Impact of physical activity on cognitive outcomes in youth with pediatric-onset multiple sclerosis

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Protocol Title:	Impact of physical activity on cognitive outcomes in youth with pediatric-onset multiple sclerosis
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Population:	24 subjects aged ≤ 25 years with a confirmed diagnosis of Pediatric-Onset Multiple Sclerosis (POMS)
Number of Sites:	UT Houston
Study Duration:	1 year
Subject Duration:	6 months of intervention, 6 months follow-up

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General Information

Pediatric Onset Multiple sclerosis (POMS) is associated with a higher disease burden compared to adults with frequent relapses early in disease[1], a higher load of T2 lesions on magnetic resonance imaging (MRI)[2] and a more prevalent risk of motor and cognitive disability by early adulthood. Although disease modifying therapies (DMT) remain the mainstay to long term management of POMS, the identification and control of environmental contributing factors has a significant impact on disease course. A sedentary lifestyle and obesity in childhood can lead to an increased risk for POMS[3] and lower physical activity is associated with a higher disease burden in adolescents with MS[4]. Furthermore, youth with MS self-report lower levels of physical activity compared to healthy controls[5]. They also present higher rates of fatigue and depression symptoms[6], cognitive impairment[7], as well as overall reduced health-related quality of life compared to their healthy peers[8]. Exercise has been proven the single most effective non-pharmacological approach to manage disabilities and improve quality of life in adults with MS[9-11]. Such beneficial effects are equally probable in children with MS but are only just emerging and their maintenance across a lifespan remains difficult in this age group.

Background Information

A current challenge to the management of patients with MS is not merely an early diagnosis or the choice of an appropriate pharmacotherapy, but increasingly, it involves the identification of potentially disease-modifying contributors. A growing number of environmental exposures have been outlined as risk factors in both disease onset and course. Among them, increased Body Mass Index (BMI) and a sedentary lifestyle have been associated with an increased disease susceptibility (odds ratio of 1.17, p-value 0.01)[3]. Children with MS reporting lower levels of physical activity have larger T2 lesion volumes on brain MRI and higher annualized relapse rates compared to those participating in strenuous physical activity[4]. Often associated with physical activity levels, nearly three-quarters of adolescents and young adults with MS have fatigue, depression and cognitive impairment[6,12]. More than 60% report a level of fatigue that interferes in their

activities of daily living and a positive correlation is found between fatigue scores and depression in this population[6]. These aspects of POMS can have a profound impact on their educational achievements as well as socio-economic and professional integration in future adult life. According to previous reports, 30 to 50% of children with MS have neuropsychological results that are below the norm average in attention, information processing speed, language and working memory[12-13]. Increasing physical activity in healthy children has resulted in improvements in cognition, academic performance and psychosocial function[14-15]. Such benefits have also been encountered in those with a chronic illness[16]. In children with MS, physical activity was negatively correlated with fatigue and depression[4,17] but such an association has only been established in cross-sectional studies.

While the benefits of physical activity are becoming well documented, current challenges in practice are its implementation in the management of MS and sustainability in the long term. This is particularly trying in contemporary children, adolescents and young adults. Barriers might be a lack of education on the role of exercise in health promotion in both parents and children, a lack of accessibility to physical activities, and the fundamental changes in society that have had the effect of reducing demand for physical activity. Changing behavior towards exercise in youth with MS thus requires educational strategies and adaptable programs that could access a large number of subjects of different fitness levels, physical ability levels and socioeconomic status. Physical activity counseling through social media may provide motivational benefits and provide a tool for long-term adherence monitoring in children and young adults. With fewer mobility means (such as driving) and less economic independence compared to adults, this age group is unlikely to benefit from gym sessions or other in-class exercises, making home programs a more sustainable option. Among activities that most adolescents and young adults invest time in, video games either through PCs or various consoles are a popular choice. Virtual Reality (VR) active games provides a powerful interface to boost physical activity in this age group. This practical potential has been demonstrated in children with obesity[18], diabetes[19] and developmental delay[20]. A Wii-fit balance-based video game was seen to improve static and performance-related balance in children with mild cerebral palsy[21]. A recent systematic review found that active video games among children could increase their levels of physical activity and energy expenditure[22]. Such a strategy has not been performed in youth with multiple sclerosis but by selecting a set of active game types, has the propensity to influence motor performance through balance, strength and endurance parameters. It could also impact fatigue, depression and cognitive impairment.

We aim to conduct a single-center randomized controlled trial to measure the impact of physical activity through virtual reality video games on the motor and cognitive performance of youth with MS. Through such a home-exercise program coupled with patient online behavior counseling, we hypothesize that we can significantly impact subjective and objective measures of disease disability in this MS age population.

Objectives

Primary objective: to assess the impact of a virtual reality video (VR) game exercise program on **objective cognitive assessments in youth with MS** (measures outlined below). The **null hypothesis** for this study is that there is no difference in the **Brief Cognitive Assessment for MS** in cognitive disability of youth with MS between those enrolled in a 6-month VR active video game program and those with routine follow-up care. The alternative hypothesis is that there is a difference in measures of cognitive disability between the two groups (two-sided hypothesis).

Secondary objectives:

- To determine the impact of VR physical activity on subjective measures of cognitive, physical and psychosocial disability in youth with MS
- To determine the impact of VR physical activity on the 6-Minute Walk Test (6MWT).

- To determine the number of clinical relapses and new T2 MRI lesions (brain)
- To determine the **safety** of implementing a VR active video game program at home
- To evaluate the effect of VR exercise programs on overall behavior towards physical activity and health promotion in youth through self-report questionnaires

Study Design

- **Single-center, single blinded, randomized controlled trial** comparing a 6-month VR active video game intervention with standard management of physical activity in youth with MS.
- Each participant will be randomly allocated to either the intervention group or the control group for a **period of 6-months** with pre- and post- assessments performed at onset, 3 months, 6 months and 12 months follow-up.
- The study will be conducted over one year with 6 months of intervention. Each group will include 12 subjects (**total subjects = 24**).
- The Microsoft VR active game program will consist of 3 weekly sessions of 45 minutes each combining 3 different types of exercise (cardiovascular and strength with 'Box VR', flexibility with 'Beat Saber', coordination with 'The Climb').
- To assess the impact of the VR exercise program, a series of subjective and objective assessments will be performed prior to onset, at 3 months, upon completion at 6 months and at 12 months follow-up. These assessments are detailed in the section 'Study procedures' below.
- **Assessment of safety** will be conducted throughout the intervention and will consist of self-reported incidents that occur during the exercise sessions, including falls or physical injuries. These events will be recorded at 1 month, 3 months and 6 months from onset by the investigators.
- **Assessment of adherence** to the program will be documented throughout the study via anonymized exercise logs provided by Microsoft that will monitor participation and overall performance for each game. Microsoft will also provide customer service for any technical difficulties with the VR headsets provided.
- **Personal sessions** with each participant in the intervention group will be conducted via phone calls to educate them on the importance of exercise and assess for any difficulties to adhere to sessions. They will take place at 1 month, 3 months and 6 months. Furthermore, a survey questionnaire will be given to all participants enrolled in the intervention group at the 6-month follow-up time to determine the degree of incorporation of physical activity into their daily life following completion of the study.

Study Population

- Inclusion criteria: (1) **age between 15-25 years**, (2) **confirmed diagnoses of Pediatric-Onset MS (<18 years)** according to the 2017 revised McDonald criteria (relapsing-remitting), (3) **Expanded Disability Status Scale (EDSS) ≤ 5.0**, (4) **relapse free for the past 30 days**, (5) **no contraindications to physical activity**, including pregnancy (6) no history of visual provoked seizures and (7) participant and parent (if between 15 and 18 years of age) **written informed consent**.
- The participants will be recruited through the neurology clinic in Houston using phone, email or postal communications. People who are interested in taking part will be contacted by the research team via phone or email and explained the study in detail. If the selection criteria are met, informed consent forms and participant information leaflets will be sent via post or email, or obtained during a routine clinic visit.
- Participants will be **randomly allocated** in **blocks** to either the intervention or control group, and the allocation group will be **concealed from the study personnel** that are analyzing the data.

Study Procedures

- Subjects in the intervention group will receive a Samsung Windows Mixed Reality headset with motion controllers that links to their PC/laptop. They will be given 3 different VR video games (Box VR, Beat Saber and The Climb) at onset. They will be instructed to play a minimum of 3 sessions per week, one session on each game, for the first 3 months. They will have the possibility of dropping one game for the remaining 3 months but maintaining a minimum of 3 sessions per week. Each session will last 45 minutes. They may play more than 3 sessions per week but will be required to document additional time.
- **Exercise logs** will be provided to document weekly sessions for monitoring adherence. Participants in both groups will be asked to document any sport activities performed during the study period, with an estimate of duration per week and type of activity, to account for physical activity done outside of the active intervention. This will be recorded during the 6-month intervention period.
- The intervention group will also receive two **education discussion sessions** on the benefits of exercise for people with MS. The investigator MS specialists will conduct these sessions either by phone or at the time of a clinic visit and will also discuss difficulties encountered by participants with adherence.
- A neuropsychologist or MS specialist will perform an **objective cognitive assessment** at the time of enrollment, at 6 months and at 12 months follow-up, consisting of the **Brief International Cognitive Assessment for MS (BICAMS)**, which includes three subtests:
    - **Symbol Digit Modalities Test** (SDMT), a measure of sustained attention, working memory and information processing speed
    - **California Verbal Learning test – II** (CVLT-II), a measure of verbal memory (immediate recall) including the first 5 recall trials
    - **Brief Visuospatial Memory Test** (BVMT) - Revised, a measure of visuo-spatial learning and delayed recall, using the first 3 recall trials

  The battery takes 15 min to complete, requires no specialist equipment and no specialist expertise in cognitive assessment.
- **Subjective assessments** will be distributed to all participants (exercise intervention group and control group) in weeks 1 and 12 of study enrollment, and at 6-month and 12-month follow-up. The time allocated to complete these assessments is estimated to be 15-20 minutes for each visit. These will include:
    - **Multiple Sclerosis Impact Scale-29** (MSIS-29): 29-item self-report measuring the physical and psychological impact of MS from the patient's perspective during the previous 2 weeks.
    - **Modified Fatigue Impact Scale** (MFIS): 21-item self-report measuring the impact of fatigue on physical, cognitive and psychosocial aspects of MS during the previous 4 weeks.
    - **Hospital Anxiety and Depression Scale** (HADS): 14-item self-report measuring the degree of anxiety and depression in participants during the previous week.
- An MS specialist will perform a pre- and post- **objective motor assessment** during a routine clinic visit at the time of study enrollment, at 6 months and 12 months follow-up. This assessment will include:
    - **Six Minute Walk Test** (6MWT): the participant is instructed to walk for six minutes as quickly and safely as possible and the distance covered will be recorded. This test has demonstrated excellent test-retest reliability and validity among people with mild to moderate MS[23].
- Study personnel will collect assessments during routine clinic visits using allocated forms that will be identifiable by date and subject study code number. An investigator blinded to group allocation will subsequently analyze the data.

Budget and financing

- This study has funding from Microsoft and from a private sponsor.
- Cost of VR headset and motion controllers from Microsoft : model Samsung HMD Odyssey+ Windows ($199.00 per unit, total of 15 units for the intervention group = $2'761.12)
- The Windows Mixed Reality headsets are compatible with a PC that will run Windows 10 Fall Creators Update, requiring no further participant equipment.
- Cost of the 3 VR video games: Box VR $19.99, Beat Saber $19.99, The Climb $9.99 (downloaded from STEAM stores) – total of $49.97 per subject, total of $600 for the intervention group.
- Additional funding is also available with assistance from Microsoft for software to support minimum system requirements for the selected VR exercise games.
- The subjective assessments will be mailed to the participants or given when seen in clinic. Study staff will perform the 6MWT at the time of a routine clinic visit and will require no additional costs.
- The three cognitive assessments per subject will be carried out by a qualified neuropsychologist or neurologist and will be performed at the time of a routine clinic visit.

Data and Safety Monitoring

- During the course of study participation, subjects might experience an adverse event related to the physical activity or to their underlying MS. These events might include falls, musculoskeletal injuries, neurological symptoms suggestive of a clinical relapse, or any other physical or psychological cause of distress. These events will be documented by participant self-reports and contacting study personnel. They will be graded from 1 to 3 according to their degree of severity with 1 = mild, no interference with daily activities, 2 = moderate, some interference with daily activities and 3 = severe, significant interference with daily activities and requiring medical intervention.
- The research team will perform a **periodic review of adverse events** recorded once every 2 months as well as an assessment of adherence to the exercise programs and any other concerns raised by the research team or the participants.
- In the event of a clinical relapse or worsening of a participant's neurological symptoms, the research team will promptly inform the MS specialist in charge of that participant's care. Subject's participation in the intervention group will cease.

Statistics

- Statistical analysis will be performed using the software program **Stata version 15**.
- Descriptive numerical or graphical summaries will be used for demographic and clinical characteristics of the sample population at baseline. Independent samples t-tests and chi-square tests will be done to assess differences between intervention and control groups on pre-trial and post-trial assessments. Only participants who completed the 6-month exercise program will be included in the analysis of the intervention group but missing data will be noted. Paired sample t-tests and chi-square tests will be conducted to determine differences in pre-trial and post-trial assessments within each group. If data reveals a skewed distribution, Kruskall Wallis tests will be used for continuous variables. All tests will be conducted using an alpha = 0.05 level of statistical significance.
- Qualitative analysis will be performed through a survey questionnaire collected at the time of the 6-month follow-up, to determine participants' experience and longer term perspectives with regards to the integration of physical activity in the management of their disease.
- The selection of subjects to be included in the analyses will comprise all of those randomized to the control group and all of those randomized to the intervention group who completed the 12-week

exercise program. Dropouts at all stages (enrollment, randomization, intervention, 6-month follow-up) will be recorded.

Ethics

- IRB approval will be sought from CPHS prior to initiation of this study.
- Prior to enrollment in the study, all subjects and parents will be explained all parts of the research in a detailed manner by one of the study investigators. This will be conducted in a quiet environment either at the UT Clinic or by phone. Participants will be given the opportunity to ask questions during the consent process and at any time for the duration of the study. There will be no time limit to obtaining patient consent. Subjects will also be allowed to withdraw their consent at any time by contacting one of the study's investigators.

Data handling and record keeping

- Upon obtaining informed consent from each participant and all selection criteria met, study personnel will access demographic characteristics and all clinical data relevant to MS. This will include past and current disease-modifying therapies (DMTs), symptomatic treatments, EDSS score at enrollment time, burden of disease on MR imagery as well as quantitative information on the degree of physical activity at the time of enrollment.
- All information obtained during the study will be stored on a password-access database that can only be viewed and modified by the PI and co-investigators.
- All subjects enrolled in the study will be attributed a coded number and all personnel information will be de-identified upon collection. The subject codes will be maintained by study staff within the secure database only accessible by study staff and on UT Health-supported servers approved for storing PHI.

Quality control and assurance

- Staff investigators will conduct the subjective and objective assessments. All assessors will be blinded to subject group allocation and subjects will be instructed not to inform them of their allocated group.

Publication Plan

- Publication of research results will take place at the end of the 1-year study period. A study protocol will be published upon IRB approval and at the time of enrollment to inform research colleagues of the project.
- The overall results of the study will be returned to research subjects in a de-identified manner upon request.

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ATTACHMENTS

1. Schematic of Study Design
2. Study Schedule
3. Consent Documents (parent, assent and adult subject)
4. Data Acquisition Form