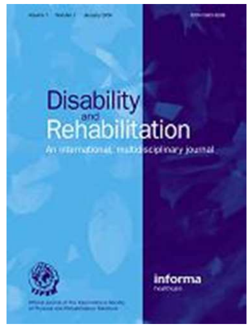


Randomized controlled trial of a web-based multi-modal therapy programme for executive functioning in children and adolescents with unilateral cerebral palsy

Journal:	*Disability and Rehabilitation*
Manuscript ID	TIDS-12-2015-063.R1
Manuscript Type:	Research Paper
Keywords:	Executive Functioning, Cerebral Palsy, Intervention, Randomised Control Trial, Children and Adolescents

IMPLICATIONS FOR REHABILITATION

1. A large RCT of the multi-modal web based training; Move It to Improve It (Mitii^{TM}) improves motor processing, visual perception, and physical capacity but does demonstrate statistically significant improvements or clinical significance in executive function in children with mild to moderate Unilateral Cerebral Palsy (UCP).
2. Mitii^{TM} training completed by an intervention group was highly variable with few children reaching the target dosage of 60 hours. Technical issues including server and internet connectively problems lead to disengagement with the program.
3. Web-based training delivered in the home has the potential to increase therapy dose and accessibility however Mitii^{TM} needs to be tailored to include tasks involving goal-setting, more complex problem solving using multi-dimensional strategies, mental flexibility, switching between two cognitively demanding tasks, and greater novelty in order to increase the cognitive component and challenge required to drive changes in EF.

Title: Randomized controlled trial of a web-based multi-modal therapy programme for executive functioning in children and adolescents with unilateral cerebral palsy

ABSTRACT

Purpose state: Determine the efficacy of Move-it-to-improve-it (Mitii™), a multi-modal web-based program, in improving Executive Function (EF) in children with unilateral cerebral palsy (UCP).

Method: Participants (n=102) were matched in pairs then randomised to: intervention (Mitii™ for 20 weeks; n=51; 26 males; mean age=11 years 8 months (SD=2y4m); Full Scale IQ=84.65 (SD=15.19); 28 left UCP; GMFCS-E&R (I=20, II=31) or waitlist control (n=50; 25 males; mean age=11y10m (SD=2y5m); Full Scale IQ=80.75 (SD=19.81); 20 left UCP; GMFCS-E&R (I=25, II=25). Mitii™ targeted working memory (WM), visual processing (VP), upper limb co-ordination and physical activity. EF capacity was assessed: attentional control (DSB; WISC-IV); cognitive flexibility (inhibition and number-letter sequencing DKEFS); goal setting (D-KEFs Tower Test); and information processing (WISC-IV Symbol Search and Coding). EF performance was assessed via parent report (BRIEF). Groups were compared at 20 weeks using linear regression (SPSS 21).

Results: There were no significant between group differences in attentional control (DSB; p=0.20;CI=-0.40,1.87); cognitive flexibility (Inhibition, p=0.34;CI=-0.73,2.11; number/letter sequencing, p=0.17; CI=-0.55,2.94); problem solving (Tower; p=0.28; CI=-0.61,2.09), information processing (Symbol; p=0.08; CI=-0.16, 2.75; Coding; p=0.07; CI=-0.12,2.52) or EF performance (*p*=0.13; CI=-10.04,1.38).

Conclusion: In a large RCT, Mitii ™ did not lead to significant improvements on measures of EF or parent ratings of EF performance in children with UCP.

Abstract word length: 200

Cerebral palsy (CP) is a neurodevelopmental condition beginning in early childhood and persisting throughout life[1]. It is non-progressive and impacts on the development of movement and posture, causing limitations in activity [1]. Cerebral Palsy is associated with a high prevalence of learning and cognitive difficulties which impact on day to day functioning[2]. Cerebral Palsy may include communication, cognitive, behaviour, perception and sensation impairments, as well as, epilepsy[3-9].

Executive functioning (EF) encompasses the skills necessary for goal directed behaviour to complete activities [9-13]. Functioning in everyday life requires EF to organise, plan, focus, attend to tasks, exercise self-control, and self-monitor[9-13]. The paediatric model by Anderson (2002) conceptualises EF as interrelated and interdependent processes which function together as a supervisory system[10]. The four distinct domains are; (i) attentional control which includes the capacity to selectively attend to specific stimuli; (ii) information processing which refers to the fluency, efficiency and speed of information processing; (iii) cognitive flexibility which refers to the ability to shift between response sets, learn from mistakes and divide attention; and (iv) goal setting which incorporates the ability to develop new initiative and concepts[10]. Various studies have demonstrated that children and adolescents with CP have EF impairments associated with damage to white matter tracts in the prefrontal and posterior brain regions[9]. A study of children with UCP found impairments in all domains of EF based on Anderson's (2002) model compared to children with typical development (CTD)[10-13].

Although approximately 50% children with CP having a moderate intellectual disability (ID) and approximately 25% having a severe ID[14], there is a paucity of research on interventions targeting cognitive abilities such as EF in UCP. There is a larger body of evidence for children related to EF with an acquired brain injury (ABI)[15-19], however, the study designs are single cases or small sample sizes [15]. Interventions showing promise in other populations include aerobic exercise, and computerised training for attention and working memory (both aspects of EF)[20,21]. Three studies in CTD have found that aerobic exercise improves EF immediately after a single bout but this was not sustained; suggesting that exercise alone may not be sufficient to improve EF[20,21]. Cogmed® is a computerised working memory intervention that improves working memory and poor attention in children with Attention Deficit Hyperactivity Disorder (ADHD), though generalizability and long term effectiveness are not clear[22]. A stepped wedge randomised trial design in children with very low birth weight found improvements in trained and non-trained working memory tasks following Cogmed®[17]. There was some generalisation to non-trained tasks, although retention effects were not assessed. Attentional control training in 4-6 year old CTD improves attentional control and performance on tests of intelligence following five days of training on computer based and stroop like tasks, however long term retention and generalizability were not examined[23]. Overall, the evidence for EF training is generally based on CTD populations and the evidence suggests that computerised training may be effective for improving working memory, though there is limited evidence for other domains of EF[20,21].

Move-it-to-Improve-It (Mitii™), a recently developed web-based multi-modal training intervention has demonstrated significant gains in visual perception, functional strength and endurance, and motor and processing skills in a pilot study of children aged 9-13 years with UCP (n=9)[24]. While the program was designed to train occupational performance and physical activity, some modules were designed to be cognitively challenging with increasingly reliance on attentional abilities. As such, Mitii™ may improve on EF. If EF can be improved in the context of an intervention targeting visuo-motor coordination and physical activity outcomes as well, this would enable cost-effective and efficient translation.

The aim of this paper is to examine the effects of Mitii™ on EF in children with UCP. This paper reports the EF results from an RCT of Mitii™. The effectiveness of Mitii on improving motor planning and physical activity outcomes in this cohort has been reported [25,26]. The primary hypothesis for the present study was that Mitii™ would improve capacity on tests of EF. A secondary hypothesis was that Mitii™ would improve parent ratings of EF performance in everyday life.

Methods

The efficacy of Mitii™ was tested in a matched-pairs randomised waitlist control RCT compared to standard care over 20 weeks between June 2012 and December 2014. Ethics approval was obtained from the relevant ethics committees. This study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12611001174976). Ethics approval was obtained from the Children's Health Service Human Research Ethics Committee at the Royal Children's Hospital Brisbane (HREC/11/QRCH/35), the Medical ethics committee at The University of Queensland (201100608) and the Cerebral Palsy Alliance's HREC (2013-04-01).

Participants

Children with UCP were recruited from Queensland and New South Wales. The inclusion criteria were (i) Gross Motor Function Classification Extended and Revised (GMFCS-E&R) I or II; Manual Abilities Classification scale (MACS) I, II, III; (ii) aged 8–18 years with sufficient cooperation and cognitive understanding to perform the tasks. Children were excluded if they had (i) received upper limb or lower-limb surgery in the previous 6 months; (ii) unstable epilepsy (i.e. frequent seizures not controlled by medication) or (iii) a respiratory, cardiovascular or other medical condition that would prevent them participating safely in the Mitii™ training [5].

Procedure

Participants were entered into the study and matched in pairs based on age (within 12 months), gender and MACS level. The participants were then randomised with the pairs to either the 20-week immediate intervention (Mitii™) or the waitlist control (standard care). The participants were randomised using a computer generated list of random numbers, which were placed into consecutively numbered opaque envelopes, which were opened by a staff member independent of the study personnel. Data was gathered in a clinic at The University of Queensland, Brisbane. Participants completed occupational therapy, physiotherapy, neuropsychology and MRI assessment at the assessment points. The full study protocol for the overall Mitii™ study has been published[5].

Intervention

Mitii™ is a web-based multimodal therapy program which is delivered in the home environment via a computer and webcam. Mitii™ consists of upper limb, cognitive, visual perceptual and physical activity training. The Mitii™ system detects and tracks body movements using a web camera that tracks green bands which are worn on the hands, knee or head. Neuropsychologists, occupational therapists and a physiotherapist developed individualised programs based on the child's baseline scores and the therapists selected from 14 training modules (e.g. gross motor, combined cognitive and visual perception, and upper limb activities). The training modules include approximately 60% visual perceptual, upper limb and cognitive games, and 40% physical activity games. The participants were encouraged to complete their Mitii™ program for 20-30 minutes, six days per week which would provide a potential dose of 60 hours over 20 weeks. Therapists updated programs weekly, increasing or decreasing difficulty (e.g. changing the task speed, accuracy, number of repetitions, cognitive difficulty) to maintain the program at an optimal level of challenge (i.e. 80% success rate). All participants were provided with green bands. If required, participants were provided with a web camera, laptop and internet access (via a sim card). Participants were contacted weekly via phone or email by the therapists to provide feedback and support. Parents/guardians completed a baseline questionnaire detailing family characteristics (e.g. marital status, family type, gross household income, and employment), and whether their child had any additional diagnoses (e.g. intellectual or learning disability, hearing or vision impairment, Attention Deficit Hyperactivity Disorder, and epilepsy). Socio-economic status (SEIFA) and Accessibility/Remoteness Level (ARIA) details were calculated using Australian postcodes of the participants. Details of standard care including physiotherapy, occupational therapy, psychological support, paediatrician, and medical visits or interventions were captured in a questionnaire at 20 weeks indicating whether the care was received and how often (dose).

Measures

1. *Intellectual ability*

Full Scale Intelligence Quotient (FSIQ) was calculated using the Wechsler Intelligence Scale for Children, Fourth Edition Short-Form (WISC-IV-SF)[27]. The WISC-IV-SF measures intellectual functioning across the four indices of Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), and Processing Speed (PSI). There are seven subtests in the short-form with Vocabulary and Similarities (VCI); Block Design and Matrix Reasoning (PRI); Digit Span (WMI); and Coding and Symbol Search (PSI). WISC-IV-SF is documented to have moderate to high levels of internal consistency in CTD (α=0.87-0.96) and is comparable to those documented in the full version of the WISC-IV[27,28].

2. *EF measures*

A neuropsychological test battery consisting of subtests from the WISC-IV[28] and Delis Kaplan EF System (D-KEFS)[29] was developed to measure the domains of EF based on the paediatric model by Anderson (2002)[10]. The model conceptualises EF into four domains: attentional control, information processing, cognitive flexibility, and goal setting[10]. The Behaviour Rating Inventory of Executive Function (BRIEF)[30] was administered to parents in order to assess EF in everyday life.

a. *Attentional control*

Attentional control was measured using the Color-word interference subtest from the D-KEFS, in particular the inhibition condition[29]. In the inhibition condition, children are required to complete a stroop like task where they are to name the colour of ink that colour words are printed in and restrain from reading the word. For example, say "Red" for the word "Blue" that is printed in red ink. Attentional control is primarily measured by the total time (seconds) taken to complete the inhibition condition with longer time and more errors suggesting poorer attentional control. The Color-word interference subtest has demonstrated excellent test-retest reliability in CTD (r=0.9)[29] but poor test-retest reliability in children with CP (r=0.69)[30].

b. *Cognitive flexibility*

Cognitive flexibility was measured using Digit span Backwards (DSB; WISC-IV)[28] and the Number-letter Switching (NLS) condition of the Trail Making Test (TMT; D-KEFS)[29]. For DSB, the child is required to recall a string of orally presented numbers in reverse order. The task increases in difficulty from a string of two digits to eight, with a correct score given for each string repeated correctly. The DSB measures the child's ability to temporarily store and manipulate information, with low scores indicating poorer cognitive flexibility. The NLS subtest requires a child to draw a line connecting numbers and letters in alternating numerical and alphabetical order (e.g. 1-A-2-B-3-C, etc). The total time taken (seconds) was used to measure cognitive flexibility, with longer time taken indicating poorer cognitive flexibility. Both DSB and NLS have demonstrated adequate test-retest reliabilities in CTD (DSB r=0.74; and NLS r=0.2-0.55)[27,29]. In the CP population, test-retest reliability was poor for DSB (r=0.62), but good for NLS (r=0.81)[30].

c. *Goal setting*

Goal setting was measured using the Tower Test from the D-KEFS[28]. For this task, children are required to build a target tower (as shown in a picture) by moving five different sized disks across three pegs. The children must follow two predetermined rules. Total achievement score and number of errors were used to measure goal setting ability, with low achievement scores and high errors indicating poorer planning, problem-solving, and goal setting. The D-KEFS Tower Test demonstrates poor test re-test reliability in CTD (r=0.51) [28] but good test-retest reliability in the CP population (r=0.74)[30].

d. *Information processing*

Information processing speed was assessed using the Coding and Symbol Search subtests from the WISC-IV. For Coding, children are required to copy simple geometric shapes that are paired with numbers using a key. For Symbol Search, children need to scan a group of five abstract symbols and indicate whether or not the target symbol appears in the group. Both tasks are timed, with total number of correct items completed in each two-minute time limit indicative of faster information processing abilities. Coding and Symbol Search both demonstrated good test-retest reliabilities in CTD (r=0.81 & r=0.80 respectively)[28]. Similarly, the test-retest reliabilities in children with CP were good (both r=0.85)[30].

e. *EF in everyday life*

The BRIEF is a parent rated questionnaire consisting of 85 items[31]. Parents must answer each statement about their child's EF in the last six-month period using a three-point scale. Two index scores were derived for analysis: Behavioural Regulation Index (BRI) and the Metacognition Index (MCI). BRI consists of the inhibit, shift, and emotional control subscales, whereas MCI consists of the working memory, initiate, planning and organization of materials, and monitoring subscales. A Global Executive Score (GEC) is also calculated by combining the BRI and MCI index scores. All raw scores are standardised using T-scores, with higher T-score indicating more clinically significant EF difficulties in everyday life. The BRIEF has been demonstrated to be an ecologically valid measure of EF in CTD[31]. In children with CP, the GEC has excellent test-retest reliability (r=0.90), and the BRI and MCI have demonstrated good test-retest reliability (both r=0.82)[30].

Statistical methods

Summary statistics are reported as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables. The association between treatment group and EF outcome at 20 weeks was investigated using least squares linear regression, with treatment group (standard care/ Mitii™) included as the main effect. Individuals were analysed in the group they were allocated to, regardless of the treatment they actually received. All assumptions for linear regression models were tested. Analyses were conducted using IBM SPSS version 22.00 (Statistical Package for the Social Sciences v22).

Results

The study recruitment, allocation, and follow-up are reported according to CONSORT guidelines. Two hundred and seventy individuals were screened, of whom 102 children eligible for participation were matched and randomised to Mitii™ (n=51) or waitlist control (n=51) (Figure 1). Based on sample size calculations the total number of participants was deemed sufficient to detect change in the primary occupational therapy outcome measure (i.e. 45 participants in each condition) [5]. Baseline demographic, social and clinical characteristics are presented in Table 1. Groups were similar at baseline. Prior to commencing one participant withdrew from the waitlist group (98% retention rate). Three participants withdrew from the intervention group due to family reasons and one due to medical reasons prior to post-intervention assessment (92% retention rate). Five participants withdrew from the waitlist group prior to the post-intervention assessment (88% retention rate).

Insert figure 1 and table 1 about here

Primary outcomes

Baseline and 20 week data for the intervention and control groups are presented in Table 2. There were no significant differences at 20 weeks in EF capacity for children who were allocated to the Mitii™ intervention group as compared to children in the control (waitlist) group. At 20 weeks, there were no significant differences between groups on all measures of EF performance; Digits span Backwards (p=0.20; CI= -0.40 to 1.87), Coding (p=0.07; CI= -0.12 to 2.52), Symbol Search (p=0.08; CI= -0.16 to 2.75), Trail Making Test (p=0.17; CI= -0.55 to 2.94), Inhibition (p=0.34; CI= -0.73 to 2.11), and Tower Test (p=0.28; CI = -0.61 to 2.09) using linear regression analysis, are presented in Table 3.

Similarly, no significant difference was observed between groups at 20 weeks for measures of EF performance as measured by the BRIEF: BRIEF GEC (p=0.13; CI = -10.04 to 1.38), BRIEF BRI (p=0.24; CI = --9.35 to 2.38), and BRIEF MI (p=0.07; CI = -10.82 to 0.51). The post-hoc per protocol analysis showed an effect of the Mitii intervention on Coding (B = 1.20, r = 0.36); Symbol Search (B = 1.29, r = 0.35); MCI (B = -5.15, r = 0.35); and GEC (B = -4.32, r = 0.31). This can be cautiously interpreted as perhaps indicating the maximum theoretical potential of the Mitii intervention of EF. No effect sizes were found over 0.36.

Participants in the Mitii™ intervention group completed an average total dose of 32.4 hours of Mitii™ intervention (ranging from 3.7–74.7 hours per participant) across an average of 78 logins, over the 20 weeks. One participant in the intervention group had seizures during the intervention period, though on neurological investigation this was thought to not be due to Mitii™, this data was included in the analysis.

Insert table 2 and 3 about here

Discussion

In this randomised controlled trial, twenty weeks of intensive multi-modal Mitii ™ therapy did not improve EF in children and adolescents with UCP. Our hypotheses were not supported in that there were no significant differences at 20 weeks in EF capacity or performance for children who were allocated to the Mitii ™ group as compared to children in the waitlist control group. This is in contrast to primary outcomes of the larger RCT, in which significant improvements in upper limb function, visual perception, and physical strength were found at 20 weeks following the Mitii™ intervention[25,26].

Mitii ™ was designed to enhance neuroplasticity by providing a multi-modal programme that is intensive, repetitive, and progressively challenging. As a multi-modal programme, a number of aspects of functioning are targeted including upper limb functioning, visual perceptual skills, physical strength, and to some degree cognition. However out of the 14 potential Mitii™ modules only Memory (i.e. memorise a sequence of images) and Balloon Mathematics (i.e. ability to complete mathematical calculations) specifically trained memory/cognition[5]. The implication is that the challenge in the cognitive component may not have been sufficient to drive changes in EF. The lack of effect on EF outcomes is consistent with the outcomes of this RCT broadly; in the sense that the improvements found were specific to the modules trained or specificity of the practice. For example, the significant outcomes of the Mitii™ group compared to the control group on upper limb functioning, visual perception, and manual dexterity were specific to the modules trained in Mitii™[25]. Overall this is also consistent with findings from other studies, in which skills practiced improve with online or web-based training, however generalisation to other skills or everyday functioning is not always evident[15,16,21,33].

Tailoring Mitii ™ to include tasks involving goal-setting, more complex problem solving using multi-dimensional strategies, mental flexibility, switching between two cognitively demanding tasks, and greater novelty may enable better targeting of EF. Having EF modules which focus on how EF is manifested in everyday life may lead to improved performance on EF ratings by parents. This would be more in line with restorative interventions implemented for those traumatic brain injuries (TBI) where the child is trained using exercises that focus on the deficient cognitive or EF ability[34] as seen in programs such as Cogmed®.

The majority of children in the current study had overall cognitive abilities (i.e. FSIQ) within the Low Average range and baseline EF scores were within the average to low average range compared to normative data. Parent reported EF performance was not in the clinically significant range. It is therefore possible that there was limited room for improvement in terms of EF performance as a result of the Mitii™ intervention as participants were already performing close to normative expectations and a ceiling effect may have occurred. Future studies evaluating the effectiveness of Mitii™ should include participants with more profound EF and cognitive impairments.

To our knowledge, this is the first randomised trial to test the effect of Mitii ™ on EF and the changes seen on other outcomes suggest that the sample size was sufficient[5]. Few participants met the proposed target dose of 60 hours, with the average dose being half of that proposed (32.4 hours). Interestingly however, increases in total intervention on the effectiveness of Mitii on generating meaningful change in measures of executive functioning is not supported. An apriori analysis on the data shows a non-significant correlation ($p < 0.05$, one-tailed test) between total training dosage and change scores (i.e. Time 2 minus Time 1 scores) for the intervention group on each of the measures of EF (r -0.07 to 0.15) with the exception of Symbol Search which may reflect the visual perception improvement seen in the James et al (2014)[25] study of the same cohort. Technical issues were also a factor in preventing some participants from reaching the maximal dose. Ongoing server issues and internet connectivity problems resulted in difficulties accessing the programme, leading to frustration and subsequent disengagement from sessions in some cases. Future Mitii™

programmes are being developed to address these issues. It should be noted that Mitii™ was not designed for children with limited standing ability so the generalizability of these results to other more severe cases of CP (GMFCS-E&R III-V) is limited.

Conclusion

In a large RCT, Mitii ™ did not lead to significant improvements on measures of EF or parent ratings of EF performance in children with UCP. Mitii ™ has demonstrated improvements in motor and processing skills, activities of daily living, and physical capacity, suggesting it can be an effective web based multimodal therapy for these functions. In its current form, Mitii™ does not seem to be effective in improving EF in children with mild to moderate UCP. It is recommended that modules specifically targeting EF be developed and tested increasing potential for specificity of practice.

Acknowledgments: The authors would like to thank all research and administrative staff involved in the project. Special thanks are also given to the participants and their families for their support and involvement in this study.

Declaration of interest statement: The authors report no declarations of interest. This study was funded by the following: Queensland Government Smart Futures Co-investment Fund, Financial Markets for Children (2011-210), Perpetual Foundation – The Aldred Charitable Endowment, Margaret Augusta Farrell, Williams H P Trust Fund, Love J S, and The Jessica and Wallace Hore Foundation (FR2012/0796) and the National Health and Medical Research Council of Australia: Research Fellowship (RNB, 1105038).

References

1. Rosenbaum P, Panteth N, Leviton A, Goldstein M, Bax M, Damiano D. A report: the definition and classification of cerebral palsy. Developmental Medicine & Child Neurology Supplement 2006;109:8-14.
2. Bottcher L, Flachs EM, Uldall P. Attentional and executive impairments in children with spastic cerebral palsy. Developmental Medicine & Child Neurology Supplement 2010;52:e42-7.
3. Brovedani P, Cioni G. Cognition. Cerebral - Cerebral Palsy. In press In press 2014.
4. Bottcher L. Children with Spastic Cerebral Palsy, Their Cognitive Functioning, and Social Participation: A Review. Child Neuropsychology 2010;16:209-228.
5. Boyd RN, Mitchell LE, James ST, Ziviani J, Sakzewski L, Smith A, Rose S, Cunnington R, Whittingham K, Ware RS and others. Move it to improve it (Mitii): study protocol of a randomised controlled trial of a novel web-based multimodal training program for children and adolescents with cerebral palsy. BMJ Open 2013;3:1-20.
6. Fennell EB, Dikel TN. Cognitive and neuropsychological functioning in children with cerebral palsy. Journal of Child Neurology 2001;16:58-63.
7. Pirila S, van der Meere JJ, Rantanen K, Jokiluoma M, Eriksson K. Executive functions in youth with spastic cerebral palsy. Journal of Child Neurology 2011;26:817-21.
8. Pueyo R. Neuropsychological impairment in bilateral cerebral palsy. Pediatric Neurology 2009;40:19-26.
9. Straub K, Obrzut J. Effects of Cerebral Palsy on Neuropsychological Function. Journal of Developmental and Physical Disabilities 2009;21:153-167.
10. Anderson P. Assessment and development of executive function (EF) during childhood. Child Neuropsychology 2002;8(2):71-82.
11. Anderson PJ, Reidy N. Assessing executive function in preschoolers. Neuropsychological Review 2012;22:345-60.
12. Anderson V, Jacobs R, Anderson PJ, editors. Executive functions and the frontal lobes: A lifespan perspective New York: Taylor & Francis Group; 2007.
13. Bodimeade HL, Whittingham K, Lloyd O, Boyd RN. Executive functioning in children with unilateral cerebral palsy: protocol for a cross-sectional study. BMJ Open 2013;3.
14. Novak I, Hines M, and Barclay, R. Clinical prognostic messages from a systematic review on cerebral palsy. Pediatrics 2012;130:e1285.
15. Limond J, Leeke R. Practitioner Review: Cognitive rehabilitation for children with acquired brain injury. Journal of Child Psychology and Psychiatry 2005;46:339-352.
16. Slomine B, Locascio G. Cognitive rehabilitation for children with acquired brain injury. Developmental Disabilities Research Reviews 2009;15:133-143.
17. Grunewaldt KH, Løhaugen GCC, Austeng D, Brubakk A-M, Skranes J. Working Memory Training Improves Cognitive Function in VLBW Preschoolers. Pediatrics 2013;131:e747-e754.
18. Missiuna C, DeMatteo C, Hanna S, Mandich A, Law M, Mahoney W, Scott L. Exploring the Use of Cognitive Intervention for Children with Acquired Brain Injury. Physical & Occupational Therapy in Pediatrics 2010;30:205-219.
19. Ross KA, Dorris L, McMillan TOM. A systematic review of psychological interventions to alleviate cognitive and psychosocial problems in children with acquired brain injury. Developmental Medicine and Child Neurology 2011;53:692-701.

20. Diamond A. Activities and programs that improve children's executive functions. Current Directions in Psychological Science 2012;21:335-341.
21. Diamond A, Lee K. Interventions shown to aid executive function development in children 4 to 12 years old. Science 2011;333:959-964.
22. Roche JD, Johnson BD. Cogmed working memory training product review. Journal of Attention Disorders 2014;18:379-384.
23. Rueda MR, Rothbart MK, McCandliss BD, Saccomanno L, Posner MI. Training, maturation, and genetic influences on the development of executive attention. Proceedings of the National Academy of Sciences of the United States of America 2005;102:14931-14936.
24. Bilde PE, Kliim-Due M, Rasmussen B, Petersen LZ, Petersen TH, Nielsen JB. Individualized, home-based interactive training of cerebral palsy children delivered through the Internet. BMC Neurology 2011;11:32.
25. James S, Ziviani J, Ware RS, Boyd R. Randomised controlled trial of web based multimodal therapy for unilateral cerebral palsy to improve occupational performance. Developmental Medicine and Child Neurology 2014;57:530-8
26. Mitchell LE, Ziviani J, Boyd R. A randomized control trial of web-based training to increase physical activity in children with cerebral palsy. Developmental Medicine and Child Neurology, 2016;58:767-73.
27. Crawford JR, Anderson A, Rankin PM, MacDonald J. An index-based short-form of the WISC-IV with accompanying analysis of the reliability and abnormality of differences. British Journal of Clinical Psychology 2010;49:235-258.
28. Wechsler D. Wechsler Intelligence Scale for Children - fourth edition: technical and interpretative manual. San Antonio, TX: The Psychological Corporation; 2003.
29. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS) examiner's manual. San Antonio, TX: The Psychological Corporation;2001.
30. Piovesana AM, Ross S, Whittingham K, Ware RS, and Boyd R. Stability of executive functioning measures in 8-17-year-old children with unilateral cerebral palsy. The Clinical Neuropsychologist 2015;29:133-149.
31. Gioia G, Isquith P, Guy S, Kenworthy L. Behavior rating inventory of executive function. Odessa, FL: Psychological Assessment Resources; 2000.
32. Baron IS. Test review: Behavior Rating Inventory of Executive Function. Child Neuropsychology 2000;6:235-8.
33. Laatsch L, Harrington D, Hotz G, Marcantuono J, Mozzoni MP, Walsh V, Hersey KP. An evidence-based review of cognitive and behavioral rehabilitation treatment studies in children with acquired brain injury. The Journal of Head Trauma Rehabilitation 2007;22:248-256.
34. Anderson V, and Catroppa C. Advances in postactute rehabilitation after childhood acquired brain injury. Brain Injury 2006;85:767-778.

Table 1. Participant and family demographics and baseline characteristics of Mitii™ and Control Groups

Characteristics	Mitii™ (n=51)	Control group (n=50)
Age, mean (SD)	11.63 SD 2.30	11.86 SD 2.45
Gender, male	26 (51%)	25 (50%)
Hemiplegia, left sided (%)	28 (55%)	20 (40%)
MACS n (%)		
Level I	11 (21.6%)	13 (26%)
Level II	39 (76.5%)	37 (74%)
Level III	1 (2%)	
GMFCS-E&R		
Level I	20 (39.2%)	25 (50%)
Level II	31 (60.8%)	25 (50%)
Epilepsy	11 (21.6%)	7 (14%)
Intellectual disability		
FSIQ <80 below average (%)	4 (7.8%)	7 (14%)
Other diagnoses n (%)		
Learning disorder	14 (27.5%)	9 (18%)
Hearing impairment	1 (2%)	3 (5.9%)
Vision impairment	5 (9.8%)	6 (12%)
ADHD	4 (7.8%)	6 (12%)
Autism spectrum disorder	3 (5.9%)	1 (2%)
Other	11 (21.6%)	3 (6%)
School	n = 48	n = 47
Primary School	39 (76.5%)	38 (76%)
Special Education	2 (4%)	2 (4%)
Secondary School	4 (7.8%)	6 (12%)
Home Schooled	3 (5.9%)	-
Other	-	1 (2%)
VCI (WISC-IV)	93.12 SD 15.26 (n = 49)	88.38 SD 16.94 (n = 48)
PRI (WISC-IV)	82.94 SD 14.90 (n = 49)	81.98 SD 18.00 (n = 48)
WMI (WISC-IV)	88.88 SD 12.84 (n = 49)	86.35 SD 15.84 (n = 48)
PSI (WISC-IV)	87.24 SD 13.96 (n = 49)	83.46 SD 18.78 (n = 48)
FSIQ (WISC-IV)	84.65 SD 15.19 (n = 49)	80.75 SD 19.81 (n = 48)
Gross household income	n = 47	n = 44
Under $25000	4 (7.8%)	7 (14%)
$25,000 - $50, 000	5 (9.8%)	7 (14%)
$50,000-$75,000	8 (15.7%)	9 (18%)
Over $75,000	30 (58.8%)	21 (42%)
Family type child living in, n (%)	n = 48	n = 47
Original	33 (64.7%)	29 (58%)
Step-family	8 (15.7%)	9 (18%)
Sole parent	5 (9.8%)	6 (12%)
Other (e.g. foster)	2 (3.9%)	3 (6%)
Parent marital status, n (%)	n = 48	n = 47
Married	37 (72.5%)	34 (68%)
Single	1 (2%)	5 (10%)
Defacto	6 (11.8%)	5 (10%)
Divorced/separated	2 (3.9%)	3 (6%)
Widower	2 (3.9%)	-

Employment	n = 48	n = 47
Fulltime	17 (33.3%)	14 (28%)
Part time	16 (31.4%)	15 (30%)
House Duties	14 (27.5%)	15 (30%)
Unemployed	1 (2%)	3 (6%)
Rural/remote location (ARIA)		n = 49
Major Cities of Australia	21 (41.2%)	25 (50%)
Inner and Outer Regional Australia	26 (51%)	22 (44%)
Remote and Very Remote Australia	4 (7.8%)	2 (4%)
SEIFA Socio-Economic Disadvantage Decile	6.04 SD 2.73	6.45 SD 2.93

MACS, Manual ability level; GMFCS-E&R, Gross motor function classification scale Extended and Revised; ADHD, Attention Deficit Hyperactivity Disorder; FSIQ, Full Scale Intellectual Quotient; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index; WISC-IV, Wechsler Intelligence Scale for Children – Fourth Edition; ARIA, Accessibility/Remoteness Index of Australia; SEIFA, Socio-Economic Indexes for Areas

Table 2: Measures of Executive Functioning at baseline and 20 week follow up of Mitii™ and control groups (Mean, SD)

Characteristics	Mitii™	Control group
Digit span Backwards		
Baseline	8.34 SD 2.63	7.96 SD 2.99
20 weeks	8.26 SD 2.81	7.52 SD 2.65
Coding		
Baseline	7.30 SD 2.78	7.10 SD 3.26
20 weeks	8.40 SD 2.91	7.20 SD 3.41
Symbol Search		
Baseline	7.73 SD 3.24	7.06 SD 3.91
20 weeks	8.96 SD3.00	7.66 SD 0.59
TMT Number Letter Sequencing		
Baseline	7.22 SD 4.17	6.51 SD 4.02
20 weeks	8.51 SD 4.14	7.32 SD 4.25
Inhibition		
Baseline	7.90 SD 3.51	8.22 SD 3.60
20 weeks	9.55 SD 3.07	8.86 SD 3.77
Tower Achievement Score		
Baseline	8.50 SD 3.02	8.08 SD 3.01
20 weeks	10.49 SD 3.16	9.75 SD 3.32
BRIEF BRI		
Baseline	58.31 SD 12.47	60.55 SD 14.15
20 weeks	57.59 SD 13.78	61.07 SD 13.87
BRIEF MI		
Baseline	60.04 SD 13.19	61.80 SD 11.64
20 weeks	59.65 SD 14.05	64.81 SD 12.57
BRIEF GEC		
Baseline	60.80 SD 13.29	62.00 SD 12.90
20 weeks	59.46 SD 13.80	63.79 SD 13.10

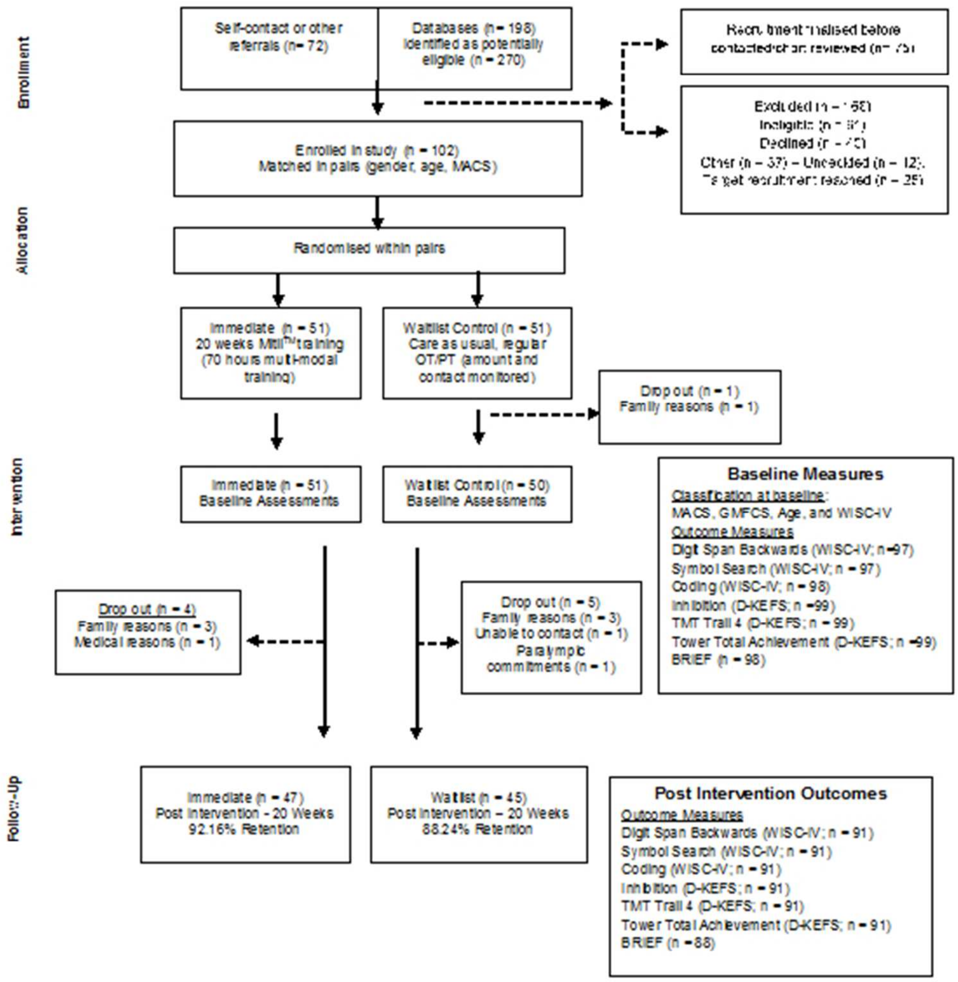
TMT, Trail Making Test of D-KEFS; D-KEFS, Delis-Kaplan Executive Function System; BRIEF, Behaviour Rating Inventory of EF; BRI, Behaviour Regulation Index (BRI); MCI, Metacognition Index; GEC, Global Executive

Table 3: Associations between Mitii™ intervention/control group and outcome measure using linear regression

Characteristics	Mean Difference	95 % CI	P-Value
Digit span backwards	0.73	-0.40, 1.87	0.20
Coding	1.20	-0.12, 2.52	0.07
Symbol Search	1.29	-0.16, 2.75	0.08
TMT Number Letter Sequencing	1.19	-0.55, 2.94	0.17
Inhibition	0.69	-0.73, 2.11	0.34
Tower Achievement Score	0.73	-0.61, 2.09	0.28
BRIEF BRI	-3.48	-9.35, 2.38	0.24
BRIEF MI	-5.15	-10.82, 0.51	0.07
BRIEF GEC	-4.32	-10.04, 1.38	0.13

TMT, Trail Making Test of D-KEFS; D-KEFS, Delis-Kaplan Executive Function System; BRIEF, Behaviour Rating Inventory of EF; BRI, Behaviour Regulation Index (BRI); MCI, Metacognition Index; GEC, Global Executive

Figure 1: Consort flow chart



Abbreviations: MACS = Manual Ability Classification System; GMFCS = Gross Motor Function Classification System; WISC-IV = Wechsler Intelligence Scale for Children – Fourth Edition; D-KEFS = Delis-Kaplan Executive Function System; TMT = Trail Making Test; BRIEF = Behaviour Rating Inventory of Executive Function.

Figure 1: Consort flow chart
Insert Figure 1 about here
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