Title

A Videogame-Based Digital Therapeutic to Improve Processing Speed in People with Multiple Sclerosis: A Feasibility Study.

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A videogame-based digital therapeutic to improve processing speed in people with multiple sclerosis: A feasibility study

--Manuscript Draft--

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Abstract:	BACKGROUND. Self-administered in-home digital therapeutics could expand access to cognitive rehabilitation for individuals with multiple sclerosis (MS), over half of whom experience cognitive impairment (CI). However, feasibility in an MS population must be clarified. OBJECTIVES To assess the feasibility of deploying a videogame-like digital treatment for CI in MS, including initial efficacy and barriers to adherence. METHODS In this pilot study, 21 participants with MS completed an in-clinic baseline neurological

	evaluation. Cognitive tests included paper-and-pencil Brief International Cognitive Assessment for Multiple Sclerosis [BICAMS – which included the Symbol Digit Modalities Test (SDMT)] and other unsupervised tablet-based tests (including Match: an unsupervised test of executive functions and processing speed, developed at UCSF; and the Cogstate MS Battery). Participants then completed an in-home, tablet-based, videogame-like investigational digital treatment (Project: EVO™) for 25 minutes daily, 5 days weekly, for 4 weeks. This was followed by a repeat in-clinic evaluation. RESULTS Of the 21 participants (mean [standard deviation, SD] age 53.8 [11.6] years, median Expanded Disability Status Scale (EDSS) 2.5 [SD 2.0, IQR [2-3.5]]) enrolled to use the digital therapeutic at home (mean [SD] SDMT z-score: -0.21 [1.16]), 18 completed the study, during which they completed an average of 19.7 days (median [SD]: 20.5 [8.4]). Overall, 78% of these 18 participants completed 75% of prescribed days (i.e. at least 15), and 50% completed all 20 days or more. Over the 4-week period, scores of processing speed improved significantly (based on one-sided t-test), including SDMT (p=0.003) and Match (p=0.006). The Cogstate DET test (psychomotor function) also increased (p=0.006). Mean increase in SDMT was 3.6 points. Male sex, not being employed, and higher baseline anxiety all were significantly associated with greater improvement in SDMT over the 4-week period. Interestingly, lower baseline cognitive scores were associated with greater number of sessions completed (e.g. SDMT: p = 0.003, R^2 = 0.44). Adjusting for employment, a proxy for time available, did not significantly improve the model fit. DISCUSSION Deploying an in-home digital tool to improve processing speed in MS is feasible, and shows preliminary efficacy. A larger, randomized controlled clinical trial is ongoing.
Response to Reviewers:	November 7, 2018 To: Drs. M.N. Sabbagh and A. Bertolotto Co-Editors in Chief Neurology and Therapy Dear Drs. Sabbagh and Bartolotto, We thank you for the opportunity to submit a revision to our manuscript, entitled “: A videogame-based digital therapeutic to improve processing speed in people with multiple sclerosis: A feasibility study” (NETH-D-18-00040R1), for your consideration. We thank the Reviewers for their thoughtful and detailed suggestions and have made every effort to revise the manuscript accordingly. We hope that in so doing we have substantially improved the quality of the manuscript. Thank you for your consideration. Best wishes, Riley Bove, MD MMSc Assistant Professor of Neurology MS Research Group University of California, San Francisco http://profiles.ucsf.edu/riley.bove

RESPONSE TO REVIEW

Manuscript number: NETH-D-18-00040R1

Title: A videogame-based digital therapeutic to improve processing speed in people with multiple sclerosis: A feasibility study

Reviewer #1:

The topic is interesting and it's useful to evaluate the feasibility of a home-based rehabilitation program for PwMS.

RESPONSE: Thank you.

As you reported in the title of the paper, the aim of the study is to test the feasibility of a videogame-based digital therapeutic to improve processing speed in PwMS. So I think that it's necessary to report in the reason why you decided to treat that function referring to the cognitive deficits of PwMS and to their needs.

RESPONSE: We thank the Reviewer for requesting this specification, and in the introduction we have provided greater detail for why we addressed processing speed specifically.

It's not clear if in the inclusion criteria you considered patient with attentive deficit or not.

RESPONSE: We did not specifically target patients with attention deficit disorder. We have now included the inclusion and exclusion criteria specifically.

Than you described the participant as CIS or MS but in the table you divided the patient as RR, PP and SP (not CIS).

RESPONSE: We thank the Reviewer for highlighting this oversight and have removed CIS from our manuscript.

Considering that the aim of the study is to evaluate the feasibility of this kind of treatment I think that it could be better to considered a simple of people with mild or moderate CI, in order to understand how people with CI are able to manage this type of instrument.

RESPONSE: We agree with the Reviewer that ideally a feasibility study would be primarily deployed in the patient population most likely to be targeted.
However, when we began this study, reviewers for digital health projects routinely expressed concern that use of digital tools would be too difficult for participants with MS, especially those with limitations. Therefore, we adopted a more permissive inclusion criteria initially, that included “general personal concerns about cognition”. Reassuringly, in the current study we found that participants with worse performance on the BICAMS measures were more likely to use the tool, suggesting that deploying the tool is feasible in participants with mild to moderate impairments.

In response to the Reviewer’s suggestion, we modified the Discussion as follows: “Interestingly, while we did not specifically enroll patients with specific levels of CI, both cognitive deficits and anxiety at baseline were associated with greater use of the treatment over the course of the study, indicating feasibility of such an intervention in a group with mild to moderate impairments.”

I also suggest to specify the recruitment period in order to considered the

appropriateness of the references.

RESPONSE: We have specified the recruitment period, as follows: “A total of 21 participants with MS were recruited from the UCSF Multiple Sclerosis and Neuroinflammation Center between January and March 2017.”

Reviewer #2:

I read with interest the manuscript entitled "A videogame-based digital therapeutic to improve processing speed in people with multiple sclerosis: A feasibility study". In it, the authors describe a small pilot study of an at-home cognitive rehabilitation tool, and present some positive results. It is particularly nice to see the use of an adaptive software tool. This is likely an important first step for improving restorative cognitive rehabilitation programs. Although this study is admittedly small and lacks a control group, it is of interest and contributes to a subfield that is in need of more empirical data to inform clinicians and other researchers.

RESPONSE: Thank you.

A few suggestions may help improve the manuscript for publication, as follows:

Please describe the EVO intervention itself in more detail. It is clear that it is adaptive and that it targets prefrontal cortex, but what is actually presented to the patients and how it works are not clear.

RESPONSE: In response to the Reviewer’s suggestion, we have amended the description of the EVO intervention as follows: ”Project: EVO™ is an investigational digital treatment developed by Akili Interactive. It uses the Selective Stimulus Management (SSME™) engine, designed to improve attention and inhibitory control through a video game-like interface. The SSME™ engine involves simultaneous engagement in visual targeting and continuous motor tasks in an adaptive, autonomous algorithm that continuously pushes an individual’s cognitive control performance within the context of multi-tasking interference. This enables the administration of a personalized treatment experience specific to the needs of each individual patient."

In the abstract and main text, the use of the 4-point SDMT increase as a clinically significant cutoff is used correctly when interpreting the mean increase of the group. However it is being misused in relation to individual patient improvement. This 4-point cutoff was not validated to demonstrate a clinically meaningful "responder" cutoff for individual patients. Rather, it was meant to establish a clinically meaningful cutoff in average performance of groups - for instance in clinical trials. This was discussed to some degree in the original paper and was also discussed by Benedict et al. at length at this year's IMSCOGS conference. Please revise.

RESPONSE: In response to the Reviewer’s suggestion, we have removed the sentence that read: “Eight participants (44%) did meet this threshold for improvement.”

The section included in the results about predictors of treatment response lacks detail, even in the supplement. Some indication of statistical significance would be helpful. Given the small sample size, lack of significance should also be interpreted with great caution, and it would be helpful to provide data for individual predictors rather than in one complex model at this point.

RESPONSE: We agree with the Reviewer, that based on the rule of thumb, we should deploy simple linear regression (one predictor in each model) rather than one complex model, as the number of predictors (demographic and clinical variables) is greater than the sample size (N = 18). Similar to how the random forest algorithm determined the variable importance, the values of each predictor were shuffled in each SLR model to see whether MSE increased compared with the MSE from the original model. The procedure was repeated 20 times, and the average MSE changes were compared

between all the predictors. Based on random forest, here we only focused on average MSE increase rather than decrease since we assumed the original predictor values were true and most accurate from the real world.

This approach indirectly showed how much each predictor impacted the outcome (delta SDMT), although we did not observe any statistically significant relationship (p of beta coefficient) between predictor and outcome in each SLR model due to lower power (small sample size). In the classic random forest, the variables' importance was also determined by the MSE increase without any p value.

For instance: simple linear regression: Delta SDMT ~ EDSS

Delta SDMTEDSS
-21
23.5
31.5
52
62.5
……

Delta SDMTEDSS
-22.5
22
33.5
51
61.5
……

Delta SDMTEDSS
-21
22.5
32
51.5
63.5
……

The comparison of this study to a previous BrainHQ study by Charvet et al (cited in your manuscript) in the discussion is valuable. However, that study was substantially different because SDMT was not included as an outcome, and because changes were assessed compared to a control group, not with simple paired t-tests as done here. The composite outcome was also significantly improved, which is not mentioned here. Please note these important points. It would also be helpful if the authors could speculate a bit more about why they think there might be differences - e.g., in what specifics does EVO differ from BrainHQ?

RESPONSE: We note that we do mention the important effect observed on the composite outcome, as well as the controlled nature of the study, as follows: "Training was reported to result in a significant cognitive composite score improvement in the 74 participants randomized to the PositScience BrainHQ® tool vs. in the 61 patients playing non-specific video games.[14]"

We have added the important point about SDMT not being an outcome: "There was no improvement in individual cognitive tests, but SDMT was not included as an outcome measure."

We appreciate the Reviewer's desire for more in-depth comparison between the two interventions, so we have expanded it as follows: "The tool tested in the current study is also unsupervised, but much less time-intensive (25 minutes daily for 4 weeks, vs. one hour daily for 12 weeks), suggesting possible advantages in terms of overall burden to patients, and hence adherence, as demonstrated by adherence reported in the respective studies. Additionally, we found improvements in processing speed using several different tests, while we detected no change in other domains of cognition,

suggesting a specific and fairly robust effect. The PositScience BrainHQ® exercises do not employ a multi-task interference paradigm, which could contribute to differences in effects."

Minor

The results say that gender, employment, and anxiety predicted improvement, but the discussion says education was predictive. Please clarify.

RESPONSE: We thank the Reviewer for highlighting this error (which was due to results from an additional analysis later shown to be inaccurate). We have removed the section on education.

Some minor points, like vertigo as an impediment to use, are mentioned as being discovered by the study but are only brought up in the discussion.

RESPONSE: We thank the Reviewer for highlighting this omission and have included the following sentence in the Results: "Reasons for non-adherence included logistical (n=1), vertigo induced by the game, (n=1), and ohysical discomfort due to prolonged use of the tablet (n=1)."

Editor Comments

RESPONSE: We confirm that we have modified the manuscript to comply with all the instructions below.

- Please ensure that the main text is structured using the following headings: Introduction, Methods, Results, Discussion, Conclusions.

- Please ensure that abbreviations are defined on first mention in both the abstract and the main text. Check that these are then abbreviated throughout after first mention. Abbreviations are acceptable in headings providing they have been abbreviated earlier in the body text.

- Please ensure that the title includes the following information (where applicable): the drug name, the indication, and the study design (e.g., randomized controlled trial).

- Please check that all author names and affiliations are correctly spelt and are provided in the following format: First_Name Middle_Initial(s) Last_Name. We are only able to publish errata for serious errors so it is important that smaller issues are addressed at this stage.

- Please include a paragraph at the end of the introduction which clearly states the aim(s)/purpose of the current study.

- All articles published in this journal must include a statement of ethics compliance BOTH in the main text and in the acknowledgments. Please add a statement of ethics compliance in the methods (or at an appropriate place in the main body of text if there are no methods) AND within the acknowledgments, under the heading 'Compliance with Ethics Guidelines'.

- Please check all data presented within the manuscript are accurate and correct. We are only able to publish errata for serious errors so it is important that smaller issues are addressed at this stage. These checks include but are not limited to:
- Checking that data presented within the main text matches data presented within the figures, tables, and abstract.
- Checking that any previously published data matches that in the original publication.
- Checking that all original data is accurate.
- Checking that all data is presented to the same number of decimal places where

possible.

- At the end of the discussion section please include a short paragraph stating the limitations of the current study. These limitations may have been highlighted in the reviewer comments given above.

- Please ensure that the conclusion section clearly links to the aims or hypothesis of the study but avoids statements not adequately supported by the data.

- Please clarify whether the study sponsor is also funding the journal's article processing charges. Please amend the disclosure of funding to make this clear.

- Please ensure that any medical writing or editorial assistance received during the writing of this article is declared in the acknowledgments, including: the name and company of the person providing the assistance and the source of funding for this assistance.

- We encourage authors to ensure that their datasets, software code and/or model underpinning their research are either deposited in publicly available repositories where possible or published alongside the paper as supplementary material. Please include one of the following statements where applicable at the end of the 'Acknowledgments' section under the title 'Data Availability':
1. The datasets generated during and/or analyzed during the current study are available in the [NAME] repository, [WEB LINK TO DATASETS]
2. The datasets generated during and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
3. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.
4. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.
5. All data generated or analyzed during this study are included in this published article/as supplementary information files.

- We encourage authors to thank the participants of the study. Please include (at least) the following statement under the acknowledgements section:
"We thank the participants of the study."

- Please confirm that the tables/figures are original and have been produced by the authors for this particular publication. If any of the tables/figures require permission to reuse them here then please provide evidence that you have this permission when resubmitting your manuscript.

- Please provide the figures as separate figure files (JPG/TIFF) when resubmitting your manuscript. The figure files will be used as provided in the final publication so please provide as high quality figures as possible.

TITLE

A videogame-based digital therapeutic to improve processing speed in people with multiple sclerosis: A feasibility study.

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ABSTRACT

BACKGROUND. Self-administered in-home digital therapeutics could expand access to cognitive rehabilitation for individuals with multiple sclerosis (MS), over half of whom experience cognitive impairment (CI). However, feasibility in an MS population must be clarified.

OBJECTIVES

To assess the feasibility of deploying a videogame-like digital treatment for CI in MS, including initial efficacy and barriers to adherence.

METHODS

In this pilot study, 21 participants with MS completed an in-clinic baseline neurological evaluation. Cognitive tests included paper-and-pencil Brief International Cognitive Assessment for Multiple Sclerosis [BICAMS – which included the Symbol Digit Modalities Test (SDMT)] and other unsupervised tablet-based tests (including Match: an unsupervised test of executive functions and processing speed, developed at UCSF; and the Cogstate MS Battery). Participants then completed an in-home, tablet-based, videogame-like investigational digital treatment (Project: EVO™) for 25 minutes daily, 5 days weekly, for 4 weeks. This was followed by a repeat in-clinic evaluation.

RESULTS

Of the 21 participants (mean [standard deviation, SD] age 53.8 [11.6] years, median Expanded Disability Status Scale (EDSS) 2.5 [SD 2.0, IQR [2-3.5]]) enrolled to use the digital therapeutic at home (mean [SD] SDMT z-score: -0.21 [1.16]), 18 completed the study, during which they

completed an average of 19.7 days (median [SD]: 20.5 [8.4]). Overall, 78% of these 18 participants completed 75% of prescribed days (i.e. at least 15), and 50% completed all 20 days or more.

Over the 4-week period, scores of processing speed improved significantly (based on one-sided t-test), including SDMT (p=0.003) and Match (p=0.006). The Cogstate DET test (psychomotor function) also increased (p=0.006). Mean increase in SDMT was 3.6 points. Male sex, not being employed, and higher baseline anxiety all were significantly associated with greater improvement in SDMT over the 4-week period. Interestingly, lower baseline cognitive scores were associated with greater number of sessions completed (e.g. SDMT: p = 0.003, R^2 = 0.44). Adjusting for employment, a proxy for time available, did not significantly improve the model fit.

DISCUSSION

Deploying an in-home digital tool to improve processing speed in MS is feasible, and shows preliminary efficacy. A larger, randomized controlled clinical trial is ongoing.

Key Words

Cognition, digital health, mHealth, Multiple Sclerosis, processing speed

INTRODUCTION

Accessible and self-administered tools are urgently needed to screen for, monitor and treat the cognitive impairment (CI) experienced by almost half of patients living with multiple sclerosis (MS).[1] MS is a chronic inflammatory and neurodegenerative disorder afflicting three times more women than men. Its first symptoms begin prior to age 50 in over 90% cases, in the prime of patients' productive lives. CI afflicts individuals with both relapsing and progressive forms of MS.[1, 2] Worsening of CI is in turn predictive of loss of employment, and loss of quality of life (QOL), affecting function in all spheres of activities of daily living.[3-5] Furthermore, early CI predicts subsequent functional decline. Loss of information processing speed is the most common type of CI in MS,[6] and over time, the Symbol Digit Modalities Test (SDMT) has been established as the most sensitive test for detection of loss of processing speed even early in the MS disease course.[7] Consequently, SDMT is the mainstay for both CI screening as well as measuring outcomes, including as a component of the widely used three-part Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS),[8] among other batteries for MS.[9]

Recently cognitive remediation trials, now targeting specific cognitive domains impacted by MS,[10] have shown efficacy, most notably the landmark MEMREHAB trial that resulted in improvements in verbal memory.[11-14] Unfortunately, there is a shortage of cognitive therapists, and access to qualified providers may be limited for many patients with mobility or cognitive impairments who are living outside of urban centers and specialized MS care centers. Even for patients with access to MS Centers, management of CI and other domains affected by MS often takes a back seat to the need to discuss and monitor an increasingly complex array of disease

modifying therapies (DMTs). To date, therefore, care delivery systems targeting cognitive function in MS are overwhelmingly inaccessible or inconvenient.

Game-based technologies, especially when deployed remotely, may play a substantial role in bridging this unmet need.[15] The purpose of the current pilot study was to evaluate the feasibility of treating processing speed in patients with MS using a tablet-based, videogame-like digital treatment.

METHODS

Participants and study setting. A total of 21 participants with MS were recruited from the University of California, San Francisco Multiple Sclerosis and Neuroinflammation Center between January and March 2017. Inclusion criteria included: age 18 years or older; a diagnosis of MS by 2010 Revised McDonald criteria[16]; internet connectivity available in the home or work environment; and general personal concerns about cognition. Exclusion criteria included: visual, dexterity or cognitive deficit so severe that it precluded the use of a tablet-based tool. Participants completed a baseline neurological and cognitive evaluation. Then, participants utilized an in-home tablet-based tool for 25 minutes a day, 5 days a week, for 4 weeks, after which they returned for a repeat in-clinic evaluation.

Standard clinical and cognitive measures.

- Demographic (age, gender, ancestry, education, employment) variables were obtained from all participants, and MS type, duration since first symptoms, Neurostatus Expanded Disability

Status Scale (EDSS)[17] and MS DMT were obtained from the medical record for MS participants. The neurological evaluation included:

- MS Functional Composite 4 (MSFC4) components, as outlined by Cohen et al[18]
    - Walking speed: T25FW Timed 25 Foot Walk (T25FW).
    - Dexterity: Nine-hole peg test (9HPT).
    - Sloan low-contrast letter acuity test (LCVA).
    - Cognition: the paced auditory serial addition task (PASAT) was replaced by the SDMT[19] as the SDMT is more congenial for patients and clinicians, rapid, and forms a component of the BICAMS. Serial versions of the test were used to minimize practice effects.
- Paper and pencil cognitive tests
    - Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), a standardized, internationally validated battery requiring 15 minutes or less.
        - Information processing speed: SDMT (as above; written version was administered to allow adequate comparison with the digital tools).[19]
        - Verbal memory (immediate recall): CVLT II Trials 1-5.[20] Serial versions of the test were used to minimize practice effects.
        - Visual memory (immediate recall): Brief Visuospatial Memory Test Revised (BVMT-R).[21]
- Patient-reported mood was assessed using the 14-item Hospital Anxiety and Depression Scale (HADS),[22, 23] a self-report instrument containing seven questions probing anxiety and seven questions for depression, each scored separately in a Likert fashion (0 through 3). Scores 0-7 are categorized as normal, 8-10 mild, 11-14 moderate, and 15-21 severe.[24] A threshold

score of 8 or greater on the HADS depression subscale provides a sensitivity of 90% and specificity of 87.3% for major depression, and on the anxiety subscale provides a sensitivity of 88.5% and a specificity of 80.7% for generalized anxiety disorder only.[23]

Digital cognitive measures

- The Cogstate computerized MS battery consists of 4 game-like tasks presented on a web-based platform (www.cogstate.com) and requires about 15 minutes for administration. It measures several neuropsychological constructs with considerable construct and criterion validity.[25] Cogstate is a widely used platform which can be used for both multi-center clinical trials and for screening in clinical practice settings; validity of data is ensured by expected item accuracy and outlier detection. Cogstate has been deployed in the evaluation of CI in MS.[15] The Cogstate battery has a normative database from >50,000 participants (ages 10-99), and for any measures, scores of one standard deviation or more below the age-based normative data are considered to have a mild impairment; having one or more impaired scores counts as an impaired assessment. Four tests were completed in the following order:
    - *Detection Task* (DET): a reaction time task assessing psychomotor function. The subject presses the 'Yes' key as quickly as possible when the central card turns face-up. The face-up card displayed is always the same joker card. The primary outcome on this task is reaction time.
    - *Identification Task (IDN):* a choice reaction time task assessing visual attention. A card is turned over in the center of the screen, and the subject should respond 'Yes' if the face-up card is red, or 'No' if it is black. Jokers are used again to ensure that playing

cards presented in the next task were not previously seen. The primary outcome on this task is reaction time.

- *One Card Learning (OCL):* assesses visual recognition memory and attention. Cards are sequentially shown and subjects are instructed to respond 'Yes' if the face-up card has appeared in the task before, and 'No' if it has not yet appeared. Normal playing cards are displayed without jokers. The primary outcome on this task is accuracy of responses.
- *One Back Task* (ONB): assesses working memory and attention. Subjects are instructed to respond 'Yes' if the face-up card is exactly the same as the immediately previous card, or 'No' if it is not. The primary outcome on this task is reaction time.

- The UCSF Match Test: Match is a 2-minute test of executive functions and processing speed that is based on the SDMT but delivered on a tablet using the TabCAT software platform (memory.ucsf.edu/TabCAT). Respondents are shown a number/symbol key at the bottom of the screen. Using this key as a reference, they are asked to tap the symbol that corresponds to a series of number cues as quickly and accurately as possible. In comparison to SDMT, it places less demand on motor functions and literacy because subjects tap rather than write their responses; also, it can be self-administered. Performance is scored by the total correct in 2-minutes. The Match shows expected correlations with traditional neuropsychological tests and regional gray matter volumes.[26]

<u>Digital treatment for cognitive deficits</u>

Project: EVO™ is an investigational digital treatment developed by Akili Interactive Labs. It uses the Selective Stimulus Management Engine (SSME^{TM}) engine, designed to improve attention and

inhibitory control through a video game-like interface. The SSME™ engine involves simultaneous engagement in visual targeting and continuous motor tasks in an adaptive, autonomous algorithm that continuously pushes an individual's cognitive control performance within the context of multi-tasking interference. This enables the administration of a personalized treatment experience specific to the needs of each individual patient. The Project: EVO™ investigational digital treatment has shown efficacy in a randomized, controlled trial of 348 children and adolescents diagnosed with ADHD on the predefined primary endpoint, a change in the Attention Performance Index (API), a composite score from the Test of Variables of Attention (T.O.V.A.®) system, a computerized performance test used to objectively measure attention and inhibitory control. Based on the results of the study, Akili filed AKL-T01 with the U.S. Food and Drug Administration (FDA) for clearance as a novel treatment for children and adolescents with ADHD. For the current study, we defined adherence as completion of 75% or more of prescribed days of training, i.e. 15 days or more.

Ethical approvals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the UCSF Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analyses.

To evaluate feasibility of this type of intervention in patients with MS, we defined adherence as completing ≥ 75% of prescribed days, i.e. at least 15 days, over the course of the treatment period.

To account for delays in obtaining WiFi and initiating the study, and for travel and other factors, we expanded the timeframe to 5 weeks (35 days). To determine the improvement on the scores of processing speed between baseline and return visit, either left-tailed or right-tailed paired-samples t-tests were performed. To evaluate the effect of baseline demographic and clinical variables on improvement in SDMT over the pilot study duration, simple linear regression was used to assess each variable's prediction performance on SDMT change. Then, in analyses derived from random forest algorithms, the values of each feature were randomly permuted and a new mean squared error (MSE) was calculated in each simple linear regression model. Each feature's importance was measured by the increase in the MSE. This procedure was repeated 20 times for each variable. Finally, to evaluate predictors of adherence to treatment, we used simple linear regression. All statistical analyses were performed in R 3.5.0.

RESULTS

Participant characteristics

The baseline demographic and clinical characteristics of the participants are described in Table 1. SDMT was not associated with age, sex, education, EDSS, disease duration, depression or anxiety at baseline ($p>0.05$ for each).

Table 1. Demographic, clinical and cognitive characteristics of participants (N=21).

N		21
Age, years	mean (SD)	53.8 (11.6)
Sex	Female	18 (86%)

Handedness	Right-handed	20 (95%)
Education, years	mean (SD)	15.8 (2.5)
Employment	Part- or full-time employed	7 (33%)
Ethnicity	Not Hispanic	21 (100%)
Race	White	20 (95%)
	Black or African American	1 (5%)
MS Type	RR	15 (71%)
	PP	4 (19%)
	SP	2 (10%)
Disease Duration	mean (SD)	14.5 (9.6)
EDSS	mean (median, SD, IQR, range)	3.1 (2.5, 2.0, [2.0-3.5], [0-7])
SDMT Correct	mean (SD)	47.4 (10.3)
CVLT II Total	mean (SD)	55.2 (12.7)
BVMT Total Recall	mean (SD)	27.0 (8.2)

Feasibility of in-home digital treatment for cognitive deficits: user experience

Of 21 MS participants enrolled (mean [SD] SDMT z-score: -0.21 [1.16]), 18 completed and returned for their 4-week visit. Reasons for non-adherence included logistical (n=1), vertigo induced by the game, (n=1), and physical discomfort due to prolonged use of the tablet (n=1). The 18 whom completed the study played an average of 19.7 days (median [SD]: 20.5 [8.4]) per month. Overall, 78% of these 18 participants completed ≥ 75% of prescribed days, i.e. at least 15 days (**Figure 1**), and 50% (n=9) completed all 20 days or more.

Figure 1. Participant adherence to game protocol.

Predictors of persistence with the training sessions

Lower SDMT scores at baseline were associated with greater number of days played over the 4 weeks ($p = 0.003$, $R^2 = 0.44$, **Supplementary Figure 1**; after adjusting for employment, a possible proxy for free time, partial R^2 for SDMT = 0.30), suggesting an association between cognitive deficits and motivation to complete the sessions. In fact, lower scores across the other BICAMS cognitive tests (BVMT, CVLTII, $p<0.001$ for each) as well as higher anxiety scores (HADS, $p=0.015$) were also associated with greater number of days played.

Changes in cognitive scores after 4 weeks of digital treatment

Over the 4-week period, scores improved significantly on our primary outcome, the SDMT (paired t-test, $p=0.003$, $N=18$) (**Figure 2)**. In fact, the mean increase of 3.6 points was just shy of the 4-point clinically meaningful threshold established for trials assessing cognition in MS.[27, 7]

Scores also improved in 2/5 of the computer-based tests – specifically Match, which measures processing speed, and Cogstate DET, which measures psychomotor function – ($p=0.006$ for each) (**Table 2**), showing encouraging consistency across tests of processing speed.

Figure 2. Comparison of baseline and 1-month SDMT scores in 18 participants who completed the study (left-tailed paired t-test, p = 0.003).

Table 2. Comparison of cognitive measures before and after 4 weeks of use of the Akili Interactive Project: EVO™ investigational digital treatment, in adults with MS.

Test	Domain	Pre, mean (sd)	Post, mean (sd)	N	p
BICAMS					
SDMT	Processing speed	48.3 (10.4)	51.9 (10.8)	18	**0.003**
CVLT-II	Verbal memory	54.8 (13.3)	55.3 (12.0)	19	0.385
BVMT-R	Visual memory	27.5 (8.5)	27.6 (6.9)	19	0.465
COMPUTERIZED					
Cogstate					
DET	Psychomotor function	2.6 (0.09)	2.5 (0.06)	14	**0.006**
IDN	Visual attention	2.7 (0.07)	2.7 (0.08)	14	0.755
OCL	Visual memory, attention	0.97 (0.17)	1.01 (0.14)	14	0.147
ONB	Working memory, attention	2.88 (0.09)	2.86 (0.10)	14	0.082
Match	Processing speed	50.9 (7.1)	53.1 (8.0)	16	**0.006**

<u>Predictors of improvement in the SDMT</u>

When we evaluated the contribution of baseline clinical and demographic factors to SDMT improvement over the pilot study duration, three variables were identified: gender (male), employment (not employed) and anxiety category (borderline/abnormal) **(Supplementary Figure 2).**

DISCUSSION

In the current feasibility study, we report high enthusiasm for a videogame-like digital treatment for cognition, in a cohort of older adults with MS with a high baseline level of function with 86% retention after 4 weeks, and in these 18, 78% adhered to the treatment. These adherence rates for self-managed computerized cognitive rehabilitation at home are consistent with previous reports.[28] Interestingly, while we did not specifically enroll patients with specific levels of CI, both cognitive deficits and anxiety at baseline were associated with greater use of the treatment over the course of the study, indicating feasibility of such an intervention in a group with mild to moderate impairments. Further, we confirmed that improvements were consistent across several tests of processing speed, and could be detected during tests that can be self-administered at home. Finally, we also identified specific features, such as pronounced vertigo, which might preclude use of video games as a digital therapeutic, and form a basis for exclusion from participation in larger trials.

Individuals with MS have demonstrated enthusiasm for using digital technologies to: (1) access information regarding MS, (2) pursue routine and rehabilitation care (e.g. through telemedicine-based web programs), (3) monitor their MS (e.g. through smartphone or activity trackers) and importantly (4) participate in research. Additionally, MS patients have enthusiastically embraced home-based care strategies.[29] Here, we extend these observations to report adherence to an in-home, videogame-based tool designed to improve processing speed. Recently, a videogame approach was deployed through 12-weeks using the adaptive PositScience BrainHQ® tool in 135 patients with MS and SDMT z-scores of -1 or less. Training was reported to result in a significant

cognitive composite score improvement in the 74 participants randomized to the PositScience BrainHQ® tool vs. in the 61 patients playing non-specific video games.[15] There was no improvement in individual cognitive tests, but SDMT was not included as an outcome measure. The tool tested in the current study is also unsupervised, but much less time-intensive (25 minutes daily for 4 weeks, vs. one hour daily for 12 weeks), suggesting possible advantages in terms of overall burden to patients, and hence adherence, as demonstrated by adherence reported in the respective studies. Additionally, we found improvements in processing speed using several different tests, while we detected no change in other domains of cognition, suggesting a specific and fairly robust effect. The PositScience BrainHQ® exercises do not employ a multi-task interference paradigm, which could contribute to differences in effects.

Although the SDMT is more psychometrically sound than the PASAT,[30] replacing the PASAT with the SDMT in the MSFC has not always been supported by the data.[31] The current feasibility study is also limited by small sample size, and lack of a control group to confirm that the improvements in SDMT could not simply be explained by learning effects or placebo. However other similar studies with intervention control patient groups have demonstrated improvement on the SDMT for the treatment group.[28] From prior investigations, the current mean increase (3.6 points) almost meets the clinically meaningful threshold established for trials assessing cognition in MS (4 points[27]), and is substantially greater than anticipated learning effects in a similar time period.[32] A larger blinded, randomized and controlled study is underway.

CONCLUSIONS

In summary, the current feasibility study lends further support to the role that videogame-based digital treatments may play for ameliorating CI in MS,[15] and its potential advantages (tablet-based, game-based, short and convenient session duration (25 minutes) over a fairly short timeframe [4 weeks]) support the expansion of the study to a larger, controlled trial evaluating both efficacy and sustained effects. The anticipated impact of a home-based training program to ameliorate CI in MS is large, given the scarcity of rehabilitation programs, and the improved accessibility, cost effectiveness, and rapid deployment that are afforded by remote trials.

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RB receives research support from the National Multiple Sclerosis Society, the Hilton Foundation, and the California Initiative to Advance Precision Medicine. RB has also received personal compensation for consulting from Novartis, Sanofi Genzyme, and Roche Genentech.

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AS is a full-time employee of Cogstate.

TA is a full-time employee of Akili Interactive Labs.

DL has participated in speaker bureau for Bayer, Merck, Almirall, Execemed, TEVA, Roche, Novartis, Biogen, Sanofi; has had consultancy from Novartis, Bayer, Merck, Biogen, TEVA, Sanofi; has had research grants from Bayer, Merck, Novartis, Biogen. All are paid into DL's institution.

KP reports no disclosures.

AG is co-founder, shareholder, BOD member, and advisor for Akili Interactive Labs, a company that produces therapeutic video games. AG is the inventor on a patent to interference processing on which the game-based cognitive intervention of the (Project: EVO™) investigational digital treatment that was used in this study was based.

AF reports research support from the MS society of Canada and the Progressive MS Alliance; speaker's honoraria from Sanofi-Genzyme, Merck-Serono, Novartis, Biogen and Teva; and consultancy from Akili Interactive Labs.

JA reports no disclosures.

Compliance with ethics guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the UCSF Institutional Review Board and with the 1964 Helsinki declaration

and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Benedict RH, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC neurology. 2012;12:55. doi:10.1186/1471-2377-12-55.
2. Potagas C, Giogkaraki E, Koutsis G, Mandellos D, Tsirempolou E, Sfagos C et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. Journal of the neurological sciences. 2008;267(1-2):100-6. doi:10.1016/j.jns.2007.10.002.
3. Benedict RH, Munschauer F, Linn R, Miller C, Murphy E, Foley F et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. Mult Scler. 2003;9(1):95-101.
4. Benedict R, Fischer J, Archibald C, Arnett P, Beatty W, Bobholz J et al. Minimal Neuropsychological Assessment of MS Patients: A Consensus Approach. Clin Neuropsychol. 2002;16(3):381-97.
5. Shawaryn MA, Schiaffino KM, LaRocca NG, Johnston MV. Determinants of health-related quality of life in multiple sderosis: the role of illness intrusiveness. Mult Scler. 2002;8(4):310-8.
6. Costa SL, Genova HM, DeLuca J, Chiaravalloti ND. Information processing speed in multiple sclerosis: Past, present, and future. Mult Scler. 2017;23(6):772-89. doi:10.1177/1352458516645869.
7. Benedict RH, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R et al. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler. 2017;23(5):721-33. doi:10.1177/1352458517690821.
8. Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler. 2012;18(6):891-8. doi:10.1177/1352458511431076.
9. Van Schependom J, D'Hooghe M B, Cleynhens K, D'Hooge M, Haelewyck MC, De Keyser J et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. Eur J Neurol. 2014;21(9):1219-25, e71-2. doi:10.1111/ene.12463.
10. Rosti-Otajarvi EM, Hamalainen PI. Neuropsychological rehabilitation for multiple sclerosis. The Cochrane database of systematic reviews. 2014;2:CD009131. doi:10.1002/14651858.CD009131.pub3.
11. Lincoln NB, das Nair R, Bradshaw L, Constantinescu CS, Drummond AE, Erven A et al. Cognitive Rehabilitation for Attention and Memory in people with Multiple Sclerosis: study protocol for a randomised controlled trial (CRAMMS). Trials. 2015;16:556. doi:10.1186/s13063-015-1016-3.
12. Chiaravalloti ND, Moore NB, Nikelshpur OM, DeLuca J. An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. Neurology. 2013;81(24):2066-72. doi:10.1212/01.wnl.0000437295.97946.a8.
13. Mattioli F, Bellomi F, Stampatori C, Capra R, Miniussi C. Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. Multiple sclerosis. 2016;22(2):222-30. doi:10.1177/1352458515587597.
14. Ford-Johnson L, DeLuca J, Zhang J, Elovic E, Lengenfelder J, Chiaravalloti ND. Cognitive effects of modafinil in patients with multiple sclerosis: A clinical trial. Rehabil Psychol. 2016;61(1):82-91. doi:10.1037/a0039919.

15. Charvet LE, Yang J, Shaw MT, Sherman K, Haider L, Xu J et al. Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial. PloS one. 2017;12(5):e0177177. doi:10.1371/journal.pone.0177177.
16. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292-302. doi:10.1002/ana.22366.
17. Kappos L, D'Souza M, Lechner-Scott J, Lienert C. On the origin of Neurostatus. Multiple sclerosis and related disorders. 2015;4(3):182-5. doi:10.1016/j.msard.2015.04.001.
18. Cohen JA, Reingold SC, Polman CH, Wolinsky JS, 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(5):467-76. doi:10.1016/S1474-4422(12)70059-5.
19. Smith A. Symbol Digit Modalities Test. Los Angeles: Western Psychological Services; 1982.
20. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test–II, Second Edition. San Antonio, TX: The Psychological Corporation; 2000.
21. Benedict RHB. Brief visuospatial memory test - revised: Professional manual. Lutz, FL: Psychological Assessment Resources, Inc.; 1997.
22. Snaith RP. The Hospital Anxiety And Depression Scale. Health and quality of life outcomes. 2003;1:29. doi:10.1186/1477-7525-1-29.
23. Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. Mult Scler. 2009;15(12):1518-24. doi:10.1177/1352458509347150.
24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
25. Fredrickson J, Maruff P, Woodward M, Moore L, Fredrickson A, Sach J et al. Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. Neuroepidemiology. 2010;34(2):65-75. doi:10.1159/000264823.
26. Possin KL, Moskowitz T, Erlhoff SJ, Rogers KM, Johnson ET, Steele NZR et al. The Brain Health Assessment for Detecting and Diagnosing Neurocognitive Disorders. J Am Geriatr Soc. 2018;66(1):150-6. doi:10.1111/jgs.15208.
27. Benedict RH, Morrow S, Rodgers J, Hojnacki D, Bucello MA, Zivadinov R et al. Characterizing cognitive function during relapse in multiple sclerosis. Mult Scler. 2014;20(13):1745-52. doi:10.1177/1352458514533229.
28. Campbell J, Langdon D, Cercignani M, 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. doi:10.1155/2016/4292585.
29. Hoang P, Schoene D, Gandevia S, Smith S, Lord SR. Effects of a home-based step training programme on balance, stepping, cognition and functional performance in people with multiple sclerosis - a randomized controlled trial. Multiple sclerosis. 2016;22(1):94-103. doi:10.1177/1352458515579442.
30. Sonder JM, Burggraaff J, Knol DL, Polman CH, Uitdehaag BM. Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. Mult Scler. 2014;20(4):481-8. doi:10.1177/1352458513501570.

31. Brochet B, Deloire MS, Bonnet M, Salort-Campana E, Ouallet JC, Petry KG et al. Should SDMT substitute for PASAT in MSFC? A 5-year longitudinal study. Mult Scler. 2008;14(9):1242-9. doi:10.1177/1352458508094398.
32. Benedict RH, Duquin JA, Jurgensen S, Rudick RA, Feitcher J, Munschauer FE 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(7):940-6. doi:10.1177/1352458508090923.

TITLE

A videogame-based digital therapeutic to improve processing speed in people with multiple sclerosis: A feasibility study.

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ABSTRACT

BACKGROUND. Self-administered in-home digital therapeutics could expand access to cognitive rehabilitation for individuals with multiple sclerosis (MS), over half of whom experience cognitive impairment (CI). However, feasibility in an MS population must be clarified.

OBJECTIVES

To assess the feasibility of deploying a videogame-like digital treatment for CI in MS, including initial efficacy and barriers to adherence.

METHODS

In this pilot study, 21 participants with MS completed an in-clinic baseline neurological evaluation. Cognitive tests included paper-and-pencil Brief International Cognitive Assessment for Multiple Sclerosis [(BICAMS – which included the Symbol Digit Modalities Test (SDMT)] and other unsupervised tablet-based tests (including Match: an unsupervised test of executive functions and processing speed, developed at UCSF; and the Cogstate MS Battery). Participants then completed an in-home, tablet-based, videogame-like investigational digital treatment (Project: EVO™) for 25 minutes daily, 5 days weekly, for 4 weeks. This was followed by a repeat in-clinic evaluation.

RESULTS

Of the 21 participants (mean [standard deviation, SD] age 53.8 [11.6] years, median Expanded Disability Status Scale (EDSS) 2.5 [SD 2.0, IQR [2-3.5]]) enrolled to use the digital therapeutic at home (mean [SD] SDMT z-score: -0.21 [1.16]), 18 completed the study, during which they

completed an average of 19.7 days (median [SD]: 20.5 [8.4]). Overall, 78% of these 18 participants completed 75% of prescribed days (i.e. at least 15), and 50% completed all 20 days or more.

Over the 4-week period, scores of processing speed improved significantly (based on one-sided t-test), including SDMT (p=0.003) and Match (p=0.006). The Cogstate DET test (psychomotor function) also increased (p=0.006). Mean increase in SDMT was 3.6 points. Male sex, not being employed, and higher baseline anxiety all were significantly associated with greater improvement in SDMT over the 4-week period. Interestingly, lower baseline cognitive scores were associated with greater number of sessions completed (e.g. SDMT: $p = 0.003$, $R^2 = 0.44$). Adjusting for employment, a proxy for time available, did not significantly improve the model fit.

DISCUSSION

Deploying an in-home digital tool to improve processing speed in MS is feasible, and shows preliminary efficacy. A larger, randomized controlled clinical trial is ongoing.

Key Words

Cognition, digital health, mHealth, Multiple Sclerosis, processing speed

INTRODUCTION

Accessible and self-administered tools are urgently needed to screen for, monitor and treat the cognitive impairment (CI) experienced by almost half of patients living with multiple sclerosis (MS).[1] MS is a chronic inflammatory and neurodegenerative disorder afflicting three times more women than men. Its first symptoms begin prior to age 50 in over 90% cases, in the prime of patients' productive lives. CI afflicts individuals with both relapsing and progressive forms of MS.[1, 2] Worsening of CI is in turn predictive of loss of employment, and loss of quality of life (QOL), affecting function in all spheres of activities of daily living.[3-5] Furthermore, early CI predicts subsequent functional decline. Loss of information processing speed is the most common type of CI in MS,[6] and over ~~Over~~ time, the Symbol Digit Modalities Test (SDMT) has been established as the most sensitive test for detection of loss of processing speed ~~cognitive decline~~ even early in the MS disease course.[7] Consequently, SDMT is the mainstay for both CI screening as well as measuring outcomes, including as a component of the widely used three-part Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS),[8] among other batteries for MS.[9]

Recently cognitive remediation trials, now targeting specific cognitive domains impacted by MS,[10] have shown efficacy, most notably the landmark MEMREHAB trial that resulted in improvements in verbal memory.[11-14] Unfortunately, there is a shortage of cognitive therapists, and access to qualified providers may be limited for many patients with mobility or cognitive impairments who are living outside of urban centers and specialized MS care centers. Even for patients with access to MS Centers, management of CI and other domains affected by MS often takes a back seat to the need to discuss and monitor an increasingly complex array of disease

modifying therapies (DMTs). To date, therefore, care delivery systems targeting cognitive function in MS are overwhelmingly inaccessible or inconvenient.

Game-based technologies, especially when deployed remotely, may play a substantial role in bridging this unmet need.[15] ~~Here~~The purpose of the current pilot study was to evaluate~~, we present a pilot study evaluating~~ the feasibility of treating processing speed in patients with MS ~~with~~ using a tablet-based, videogame-like digital treatment.

METHODS

Participants and study setting. A total of 21 participants with ~~a~~ MS ~~diagnosis of clinically isolated syndrome (CIS) or MS by 2010 Revised McDonald criteria,[15]~~ were recruited from the ~~UCSF~~ University of California, San Francisco Multiple Sclerosis and Neuroinflammation Center between January and March 2017. Inclusion criteria included: age 18 years or older; a diagnosis of MS by 2010 Revised McDonald criteria[16]; internet connectivity available in the home or work environment; and general personal concerns about cognition. Exclusion criteria included: visual, dexterity or cognitive deficit so severe that it precluded the use of a tablet-based tool. Participants completed a baseline neurological and cognitive evaluation. Then, participants utilized an in-home tablet-based tool for 25 minutes a day, 5 days a week, for 4 weeks, after which they returned for a repeat in-clinic evaluation.

Standard clinical and cognitive measures.

- Demographic (age, gender, ancestry, education, employment) variables were obtained from all participants, and MS type, duration since first symptoms, Neurostatus Expanded Disability Status Scale (EDSS)[17] and MS DMT were obtained from the medical record for MS participants. The neurological evaluation included:
- MS Functional Composite 4 (MSFC4) components, as outlined by Cohen et al[18]
    - Walking speed: T25FW Timed 25 Foot Walk (T25FW).
    - Dexterity: Nine-hole peg test (9HPT).
    - Sloan low-contrast letter acuity test (LCVA).
    - Cognition: the paced auditory serial addition task (PASAT) was replaced by the SDMT[19] as the SDMT is more congenial for patients and clinicians, rapid, and forms a component of the BICAMS. Serial versions of the test were used to minimize practice effects.
- Paper and pencil cognitive tests
    - Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), a standardized, internationally validated battery requiring 15 minutes or less.
        - Information processing speed: SDMT (as above; written version was administered to allow adequate comparison with the digital tools).[19]
        - Verbal memory (immediate recall): CVLT II Trials 1-5.[20] Serial versions of the test were used to minimize practice effects.
        - Visual memory (immediate recall): Brief Visuospatial Memory Test Revised (BVMT-R).[21]
- Patient-reported mood was assessed using the 14-item Hospital Anxiety and Depression Scale (HADS),[22, 23] a self-report instrument containing seven questions probing anxiety and

seven questions for depression, each scored separately in a Likert fashion (0 through 3). Scores 0-7 are categorized as normal, 8-10 mild, 11-14 moderate, and 15-21 severe.[24] A threshold score of 8 or greater on the HADS depression subscale provides a sensitivity of 90% and specificity of 87.3% for major depression, and on the anxiety subscale provides a sensitivity of 88.5% and a specificity of 80.7% for generalized anxiety disorder only.[23]

Digital cognitive measures

- The Cogstate computerized MS battery consists of 4 game-like tasks presented on a web-based platform (www.cogstate.com) and requires about 15 minutes for administration. It measures several neuropsychological constructs with considerable construct and criterion validity.[25] Cogstate is a widely used platform which can be used for both multi-center clinical trials and for screening in clinical practice settings; validity of data is ensured by expected item accuracy and outlier detection. Cogstate has been deployed in the evaluation of CI in MS.[15] The Cogstate battery has a normative database from >50,000 participants (ages 10-99), and for any measures, scores of one standard deviation or more below the age-based normative data are considered to have a mild impairment; having one or more impaired scores counts as an impaired assessment. Four tests were completed in the following order:
    - *Detection Task* (DET): a reaction time task assessing psychomotor function. The subject presses the 'Yes' key as quickly as possible when the central card turns face-up. The face-up card displayed is always the same joker card. The primary outcome on this task is reaction time.
    - *Identification Task (IDN):* a choice reaction time task assessing visual attention. A card is turned over in the center of the screen, and the subject should respond 'Yes' if the

face-up card is red, or ‘No’ if it is black. Jokers are used again to ensure that playing cards presented in the next task were not previously seen. The primary outcome on this task is reaction time.

- *One Card Learning (OCL):* assesses visual recognition memory and attention. Cards are sequentially shown and subjects are instructed to respond ‘Yes’ if the face-up card has appeared in the task before, and ‘No’ if it has not yet appeared. Normal playing cards are displayed without jokers. The primary outcome on this task is accuracy of responses.
- *One Back Task* (ONB): assesses working memory and attention. Subjects are instructed to respond ‘Yes’ if the face-up card is exactly the same as the immediately previous card, or ‘No’ if it is not. The primary outcome on this task is reaction time.

- The UCSF Match Test: Match is a 2-minute test of executive functions and processing speed that is based on the SDMT but delivered on a tablet using the TabCAT software platform (memory.ucsf.edu/TabCAT). Respondents are shown a number/symbol key at the bottom of the screen. Using this key as a reference, they are asked to tap the symbol that corresponds to a series of number cues as quickly and accurately as possible. In comparison to SDMT, it places less demand on motor functions and literacy because subjects tap rather than write their responses; also, it can be self-administered. Performance is scored by the total correct in 2-minutes. The Match shows expected correlations with traditional neuropsychological tests and regional gray matter volumes.[26]

Field Code Changed

Digital treatment for cognitive deficits

Project: EVO™ is an investigational digital treatment ~~clinical prototype~~ developed by Akili Interactive Labs. It ~~is designed~~ using aes the Selective Stimulus Management Engine (SSME™) engine, designed to improve attention and inhibitory control through a video game-like interface. The SSME™ engine involves simultaneous engagement in visual targeting and continuous motor tasks in an adaptive, autonomous algorithm that continuously pushes an individual's cognitive control performance within the context of multi-tasking interference. This enables the administration of~~that uses specific sensory stimuli and simultaneously assesses patient motor responses to target and activate the prefrontal cortex. 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~~specific to the needs of each individual patient. The ~~This enables second-by-second monitoring of patient progress and continuously challenges each patient so it is never too easy or too difficult, encouraging patients to improve their performance.~~ Project: EVO™ investigational digital treatment has shown efficacy in a randomized, controlled trial of 348 children and adolescents diagnosed with ADHD on the predefined primary endpoint, a change in the Attention Performance Index (API), a composite score from the Test of Variables of Attention (T.O.V.A.®) system, a computerized performance test used to objectively measure attention and inhibitory control. Based on the results of the study, Akili filed AKL-T01 with the U.S. Food and Drug Administration (FDA) for clearance as a novel treatment for children and adolescents with ADHD. For the current study, we defined adherence as completion of 75% or more of prescribed days of training, i.e. 15 days or more.

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Ethical approvals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the UCSF Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analyses.

To evaluate feasibility of this type of intervention in patients with MS, we defined adherence as completing ≥ 75% of prescribed days, i.e. at least 15 days, over the course of the treatment period. To account for delays in obtaining WiFi and initiating the study, and for travel and other factors, we expanded the timeframe to 5 weeks (35 days). To determine the improvement on the scores of processing speed between baseline and return visit, either left-tailed or right-tailed paired-samples t-tests were performed. To evaluate the effect of baseline demographic and clinical variables on improvement in SDMT over the pilot study duration, simple linear regression was used to assess each variable's prediction performance on SDMT change. Then, in analyses derived from random forest algorithms, the values of each feature were randomly permuted and a new mean squared error (MSE) was calculated in each simple linear regression model. Each feature's importance was measured by the increase in the MSE. This procedure was repeated 20 times for each variable. ~~To evaluate predictors of change in SDMT, we deployed similar analyses derived from random forest algorithms.~~ Finally, to evaluate predictors of adherence to treatment, we used simple linear regression. All statistical analyses were performed in R 3.5.0.

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RESULTS

Participant characteristics

The baseline demographic and clinical characteristics of the participants are described in Table 1. SDMT was not associated with age, sex, education, EDSS, disease duration, depression or anxiety at baseline ($p>0.05$ for each).

Table 1. Demographic, clinical and cognitive characteristics of participants (N=21).

N		21
Age, years	mean (SD)	53.8 (11.6)
Sex	Female	18 (86%)
Handedness	Right-handed	20 (95%)
Education, years	mean (SD)	15.8 (2.5)
Employment	Part- or full-time employed	7 (33%)
Ethnicity	Not Hispanic	21 (100%)
Race	White	20 (95%)
	Black or African American	1 (5%)
MS Type	RR	15 (71%)
	PP	4 (19%)
	SP	2 (10%)
Disease Duration	mean (SD)	14.5 (9.6)
EDSS	mean (median, SD, IQR, range)	3.1 (2.5, 2.0, [2.0-3.5], [0-7])
SDMT Correct	mean (SD)	47.4 (10.3)
CVLT II Total	mean (SD)	55.2 (12.7)

BVMT Total Recall	mean (SD)	27.0 (8.2)

Feasibility of in-home digital treatment for cognitive deficits: user experience

Of 21 MS participants enrolled (mean [SD] SDMT z-score: -0.21 [1.16]), 18 completed and returned for their 4-week visit. Reasons for non-adherence included logistical (n=1), vertigo induced by the game, (n=1), and physical discomfort due to prolonged use of the tablet (n=1). ~~These~~ The 18 whom completed the study played an average of 19.7 days (median [SD]: 20.5 [8.4]) per month. Overall, 78% of these 18 participants completed ≥ 75% of prescribed days, i.e. at least 15 days (**Figure 1**), and 50% (n=9) completed all 20 days or more.

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Figure 1. Participant adherence to game protocol.

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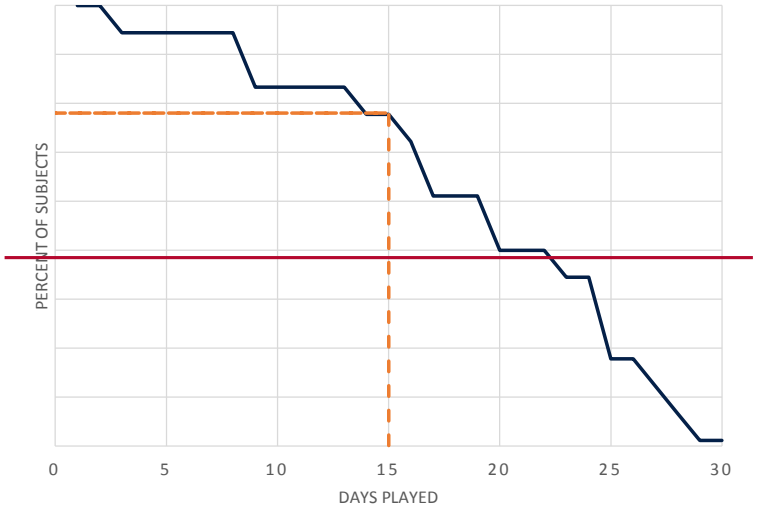

Predictors of persistence with the training sessions

Lower SDMT scores at baseline were associated with greater number of days played over the 4 weeks ($p = 0.003$, $R^2 = 0.44$, **Supplementary Figure 1**; after adjusting for employment, a possible proxy for free time, partial R^2 for SDMT = 0.30), suggesting an association between cognitive deficits and motivation to complete the sessions. In fact, lower scores across the other BICAMS cognitive tests (BVMT, CVLTII, $p<0.001$ for each) as well as higher anxiety scores (HADS, $p=0.015$) were also associated with greater number of days played.

Changes in cognitive scores after 4 weeks of digital treatment

Over the 4-week period, scores improved significantly on our primary outcome, the SDMT (paired t-test, $p=0.003$, $N=18$) (**Figure 2)**. In fact, the mean increase of 3.6 points was just shy of the 4-point clinically meaningful threshold established for trials assessing cognition in MS.[27, 7] ~~Eight participants (44%) did meet this threshold for improvement.~~

Scores also improved in 2/5 of the computer-based tests – specifically Match, which measures processing speed, and Cogstate DET, which measures psychomotor function – ($p=0.006$ for each) (**Table 2**), showing encouraging consistency across tests of processing speed.

Figure 2. Comparison of baseline and 1-month SDMT scores in 18 participants who completed the study (left-tailed paired t-test, p = 0.003).

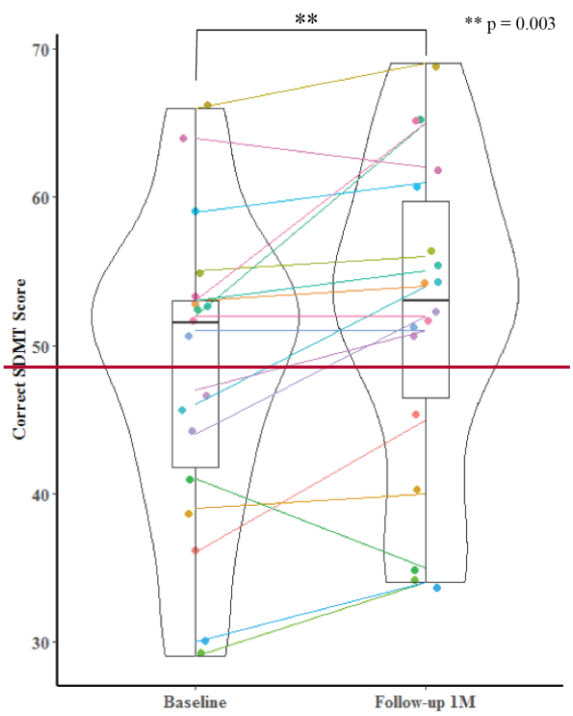

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Table 2. Comparison of cognitive measures before and after 4 weeks of use of ~~a digital therapeutic tool,~~ the Akili Interactive ~~Evo~~Project: EVO™ investigational digital treatment, in adults with MS.

Test	Domain	Pre, mean (sd)	Post, mean (sd)	N	p
BICAMS					
SDMT	Processing speed	48.3 (10.4)	51.9 (10.8)	18	**0.003**
CVLT-II	Verbal memory	54.8 (13.3)	55.3 (12.0)	19	0.385
BVMT-R	Visual memory	27.5 (8.5)	27.6 (6.9)	19	0.465

COMPUTERIZED					
Cogstate					
DET	Psychomotor function	2.6 (0.09)	2.5 (0.06)	14	**0.006**
IDN	Visual attention	2.7 (0.07)	2.7 (0.08)	14	0.755
OCL	Visual memory, attention	0.97 (0.17)	1.01 (0.14)	14	0.147
ONB	Working memory, attention	2.88 (0.09)	2.86 (0.10)	14	0.082
Match	Processing speed	50.9 (7.1)	53.1 (8.0)	16	**0.006**

Predictors of improvement in the SDMT

When we evaluated the contribution of baseline clinical and demographic factors to SDMT improvement over the pilot study duration, three variables were identified: gender (male), employment (not employed) and anxiety category (borderline/abnormal) **(Supplementary Figure 2).**

DISCUSSION

In the current feasibility study, we report high enthusiasm for a videogame-like digital treatment for cognition, in a cohort of older adults with MS with a high baseline level of function with 86% retention after 4 weeks, and in these 18, 78% adhered to the treatment. These adherence rates for self-managed computerized cognitive rehabilitation at home are consistent with previous reports.[28] Interestingly, while we did not specifically enroll patients with specific levels of CI, ~~anxiety and~~both cognitive deficits and anxiety at baseline were associated with greater use of the

treatment over the course of the study, indicating feasibility of such an intervention in a group with mild to moderate impairments. Further, we confirmed that improvements were consistent across several tests of processing speed, and could be detected during tests that can be self-administered at home. Finally, we also identified specific features, such as pronounced vertigo, which might preclude use of video games as a digital therapeutic, and form a basis for exclusion from participation in larger trials.

Individuals with MS have demonstrated enthusiasm for using digital technologies to: (1) access information regarding MS, (2) pursue routine and rehabilitation care (e.g. through telemedicine-based web programs), (3) monitor their MS (e.g. through smartphone or activity trackers) and importantly (4) participate in research. Additionally, MS patients have enthusiastically embraced home-based care strategies.[29] Here, we extend these observations to report adherence to an in-home, videogame-based tool designed to improve processing speed. Recently, a videogame approach was deployed through ~~a~~ 12-weeks using the adaptive PositScience BrainHQ® tool in 135 patients with MS and SDMT z-scores of -1 or less. Training was reported to result in a significant cognitive composite score improvement in the 74 participants randomized to the PositScience BrainHQ® tool vs. in the 61 patients playing non-specific video games.[15] There was no improvement in individual cognitive tests, but~~but~~ SDMT was not included as an outcome measure. The tool tested in the current study is also unsupervised, but much less time-intensive (25 minutes daily for 4 weeks, vs. one hour daily for 12 weeks), suggesting possible advantages in terms of overall burden to patients, and hence adherence, as demonstrated by adherence reported in the respective studies. Additionally, we found improvements in processing speed using several different tests, while we detected no change in other domains of cognition, suggesting a specific

and fairly robust effect. The PositScience BrainHQ® exercises do not employ a multi-task interference paradigm, which could contribute to differences in effects. ~~Cognitive reserve appears to protect against decline in MS,[29] and in the current study we found that education – which is an accepted proxy for cognitive reserve [30] – was a predictor of SDMT improvement.~~

Although the SDMT is more psychometrically sound than the PASAT,[30] replacing the PASAT with the SDMT in the MSFC has not always been supported by the data.[31] The current feasibility study is also limited by small sample size, and lack of a control group to confirm that the improvements in SDMT could not simply be explained by learning effects or placebo. However other similar studies with intervention control patient groups have demonstrated improvement on the SDMT for the treatment group.[28] From prior investigations, the current mean increase (3.6 points) almost meets the clinically meaningful threshold established for trials assessing cognition in MS (4 points[27]), and is substantially greater than anticipated learning effects in a similar time period.[32] A larger blinded, randomized and controlled study is underway.

CONCLUSIONS

In summary, the current feasibility study lends further support to the role that videogame-based digital treatments may play for ameliorating CI in MS,[15] and its potential advantages (tablet-based, game-based, short and convenient session duration (25 minutes) over a fairly short timeframe [4 weeks]) support the expansion of the study to a larger, controlled trial evaluating both efficacy and sustained effects. The anticipated impact of a home-based training program to ameliorate CI in MS is large, given the scarcity of rehabilitation programs, and the improved accessibility, cost effectiveness, and rapid deployment that are afforded by remote trials.

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Akili Interactive Labs provided the Project: EVO~~vo~~™ ~~tool~~ investigational digital treatment for use during the study but did not contribute to the design or execution of the study or fund the journal's article processing charges.~~.~~

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Disclosures

RB receives research support from the National Multiple Sclerosis Society, the Hilton Foundation, and the California Initiative to Advance Precision Medicine. RB has also received personal compensation for consulting from Novartis, Sanofi Genzyme, and Roche Genentech.

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AS is a full-time employee of Cogstate.

TA is a full-time employee of Akili Interactive Labs.

DL has participated in speaker bureau for Bayer, Merck, Almirall, Execemed, TEVA, Roche, Novartis, Biogen, Sanofi; has had consultancy from Novartis, Bayer, Merck, Biogen, TEVA,

Sanofi; has had research grants from Bayer, Merck, Novartis, Biogen. All are paid into DL's institution.

KP reports no disclosures.

AG is co-founder, shareholder, BOD member, and advisor for Akili Interactive Labs, a company that produces therapeutic video games. AG is the inventor on~~has~~ a patent to interference processing on which the~~for a~~ game-based cognitive intervention ~~on which~~of the ~~app~~ (Project: EVO™) investigational digital treatment that was used in this study was based.

AF reports research support from the MS society of Canada and the Progressive MS Alliance; speaker's honoraria from Sanofi-Genzyme, Merck-Serono, Novartis, Biogen and Teva; and consultancy from Akili Interactive Labs.

JA reports no disclosures.

~~The authors report no conflicts of interest with respect to this manuscript.~~

Compliance with ethics guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the UCSF Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Benedict RH, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC neurology. 2012;12:55. doi:10.1186/1471-2377-12-55.
2. Potagas C, Giogkaraki E, Koutsis G, Mandellos D, Tsirempolou E, Sfagos C et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. Journal of the neurological sciences. 2008;267(1-2):100-6. doi:10.1016/j.jns.2007.10.002.
3. Benedict RH, Munschauer F, Linn R, Miller C, Murphy E, Foley F et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. Mult Scler. 2003;9(1):95-101.
4. Benedict R, Fischer J, Archibald C, Arnett P, Beatty W, Bobholz J et al. Minimal Neuropsychological Assessment of MS Patients: A Consensus Approach. Clin Neuropsychol. 2002;16(3):381-97.
5. Shawaryn MA, Schiaffino KM, LaRocca NG, Johnston MV. Determinants of health-related quality of life in multiple sderosis: the role of illness intrusiveness. Mult Scler. 2002;8(4):310-8.
6. Costa SL, Genova HM, DeLuca J, Chiaravalloti ND. Information processing speed in multiple sclerosis: Past, present, and future. Mult Scler. 2017;23(6):772-89. doi:10.1177/1352458516645869.
7. Benedict RH, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R et al. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler. 2017;23(5):721-33. doi:10.1177/1352458517690821.
8. Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler. 2012;18(6):891-8. doi:10.1177/1352458511431076.
9. Van Schependom J, D'Hooghe M B, Cleynhens K, D'Hooge M, Haelewyck MC, De Keyser J et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. Eur J Neurol. 2014;21(9):1219-25, e71-2. doi:10.1111/ene.12463.
10. Rosti-Otajarvi EM, Hamalainen PI. Neuropsychological rehabilitation for multiple sclerosis. The Cochrane database of systematic reviews. 2014;2:CD009131. doi:10.1002/14651858.CD009131.pub3.
11. Lincoln NB, das Nair R, Bradshaw L, Constantinescu CS, Drummond AE, Erven A et al. Cognitive Rehabilitation for Attention and Memory in people with Multiple Sclerosis: study protocol for a randomised controlled trial (CRAMMS). Trials. 2015;16:556. doi:10.1186/s13063-015-1016-3.
12. Chiaravalloti ND, Moore NB, Nikelshpur OM, DeLuca J. An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. Neurology. 2013;81(24):2066-72. doi:10.1212/01.wnl.0000437295.97946.a8.
13. Mattioli F, Bellomi F, Stampatori C, Capra R, Miniussi C. Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. Multiple sclerosis. 2016;22(2):222-30. doi:10.1177/1352458515587597.
14. Ford-Johnson L, DeLuca J, Zhang J, Elovic E, Lengenfelder J, Chiaravalloti ND. Cognitive effects of modafinil in patients with multiple sclerosis: A clinical trial. Rehabil Psychol. 2016;61(1):82-91. doi:10.1037/a0039919.

15. Charvet LE, Yang J, Shaw MT, Sherman K, Haider L, Xu J et al. Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial. PloS one. 2017;12(5):e0177177. doi:10.1371/journal.pone.0177177.
16. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292-302. doi:10.1002/ana.22366.
17. Kappos L, D'Souza M, Lechner-Scott J, Lienert C. On the origin of Neurostatus. Multiple sclerosis and related disorders. 2015;4(3):182-5. doi:10.1016/j.msard.2015.04.001.
18. Cohen JA, Reingold SC, Polman CH, Wolinsky JS, 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(5):467-76. doi:10.1016/S1474-4422(12)70059-5.
19. Smith A. Symbol Digit Modalities Test. Los Angeles: Western Psychological Services; 1982.
20. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test–II, Second Edition. San Antonio, TX: The Psychological Corporation; 2000.
21. Benedict RHB. Brief visuospatial memory test - revised: Professional manual. Lutz, FL: Psychological Assessment Resources, Inc.; 1997.
22. Snaith RP. The Hospital Anxiety And Depression Scale. Health and quality of life outcomes. 2003;1:29. doi:10.1186/1477-7525-1-29.
23. Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. Mult Scler. 2009;15(12):1518-24. doi:10.1177/1352458509347150.
24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
25. Fredrickson J, Maruff P, Woodward M, Moore L, Fredrickson A, Sach J et al. Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. Neuroepidemiology. 2010;34(2):65-75. doi:10.1159/000264823.
26. Possin KL, Moskowitz T, Erlhoff SJ, Rogers KM, Johnson ET, Steele NZR et al. The Brain Health Assessment for Detecting and Diagnosing Neurocognitive Disorders. J Am Geriatr Soc. 2018;66(1):150-6. doi:10.1111/jgs.15208.
27. Benedict RH, Morrow S, Rodgers J, Hojnacki D, Bucello MA, Zivadinov R et al. Characterizing cognitive function during relapse in multiple sclerosis. Mult Scler. 2014;20(13):1745-52. doi:10.1177/1352458514533229.
28. Campbell J, Langdon D, Cercignani M, 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. doi:10.1155/2016/4292585.
29. Hoang P, Schoene D, Gandevia S, Smith S, Lord SR. Effects of a home-based step training programme on balance, stepping, cognition and functional performance in people with multiple sclerosis - a randomized controlled trial. Multiple sclerosis. 2016;22(1):94-103. doi:10.1177/1352458515579442.
30. Sonder JM, Burggraaff J, Knol DL, Polman CH, Uitdehaag BM. Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. Mult Scler. 2014;20(4):481-8. doi:10.1177/1352458513501570.

31. Brochet B, Deloire MS, Bonnet M, Salort-Campana E, Ouallet JC, Petry KG et al. Should SDMT substitute for PASAT in MSFC? A 5-year longitudinal study. Mult Scler. 2008;14(9):1242-9. doi:10.1177/1352458508094398.
32. Benedict RH, Duquin JA, Jurgensen S, Rudick RA, Feitcher J, Munschauer FE 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(7):940-6. doi:10.1177/1352458508090923.

Figure 1

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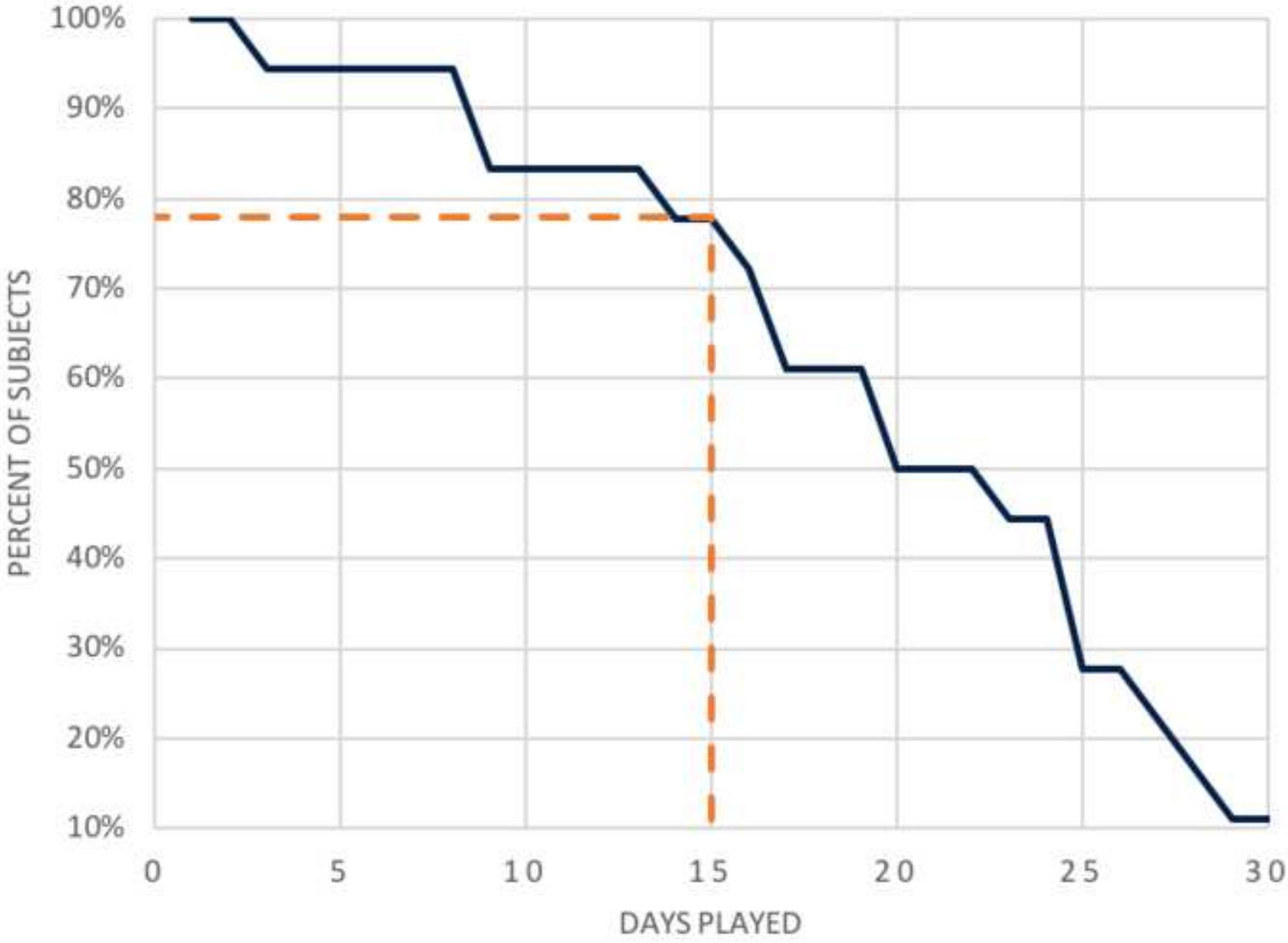

Figure 2

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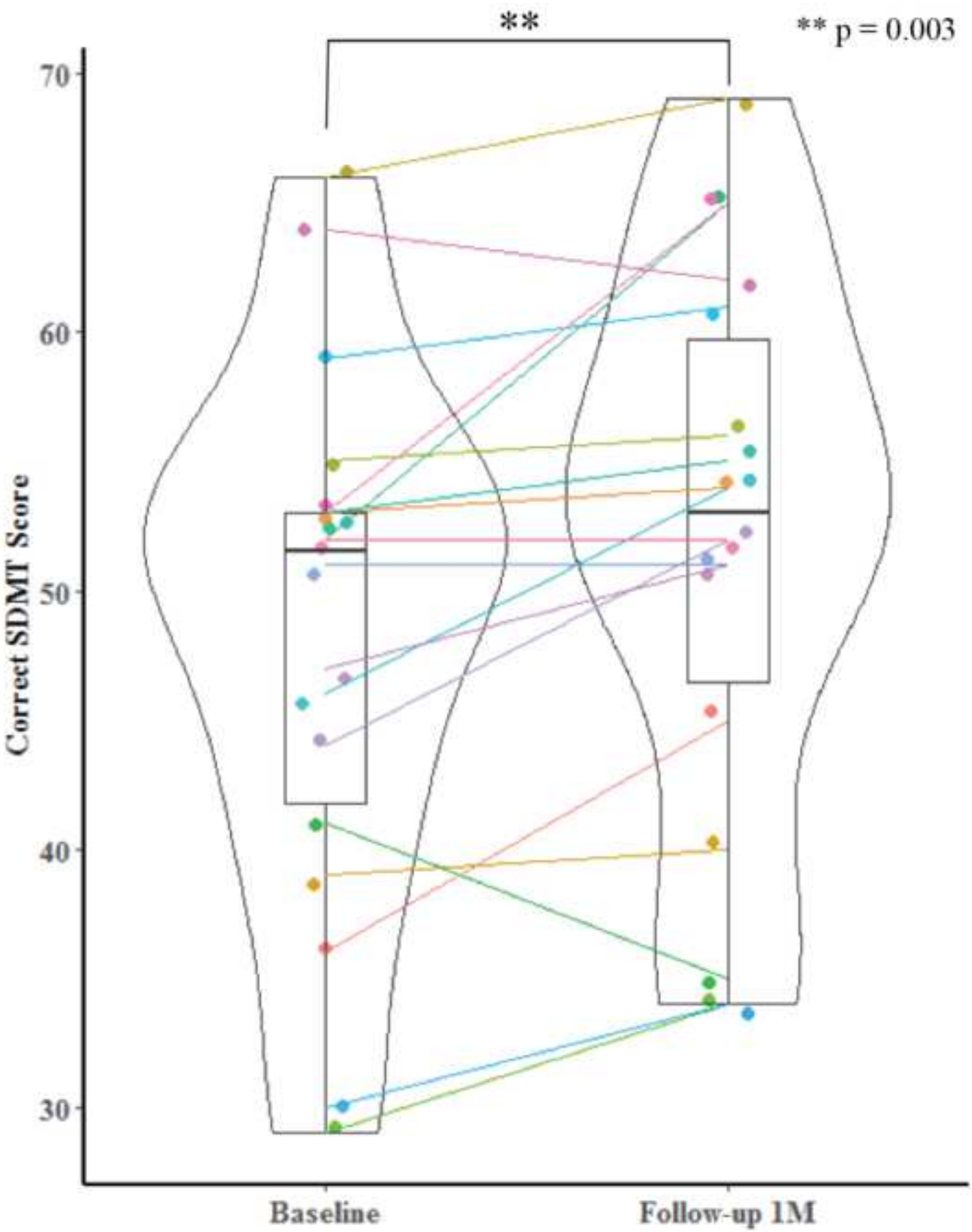

DigCog Feasibility Paper – Summary Slide 11.07.18

Why carry out this study?

- Very brief background leading to the study, including for example disease population, economic burden and/or unmet need. (1–2 bullet points)
    - Almost half of patients living with multiple sclerosis (MS) develop cognitive impairment (CI). Worsening of CI is predictive of loss of employment, and loss of quality of life (QOL), affecting function in all spheres of activities of daily living.
    - Accessible and self-administered tools are urgently needed to screen for, monitor and treat the cognitive impairment (CI) experienced by patients with MS. Game-based technologies, especially when deployed remotely, could play a role in bridging this unmet need.

- What did the study ask?/What was the hypothesis of the study? (1 bullet point) What was learned from the study?
    - Here, we present a pilot study evaluating the feasibility of treating patients with MS with a tablet-based, videogame-like digital treatment.

- What were the study outcomes/conclusions? (data) (1 bullet point)
    - 18 of 21 participants completed the 4-week study, and among these completers, 78% completed at least 75% prescribed sessions.
    - Scores of processing speed improved significantly, including the Symbol Digit Modalities Test (SDMT), with a mean increase of 3.6 points ($p=0.003$).

- What has been learned from the study? This can be any outcome even if it contradicts the initial study hypothesis. If the findings were negative, neutral or purely confirmatory, how might this affect research and/or treatment in future? (1–2 bullet points)
    - Deploying an in-home digital tool to improve processing speed in MS is feasible, and shows preliminary efficacy. A larger, randomized controlled clinical trial is ongoing.

Authorship and Disclosure Form

Manuscript ID number (if known):

Article title (first few words): A videogame-based digital therapeutic to improve processing speed in people with multiple sclerosis: A feasibility study.

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- I/we have drafted the work or revised it critically for important intellectual content; AND
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All persons who have made substantial contributions to the work reported in the manuscript (e.g., data collection, data analysis, or writing or editorial assistance) but who do not fulfil the authorship criteria must be named with their specific contributions in the Acknowledgments section. All persons named must give the authors their written permission to be named in the manuscript.

I/we have had full access to all the data in the study (if applicable) and thereby accept full responsibility for the integrity of the data and the accuracy of the data analysis.

By signing below, I, on behalf of all named authors, assert that there are no undisclosed conflicts of interest (both personal and institutional) regarding specific financial interests that are relevant to the work conducted or reported in this manuscript that have not been disclosed within this manuscript.

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