improvements in other cognitive domains (CVLT-II, BVMT). The primary analysis was an Intend to Treat (ITT) Superiority analysis (two-tailed t-tests). Secondarily, we performed Per-protocol analyses. Within treatment and placebo control groups, one-tailed, paired samples t-tests were used to evaluate post-training- and follow-up- improvements in primary, secondary and exploratory outcomes.

Predictors of improvement. First, to assess the correlation between baseline covariates and post-training improvement on SDMT, we performed Pearson's and Spearman's correlations on demographic, MS clinical, comorbidity and cognitive variables. Then, we performed a forwards-selection stepwise regression to identify features with predictive value and included the selected variables in a multiple

regression analysis to measure their effect on improvement in processing speed, as assessed by change in SDMT.

In sensitivity analyses to evaluate whether MRI metrics predicted improvement, we *a priori* selected T2 lesion volume and thalamic volume, given their reported relationships with processing speed both cross-sectionally and longitudinally.[28, 29] We performed multiple linear regression for both MRI metrics, adjusting for age, sex and disease duration.

Persistence of Effects. We compared the groups (AKL-T03 and AKL-T09) for changes in primary, secondary and exploratory outcomes between Visits 2 and 3.

Exploration of clinically meaningful response. SDMT scores have been reported to drop 3-4 points after a clinical attack, then to return to their baseline.[30] Therefore, we defined 4 points as the clinically meaningful change. We performed a chi-squared analysis to compare the proportion of participants in each group who met or exceeded this threshold.

All statistical analyses were performed in R 3.6.1.

Data Availability

The trial protocol and statistical analysis plan are available at https://clinicaltrials.gov/ct2/show/NCT03569618. De-identified data will be shared with any qualified investigator by request.

RESULTS

Participants.

The 60 participants completing Visit 1 were broadly representative of patients currently living with MS, with mean age of 51.7 years (SD 12.6), median EDSS of 3.5 (IQR 2.5-4.5), and mean disease duration of 13.2 years (SD 8.0).

Of the 44 participants included in the efficacy analyses, 23 were randomized to receive AKL-T03, and 21 to AKL-T09. The two groups did not differ in terms of age, sex, EDSS, or baseline SDMT scores ($p>0.10$ for each); but the participants randomized to AKL-T09 did have longer MS duration ($p=0.036$) (**Table 1**).

Study Completion and Adherence

Of 44 participants, 40 returned for Visit 2 and were included in the ITT analyses. Among these, 37 (92.5%) were considered adherent (i.e. they had completed at least 50% of all prescribed sessions) and were included in the per-protocol analyses, indicating strong acceptability. Further, > 95% of participants in both groups reported enjoying their assigned intervention when surveyed at Visit 2. Overall, the average proportion of prescribed sessions played was 0.84 for AKL-T03 and 1.06 for AKL-T09 (AKL-T09 did not lock out even once 100% sessions were completed). Reasons for study discontinuation included active relapse (n=1), poor compliance to protocol (n=2), and a concurrent medical complication (n=1). Of the 40 participants returning for Visit 2, 39 (97.5%) returned for Visit 3. None of the demographic or clinical variables was a significant predictor of adherence to the study protocol.

Efficacy.

In our primary ITT analysis, as shown in **Table 2**, between Visits 1 and 2, SDMT did increase significantly both for participants randomized to AKL-T03 ($p<0.001$) and for those randomized to AKL-T09 ($p=0.024$), using one-tailed t-tests. The mean increase in SDMT was 6.10 for AKL-T03, compared with 3.55 for AKL-T09 (**Figure 2**), but our primary outcome, the degree of improvement, was not significantly different between groups ($p=0.21$, two-tailed t-test). As shown in **Table 2**, PASAT showed a similar trend. Interestingly, in the exploratory outcomes, participants randomized to AKL-T09 showed greater improvement on BVMT-R and CVLT-II tasks as compared to participants randomized to AKL-T03. When we repeated the analyses for participants completing the study per protocol, the pattern of results was similar.

Predictors of response.

Then, we evaluated predictors of SDMT improvement (increase in # correct), including baseline demographic and clinical variables, as well as adherence (% sessions played). The primary predictors, at baseline, of improvement in SDMT over the 6 weeks in adjusted analyses were lower SDMT z score ($\beta = -6.9$, $p<0.001$), employment (unemployed vs employed, $\beta = -6.4$, $p = 0.001$, part-time vs employed, $\beta = -11.9$, $p<0.001$), older age ($\beta = 0.24$, $p = 0.001$), higher education level ($\beta = 0.46$, $p = 0.10$), lower red color sensitivity (left eye, $\beta = -0.07$, $p = 0.01$), and higher MFIS score ($\beta = 0.16$, $p = 0.002$) (**Figure 4)**.

To evaluate whether baseline MRI features predicted SDMT improvement, given the overall low number of samples, we categorized each feature according to whether a patient scores below or above the group median. While no associations were significant, in analyses adjusted for age, sex and disease duration, a lower T2 lesion volume ($\beta = 5.99$, $-0.47 – 12.45$, $p = 0.07$) revealed a trend towards greater improvement in SDMT.

Persistence of effects.

Finally, we compared persistence of effects in both groups. At the 8-week post-intervention follow up visits, 70.0% participants randomized to AKL-T03 showed at least 4-point increase in SDMT above their baseline value, compared with 36.8% in the participants randomized to AKL-T09 (p=0.038, **Table 3**).

DISCUSSION

In this study, 6 weeks of treatment with a videogame-like digital treatment resulted in significant improvements in SDMT, that persist after another 8 weeks of observation. In fact, 70% of participants maintained a clinically meaningful improvement in SDMT[30] (4 points) at the end of the post-treatment observation period, compared with 37% of the participants randomized to the active placebo control intervention. Persistent improvements were also noted for fatigue (MFIS).

Over the past decade, technological approaches, in particular computerized neuropsychological training and serious video games, have shown promise in cognitive neurorehabilitation across a variety of cognitive domains.[5] In the domains of processing speed and executive function, a number of interventions including Attention Processing Training[7], PositScience InSight® and Brain Twister[8], Dr. Kawashima's Brain Training[9], and Hasomed RehaCom® [10-12] were all reported to improve SDMT or other components of processing speed. Notably, in most of these interventions, the control was either no treatment, or reading exercises. In perhaps the largest study to date, a 12-week adaptive PositScience BrainHQ® training for MS patients with baseline SDMT deficits, significant cognitive composite score improvement was observed for a group of 74 patients using an adaptive training program as compared to 61 patients playing

non-specific video games, though improvements across specific measures of processing speed were not seen.[6] Use of adaptive training tools based on NeuroRacer[31] (the engine underlying the current active intervention, AKL-T03) have also demonstrated encouraging effects on cognitive performance in pilot clinical cohorts, including children with neurodevelopmental disabilities[32] and adults with depression.[33] Together with our feasibility pilot in 21 patients with MS,[16] these studies highlight the feasibility of technology-based approaches to cognitive remediation in diverse context.

Interestingly, not only were we able to demonstrate improvements in cognition that were sustained, we also showed that demographic and clinical features typically associated with cognitive impairments appeared to predict the magnitude of response. This included not only baseline cognitive performance, education and age, but also baseline fatigue, color vision deficits, and suggested that MRI features (T2 lesion volume) might also determine how well a patient responds to a cognitive challenge. While this suggested link between T2 lesion volume and improvement in information processing speed only reaches trend-level significance, our observations are in line with cross-sectional associations between these measures.[34] Together, these demographic and clinical features can be used in larger clinical trials and real-world clinical settings to determine selection criteria for participants most likely to improve.

This study had several strengths. First, patients' age and EDSS were fairly representative of individuals living with MS, i.e. they did not represent primarily younger 'digital natives'. Second, we included in this study not only participants with clear cognitive deficits (i.e. whose SDMT z-scores were -1 or lower), but also participants with subjective complaints whose z-scores ranged from -1 to 0. This latter group were included because while not yet meeting criteria for impairment, they reported subjective deficits that might have been amenable to treatment. However, they did not demonstrate as robust training effects, possibly

decreasing our statistical power. Third, we used a tablet-based active placebo control with similar usage and expectancy. Fourth, the intervention was low-cost, low-risk and could be performed unsupervised, resulting in high adherence rates. Among the limitations, were the overall low number of participants, as well as the fact that AKL-T09 did not lock out, leading to differences in numbers of sessions played between the two groups. While we used a written form of SDMT, there was no association between improvements in SDMT and improvements in LCLA or 9HPT, implying that we were not primarily capturing sensorimotor improvements. While there is a known learning curve associated with SDMT testing that could explain some of the observed improvements in SDMT, we took several measures to reduce this, including delivery of several computerized exploratory tests prior to SDMT at Visit 1, and use of alternating forms of the tool.[35] Finally, for this pilot study, we leveraged clinically acquired MRI scans in order to maximize our exploration of predictors of improvement. The number of MRIs available was low (n = 32). Further, while we took steps to minimize the impact of acquisition protocol heterogeneity on our MRI metrics by using a robust image processing pipeline, a single scanner acquisition protocol performed at the time of the baseline visit would have reduced heterogeneity.

The active placebo control selected for the present study represented both a limitation and a strength. We selected a videogame control rather than no intervention, in order to account for possible placebo effects of actually using a device. Processing speed improved in both tests between Visits 1 and 2, suggesting either a learning curve or that both interventions were at least partially effective in improving processing speed. Further, the improvements in BVMT-R and CVLT-II noted only with AKL-T09 suggest that this intervention, focused on visuospatial and verbal abilities, may have promising effects on another cognitive domain affected by MS, i.e. verbal learning and memory. Hence, AKL-T09 might at face value be considered to be an active comparator rather than a control. This is supported by the fact that patient's

perceived deficits showed greater responses (i.e. great self-perceived cognitive improvements) to AKL-T09 than to AKL-T03. A similar effect was seen with the control intervention in the PositScience BrainHQ® study.[8] However, the fact that greater increases in SDMT were noted with AKL-T03 than with AKL-T09 (even though adherence to AKL-T09 was higher), and the fact that more patients maintained persistent improvements at Visit 3 after AKL-T03 than AKL-T09, suggests that AKL-T03 has specific and superior effects on processing speed relative to a robust control.

Taken together, our findings suggest that this enjoyable, low-risk, non-pharmacological intervention could represent a clinically valuable approach to improving processing speed in adults with MS experiencing a range of minor to moderate impairment in processing speed. Further studies are planned to determine ideal treatment conditions, including duration of a given treatment cycle and interval between cycles. Additionally, mechanisms underlying these improvements, such as improved network efficiency, synaptic plasticity or activity-dependent myelin repair, should be elucidated.

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RH has received research support from Roche, Genentech and MedDay, and personal compensation for consulting from Roche, Novartis and Sanofi.

AG is co-founder, shareholder, BOD member, and advisor for Akili Interactive Labs, a company that manufactures investigational digital treatments delivered through a video game-like interface. AG has a patent for a game-based cognitive intervention on which the tool (AKL-T03) that was used in this study was based.

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BIBLIOGRAPHY

1. Benedict RH, Amato MP, Boringa J, et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. *BMC Neurol*. 2012; 12: 55.
2. Benedict R, Fischer J, Archibald C, et al. Minimal Neuropsychological Assessment of MS Patients: A Consensus Approach. *Clin Neuropsychol*. 2002; 16: 381-97.
3. Chiaravalloti ND, Moore NB, Nikelshpur OM and DeLuca J. An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. *Neurology*. 2013; 81: 2066-72.
4. Mattioli F, Bellomi F, Stampatori C, Capra R and Miniussi C. Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. *Multiple sclerosis*. 2016; 22: 222-30.
5. Sokolov AA, Grivaz P and Bove R. Cognitive Deficits in Multiple Sclerosis: Recent Advances in Treatment and Neurorehabilitation. *Current treatment options in neurology*. 2018; 20: 53.
6. Charvet LE, Yang J, Shaw MT, et al. Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial. *PLoS One*. 2017; 12: e0177177.
7. Amato MP, Goretti B, Viterbo RG, et al. Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. *Mult Scler*. 2014; 20: 91-8.
8. Hancock LM, Bruce JM, Bruce AS and Lynch SG. Processing speed and working memory training in multiple sclerosis: a double-blind randomized controlled pilot study. *J Clin Exp Neuropsychol*. 2015; 37: 113-27.
9. De Giglio L, De Luca F, Prosperini L, et al. A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: a pilot study. *Neurorehabil Neural Repair*. 2015; 29: 453-61.
10. Bonavita S, Sacco R, Della Corte M, et al. Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. *J Neurol*. 2015; 262: 91-100.
11. Campbell J, Langdon D, Cercignani M and Rashid W. A Randomised Controlled Trial of Efficacy of Cognitive Rehabilitation in Multiple Sclerosis: A Cognitive, Behavioural, and MRI Study. *Neural Plast*. 2016; 2016: 4292585.
12. Mattioli F, Stampatori C, Zanotti D, Parrinello G and Capra R. Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis. *J Neurol Sci*. 2010; 288: 101-5.
13. Benedict RH, DeLuca J, Phillips G, et al. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult Scler*. 2017; 23: 721-33.
14. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Mult Scler*. 2012; 18: 891-8.
15. Van Schependom J, D'Hooghe M B, Cleynhens K, et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. *Eur J Neurol*. 2014; 21: 1219-25, e71-2.
16. Bove RM, Rush G, Zhao C, et al. A Videogame-Based Digital Therapeutic to Improve Processing Speed in People with Multiple Sclerosis: A Feasibility Study. *Neurol Ther*. 2019; 8: 135-45.
17. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011; 69: 292-302.

18. Kiely KM, Butterworth P, Watson N and Wooden M. The Symbol Digit Modalities Test: Normative data from a large nationally representative sample of Australians. *Arch Clin Neuropsychol*. 2014; 29: 767-75.
19. Kappos L, D'Souza M, Lechner-Scott J and Lienert C. On the origin of Neurostatus. *Mult Scler Relat Disord*. 2015; 4: 182-5.
20. Cohen JA, Reingold SC, Polman CH, Wolinsky JS and International Advisory Committee on Clinical Trials in Multiple S. Disability outcome measures in multiple sclerosis clinical trials: current status and future prospects. *Lancet Neurol*. 2012; 11: 467-76.
21. Benedict RH, Duquin JA, Jurgensen S, et al. Repeated assessment of neuropsychological deficits in multiple sclerosis using the Symbol Digit Modalities Test and the MS Neuropsychological Screening Questionnaire. *Mult Scler*. 2008; 14: 940-6.
22. Verdier-Taillefer M-H, Gourlet V, Fuhrer R and Alperovitch A. Psychometric properties of the Center for Epidemiologic Studies-Depression scale in multiple sclerosis. *Neuroepidemiology*. 2001; 20: 262-7.
23. Santangelo G, Sacco R, Siciliano M, et al. Anxiety in Multiple Sclerosis: psychometric properties of the State-Trait Anxiety Inventory. *Acta Neurologica Scandinavica*. 2016; 134: 458-66.
24. Learmonth YC, Dlugonski D, Pilutti LA, Sandroff BM, Klaren R and Motl RW. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. *Journal of the Neurological Sciences*. 2013; 331: 102-7.
25. Tustison NJ, Cook PA, Klein A, et al. Large-scale evaluation of ANTs and FreeSurfer cortical thickness measurements. *Neuroimage*. 2014; 99: 166-79.
26. Klein A, Ghosh SS, Bao FS, et al. Mindboggling morphometry of human brains. *PLoS Comput Biol*. 2017; 13: e1005350.
27. Hsu WY, Zanto TP, Anguera JA, Lin YY and Gazzaley A. Delayed enhancement of multitasking performance: Effects of anodal transcranial direct current stimulation on the prefrontal cortex. *Cortex*. 2015; 69: 175-85.
28. Sanfilipo MP, Benedict RH, Weinstock-Guttman B and Bakshi R. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology*. 2006; 66: 685-92.
29. Randolph JJ, Wishart HA, Saykin AJ, et al. FLAIR lesion volume in multiple sclerosis: relation to processing speed and verbal memory. *J Int Neuropsychol Soc*. 2005; 11: 205-9.
30. Benedict RH, Morrow S, Rodgers J, et al. Characterizing cognitive function during relapse in multiple sclerosis. *Mult Scler*. 2014; 20: 1745-52.
31. Anguera JA, Boccanfuso J, Rintoul JL, et al. Video game training enhances cognitive control in older adults. *Nature*. 2013; 501: 97-101.
32. Davis NO, Bower J and Kollins SH. Proof-of-concept study of an at-home, engaging, digital intervention for pediatric ADHD. *PLoS One*. 2018; 13: e0189749.
33. Anguera JA, Gunning FM and Arean PA. Improving late life depression and cognitive control through the use of therapeutic video game technology: A proof-of-concept randomized trial. *Depress Anxiety*. 2017; 34: 508-17.
34. Macaron G, Baldassari LE, Nakamura K, et al. Cognitive processing speed in multiple sclerosis clinical practice: association with patient-reported outcomes, employment, and MRI metrics. *Eur J Neurol*. 2020.

35. Benedict RH, Smerbeck A, Parikh R, Rodgers J, Cadavid D and Erlanger D. Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: implications for multiple sclerosis clinical trials. *Mult Scler*. 2012; 18: 1320-5.