Title: Development and Evaluation of a Novel Treatment Intervention for People with Acquired Brain Injury

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Summary

There is a pressing need to develop more effective interventions to remediate cognitive deficits in highly prevalent disabling conditions such as stroke, head injury and other forms of acquired brain injury (ABI). Neuropsychological rehabilitation interventions developed in a clinical setting have shown some beneficial effects, but the effectiveness of clinical interventions have potential to be enhanced if informed by findings from cognitive neuroscience. Research into cognitive training using methods such as functional magnetic resonance imaging (fMRI) has contributed to an understanding of factors that promote changes in brain function, but this approach seldom includes individuals with brain damage or cognitive deficits. Its potential for application with clinical populations is therefore uncertain, meaning that people who may benefit do not have access to interventions that may improve their health and wellbeing.

The proposed research brings together methods from neuropsychological rehabilitation and cognitive neuroscience to investigate 1) the feasibility of, and effect sizes arising from, combining an existing clinical intervention targeting mental *strategies* with an adaptive training programme targeting core cognitive *processes*, and 2) whether the novel treatment combination promotes changes in brain function that are detectable using fMRI.

This project will develop and evaluate a training intervention that aims to improve outcomes from a strategy-based rehabilitation intervention, Goal Management Training (GMT), by adding process-based cognitive training with adaptive difficulty to enhance the executive function of working memory updating (WMU). People with ABI (n=32) will complete 9 sessions of GMT, a recommended treatment for deficits in frontal-lobe executive functions, with the addition of 8 WMU training sessions with or without adaptive training. Measures of feasibility, acceptability, and fidelity will be taken, and effect sizes of differences in pre- to post-training changes on neural, cognitive, and functional measurements will be determined by comparing two experimental groups in which difficulty of the WMU training tasks either adaptively increases in response to performance or is fixed.

1. Introduction

Globally, stroke and head injury are leading causes of disability. Deficits in cognitive functions are common in these conditions, including impairment in frontal-lobe 'executive' functions such as working memory and the ability to solve problems, plan, and regulate actions in order to achieve intended goals. These deficits affect individuals' ability to live independently, work, and maintain social relationships. We propose that improving outcomes for people with acquired brain injury (ABI) requires an interdisciplinary approach in which neuropsychological rehabilitation and cognitive neuroscience complement one another.

In neuropsychological rehabilitation, interventions are classified as 'restorative' (restoration of underlying core cognitive processes including executive functions) or 'compensatory' (compensation of function through the use of external aids or learned strategies). Clinical guidelines recommend the use of 'meta-cognitive strategy training' for the treatment of deficits in frontal-lobe executive functions (Cicerone et al. 2011). Goal Management Training (GMT) is one such validated meta-cognitive strategy. GMT trains compensatory mental **strategies** to manage attention during multi-step tasks. GMT has been evaluated behaviourally in randomised controlled trials with positive, albeit modest, outcomes in individuals with ABI (Tornås et al., 2016).

In cognitive neuroscience, an emerging research area concerns experience-induced neural changes referred to as neural plasticity. These may involve neural changes in: 1) task-based functional activation patterns, i.e. activity increases, decreases, or reorganisation, 2) brain structure, i.e., grey matter and white matter volume changes (Brehmer et al., 2014) and 3) functional connectivity, i.e. changes in connectivity between brain regions that are recruited for a mental procedure as well as changes in the strength and magnitude (Constantinidis & Klingberg, 2016).

Neuroimaging studies have demonstrated that programmes to train core cognitive **processes** including working memory (WM) executive functions can drive changes both in behavioural and neural measures (Klingberg, 2010; Hsu et al., 2014). Performance gains after process-based training have been observed by several authors employing different training tasks and including both younger and older populations (Westerberg and Klingberg 2007; Dahlin et al., 2008; Jaeggi et al., 2008; Jolles et al., 2010; Buschkuel et al., 2014). In addition, generalisation to broad cognitive abilities such as reasoning, episodic memory, after process-based training, has been observed in both young and older adults (Dahlin et al., 2008;2009; Brehmer et al., 2014) although this area is under debate (Melby-Lervag & Hulme 2013; Brehmer et al., 2014). This work has primarily involved healthy adults and whether the same findings apply to those with ABI needs to be investigated.

This research study aims to develop and evaluate a novel treatment intervention for people with ABI that combines a *process-based* cognitive training with a *strategy-based* GMT rehabilitation intervention, and to acquire functional magnetic resonance imaging (fMRI) data before and after the intervention to measure patterns of brain activity associated with a task requiring executive functions.

We propose that outcomes from GMT might be improved by an adaptive, process-based intervention aimed at enhancing working memory processes. Adaptive task difficulty involves dynamic adjustment of training task demands so that the individual remains within an optimal range of performance. In a cognitive training literature review, Dahlin et al. (2009) identified adaptive difficulty as a common feature of interventions that reported significant training gains. Lövdén et al. (2010) explained this by theorising that a mismatch between functional "supply" (i.e., neural resources) and environmental "demands" (e.g., a continuously challenging training task) is a necessary condition for cognitive and neural plasticity to occur. If training task difficulty does not tax the upper limits of available resources, there is no mismatch between supply and demand, thus no impetus for plastic change. However, if difficulty is progressively increased, and continues to tax increasing levels of proficiency, then more neural resources will become available through plastic change.

There is some promising evidence that cognitive deficits in clinical populations can be remediated through behavioural interventions (Bahar-Fuchs et al., 2013; Hallock et al., 2016; van de Ven et al., 2016), and clinical research is starting to use fMRI to investigate normalisation of brain activation patterns after cognitive training (Nordvik et al., 2014). Yet, the results of these studies will be more interpretable, and the design of future intervention studies will be better informed, if theoretically-driven research is carried out to identify the factors that promote training gains. Adaptive difficulty may be one such factor. A recent study conducted by Flegal et al. (2019), in which healthy adults completed a process-based intervention aimed at enhancing the executive function of working memory updating (WMU), found that adaptive training task difficulty influences neural plasticity, consistent with the Lövdén et al. (2010) theoretical framework. This is an important hypothesis to test further in the context of neurological conditions, where there is a reduction in neural resources from premorbid levels.

2. Aims

The primary aim of the study is to investigate whether it is feasible and acceptable to deliver a novel intervention combining GMT with WMU training, within a randomised controlled trial (RCT) context in a sample of ABI individuals. A further aim is to examine the behavioural and neural changes related to the novel intervention as well as the effect sizes.

3. Research Question

This project will combine methods from neuropsychological rehabilitation and cognitive neuroscience to answer the following: 1) Is it feasible to combine an existing treatment for executive dysfunction, GMT, with an adaptive WMU training and how much benefit is gained? 2) Does the novel treatment combination promote neural plasticity that is detectable using fMRI?

i. Primary

Primary outcomes will be measures of feasibility, acceptability, and fidelity.

ii. Secondary

Secondary outcomes will be pre- to post-training change in behavioural data (i.e., neuropsychological assessment battery, measures of cognitive task performance and everyday functioning) and fMRI data (i.e., task-related brain activity), analysed by training condition. In addition, exploratory analyses of individual differences in responsiveness to WMU training will be performed, by calculating correlations between amount of adaptive training task improvement and pre- to post-training change on neural, cognitive, and functional measurements.

4. Design and Methodology

i. Design

Randomised controlled trial methodology; specifically stratified randomisation in conjunction with permuted block random allocation, using an active control group will compare two conditions: (1) GMT combined with adaptive training [AT]; (2) GMT combined with non-adaptive [NA] training. Thirty-two adults with non-progressive ABI sustained in adulthood will be recruited from the NHS.. Participants will complete a combination of standard GMT (9 sessions) and 8 WMU (AT or NA) training sessions, delivered in small groups. Neuropsychological and functional assessments will be performed before and after the intervention. In addition, fMRI scanning sessions will be conducted pre- and post-training at the Clinical Research Imaging Facility (CRIF), Queen Elizabeth University Hospital (QEUH) in a 3T Prisma Siemens scanner.

ii. Participants

Adults with non-progressive ABI sustained in adulthood will be recruited primarily from the Community Treatment Centre for Brain Injury (CTCBI), the main service for community based cognitive rehabilitation in Glasgow. Participants will also be recruited from other NHS services within Scotland.

Inclusion Criteria

-Only those able to give informed consent and able to comply with the training protocol will be included.

- ⩾ 6 months post-ABI at time of recruitment (expression of interest to participate either verbally or in writing)

- Adults over the age of 18.

- English language fluency (speaking)

- a combination of self/relative/friend/carer reports of everyday organisation/memory problems

Exclusion Criteria

-Individuals with contra-indications to MRI (e.g. heart pacemaker)

-Comorbid progressive neurological disorder or neurodegenerative condition (e.g. dementia)

-Major psychiatric disorder considered likely to prevent engagement in the intervention programme (pre-ABI history of mood disorder or stable antidepressant medication will not lead to exclusion)

-History of major substance abuse problems if the clinical and research team think it is likely to prevent engagement in and/or interfere with the intervention programme. There will be a degree of flexibility on this and the clinical team will be consulted on an individual basis when deemed necessary.

-Unable to give informed consent

-Unable to cooperate with the study protocol (e.g. severe impairment of hearing, vision or language)

These criteria are necessary in order that the outcome measures can be administered validly, and to increase the likelihood that any neuropsychological impairment present is due to ABI rather than any other pre-existing disorder.

COVID-19 mitigating circumstances regarding inclusion/exclusion criteria

Even though collecting neuroimaging data remains one of the main components of this research project, we understand there may be some participants who feel uncomfortable with travelling and/or coming in contact with others during the COVID-19 crisis. Therefore, individuals with MRI contraindications can still be included to take part in the behavioural intervention sessions without completing the fMRI sessions as an exception; nevertheless the focus still remains on recruiting participants suitable for brain imaging.

iii. Procedure

The study will entail 12 visits overall. Details regarding the components and content of each visit are described in the following subsections of the protocol (please also refer to Table 1 below for a brief summary). No changes in routine care will take place while participating in the study.

Table 1: Research procedure

Visit Number	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Type of Visit	*Screening*	*Baseline T0*	*fMRI Time 1 (T1)*	*Treat Wk 1*	*Treat Wk 2*	*Treat Wk 3*	*Treat Wk 4*	*Treat Wk 5*	*Treat Wk 6*	*Treat Wk 7*	*Treat Wk 8*	*fMRI Time 2 (T2)*	*Immediate Follow-up T3*
Time since last visit			⩽ 1 wk from Visit 1	⩽ 1 wk from visit 2	1 wk from visit 3	1 wk from visit 4	1 wk from visit 5	1 wk from visit 6	1 wk from visit 7	1 wk from visit 8	1 wk from visit 9	⩽1 wk from visit 10	⩽1 wk from visit 10
fMRI session			x									x	
GMT Introductory session		x											
GMT session				x	x	x	x	x	x	x	x		
WMU AT session				x	x	x	x	x	x	x	x		
WMU NA session				x	x	x	x	x	x	x	x		
Neuropsychology Assessment		x											x
Functional Assessment		x											x

Post-Intervention Participant Feedback													x

Wk: week, T: Time, GMT: Goal Management Training, WMU: Working Memory Updating, AT: Adaptive, NA: Non Adaptive, fMRI: functional Magnetic Resonance Imaging.

iv. Recruitment

The sample will be recruited, screened and enrolled into the study from the CTCBI, NHS Greater Glasgow and Clyde (NHS GGC) and other NHS sites. The estimated recruitment period will be twelve months. Potential participants will be initially identified by the direct team working in CTCBI. These will then be approached by Dr Nicola Goudie, the clinical psychologist at the CTCBI. Dr Goudie will provide the study information sheet, discuss the study and ascertain interest. If the client expresses definite interest to participate at this point, they will undergo screening by Dr Goudie to determine eligibility according to the above criteria. If the patients have given permission, then Dr Goudie will pass their details to the PhD researcher (Katerina Pappa) undertaking the study who will then contact the participant to schedule a time to further discuss the study and obtain consent (Please see relevant **consent form document**). The PhD researcher will only obtain consent if certain the client has had sufficient time to study the participant information leaflet and is making an informed decision. Baseline neuropsychological and functional assessments will take place either the same day as taking consent or at a separate session, according to the participants' preferences and availability.

If the client has been discharged from CTCBI before being consented into the study, Dr Goudie will contact them to obtain verbal permission for the PhD researcher to make contact with them. The PhD researcher will then ascertain interest, screen the participant and obtain written informed consent. With the participant's permission, relevant medical information about their medical history will be obtained from their medical notes. The PhD researcher will not be able access this information before written informed consent has been obtained. The recruitment procedure will be adapted for other NHS sites with a member of the immediate care team performing the initial identification and then passing on the details to the PhD researcher to proceed with taking consent.

Recruitment Sites

1. *NHS GGC*
2. *NHS Lanarkshire*

The same recruitment procedure will be followed across the different sites. More specifically the lead contact for each study site is:

1. Dr Nicola Goudie, CTCBI, NHS GGC
2. Dr Jane Moir, Community Brain Injury Team, NHS Lanarkshire
3. Dr Louise Roach, Stroke team, NHS Lanarkshire

v. MRI Safety Assessment

One of the radiographers at the CRIF at QEUH, will go over the MRI Screening form to ensure the participants are safe to undergo an MRI scan (please see **the MRI screening form for further details**). This procedure will take place on two occasions: On each fMRI session prior to entering the MRI scanning room, i.e. study visits 2 and 11. The radiographers on site are*: Rosie Woodward, Evonne McLennan, Laura Dymock, Nicola Tynan and Fiona Savage.* The lead research radiographer on site is *Tracey Hopkins.*

vi. Letter to General Practitioner (GP)

The PhD researcher will inform the participants' GP of their participation in the study. The PhD researcher will send a letter addressed to the GP practice enclosing the study information sheet (Please see **GP letter** for further details)

vii. Baseline neuropsychological and functional assessments

Participants who meet all eligibility criteria following screening will undergo baseline neuropsychological and functional assessment using standardised measures prior to the study training interval. The assessments will be administered by the PhD researcher at the CTCBI or at the University of Glasgow. The assessment measures selected are those which would be most relevant for a future full-scale trial to determine treatment efficacy and mechanism of effect. Specific tests have been chosen to be relevant to current clinical practice and sensitive to key neuropsychological constructs while keeping administration time at a minimum. Equivalent parallel versions of cognitive test materials will be used during subsequent assessment sessions where available, to minimise practice effects. In recognition that some participants may experience difficulties in remembering appointments following ABI, participants will be offered a reminder phone call or text message of their appointment 1-2 days prior to neuropsychological assessment sessions.

Baseline neuropsychological and functional assessment will last between one and one and a half hours taking into consideration extra time for providing instructions, task practice and individual differences regarding speed.

The following neuropsychological tests will be used:

1. Trail Making Test (TMT) A and B (Reitan, & Wolfson, 1985) to get an estimate of attention, speed and mental flexibility (~5min).
2. Hotel task (Manly et. al., 2002) to measure executive function in daily life activities (~20min).
3. Digit Span taken from the Wechsler Adult Intelligence Scale (4th edition), (Wechsler, 2008), to assess verbal memory (~7-10min).
4. Tower test, taken from the Delis Kaplan Executive Function System battery (D-KEFS) (Delis et al., 2001) to obtain scores in a task requiring planning, rule learning and inhibition (~20min).
5. Colour Word Interference (CWI) test from the D-KEFS battery (Delis et al., 2001), assessing inhibition of an overlearned response and flexibility (~10min).
6. Functional measurements will be obtained using the Dysexecutive Questionnaire (DEX) (Burgess et al., 1996) (~5min).

These neuropsychological tests have been carefully reviewed and selected as they have been previously used for assessing individuals with ABI in the following studies examining changes after a cognitive intervention: 1. TMT (Sohlberg et al., 2000; Novakovic Agopian et al., 2011;), 2. Hotel task (Manly et al., 2002; Levine et al., 2011; Tornas et al., 2016), 3. Digit Span (Westerberg et al., 2007; Miotto et al., 2009; Vogt et al., 2009), 4.Tower test (Levine et al., 2001; Tornas et al., 2016), 5. CWI test (Lundqvist et al., 2010; Novakovic Agopian et al., 2011;) and 6. DEX (Miotto et al., 2009; Spikman et al., 2010).

These assessments are essential in characterising the participant sample in terms of cognitive function and capturing changes resulting from the cognitive intervention. Information about participant's current medications and ABI rehabilitation will also be

collected. The PhD researcher will also write to the participants' GP to let them know that they are taking part in the study.

Following all baseline neuropsychological assessments, participants will be randomly allocated to either (1) GMT combined with adaptive WMU training [AT]; (2) GMT combined with non-adaptive [NA] WMU training. The two groups will be stratified by the following factor: aetiology of brain injury (two strata, i.e. traumatic brain injury (TBI) or stroke).

Please note that these neuropsychological tests are copyrighted and the relevant references are listed below. The test forms will be uploaded but they will have no version numbers as in this case it isn't applicable. The authors of these tests are referenced in text above and in the end. Finally, in cases where the forms mention "Subject's Name", the participant ID will be used instead.

References

Burgess, P. W., Alderman, N., Wilson, B. A., Evans, J. J. and Emslie, H. 1996. "Validity of the battery: Relationship between performance on the BADS and ratings of executive problems". In BADS: Behavioural assessment of the dysexecutive syndrome manual, Edited by: Wilson, B. A. 18–19. Bury St Edmunds, , UK: Thames Valley Test Company.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001a). Delis-Kaplan executive function system: Examiner's manual. San Antonio, TX: The Psychological Corporation.

Manly, T., Hawkins, K., Evans, J., Woldt, K., & Robertson, I. H. (2002). Rehabilitation of executive function: facilitation of effective goal management on complex tasks using periodic auditory alerts. Neuropsychologia, 40(3), 271-281.

Reitan, R. M., & Wolfson, D. (1985). The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and clinical interpretation. Tucson, AZ: Neuropsychological Press.

Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition. Pearson; San Antonio, TX: 2008.

viii. Intervention

GMT

GMT teaches the use of mental strategies to support sustained attention during complex (multi-step) task performance following an interactive programme. GMT is structured into nine modules, with interactive discussions designed to raise awareness of various aspects of goal management, tasks that illustrate goal management concepts in action, and homework assignments designed to facilitate the transfer of concepts to real life. GMT comes as a complete kit, with slides, a trainer's manual, participant workbooks, and all the necessary components to run GMT sessions in a group setting (https://shop.baycrest.org/products/copy-of-the-goal-management-training-program).
Except for the first introductory session, all GMT interventions will be delivered by the PhD researcher on a group basis (group size N = 2 - 6) taking place either at the CTCBI or Psychology department, University of Glasgow. Additional groups may also be run at other recruiting services, providing that premises, numbers and space requirements allow it. The GMT group sessions will last two hours.

The first GMT module will be conducted on an individual basis for each participant separately prior to starting the combined GMT-WMU intervention. It will last about one hour and will take place on the same day as the baseline neuropsychology assessment (please see table 1).

The reason for administering Module 1 individually is to introduce the idea of the intervention, explain some key concepts, give the participant the opportunity to familiarise themselves with the general notion of the GMT as well as to discuss questions and concerns they might have. Thus, the PhD researcher will ensure each individual participant has understood and familiarised themselves with the GMT concepts before entering the fully combined GMT-WMU group-based intervention. The GMT sessions will be run by the PhD researcher plus another member either from the supervisory research team or the clinical team from the respective research site.

Brief overview of the GMT modules (Levine et al., 2012)

In the first module the intervention begins by defining the concepts of absent mindedness, and present mindedness and by providing patients with illustrative examples. Absentminded slip-ups (e.g., forgetting to pick up your dry-cleaning on the way home) are introduced during module two. The "automatic pilot," a metaphor for habitual or stimulus-bound task execution, is introduced in module 3. Module 4 teaches patients how to stop the automatic pilot. The "mental blackboard," a metaphor for working memory (i.e., where goals are kept in mind), is introduced in module 5. Modules 6–9 are devoted to teaching patients how to stop, state their goal, and make decisions in the context of competing tasks. Patients are also taught to create to-do lists and to split more complex tasks into sub-tasks. Module 9 is devoted to checking ongoing behaviour to ensure that the patient is still staying on task. Please see table 2 below for further details. At the end of each training module patients are given homework assignments to practice the concepts they learn during each session. These will be reviewed and discussed during the following session. In addition, patients will perform mindfulness and breathing exercises both at home and during the training sessions.

Table 2: GMT modules and concepts covered

Module	Concepts covered
Module 1 Introductory module	Introduction of goal hierarchies, mental laboratory, absentmindedness and present-mindedness by providing patients with illustrative examples.
Module 2	Relation of absentmindedness to other abilities, consequences of slips, conditions for slips and how the GMT will reduce slips.
Module 3	The automatic pilot and how it leads to errors.
Module 4	Training to stop the automatic pilot.
Module 5	Mental blackboard.
Module 6	Goal loss and reinstatement.
Module 7	Goal conflict and decision-making.
Module 8	Dealing with overwhelming tasks by splitting them into smaller tasks.
Module 9	Checking (reducing-slip-ups).

WMU

The training consists of computerised working memory updating tasks in which trial accuracy and response time are recorded. All 8 WMU interventions will be delivered by the PhD researcher on a group basis (group size N = 2 – 6). Two computerised WMU tasks will be trained based on the study conducted by Dr Flegal on healthy adults (Flegal et al., 2019). These tasks will be delivered via two modalities: (1) a visuospatial WMU task, i.e. Matrix Updating (MU) and (2) a verbal WMU task, i.e. Keep Track (KT). MU requires updating the location of multiple dots within a 4 x 4 matrix (Chen and Li, 2007) while KT requires updating the identity of the most recently studied words in multiple semantic categories (Yntema, 1963). For both training tasks, level of difficulty can be modulated by increasing or decreasing the update level, i.e., the number of updates on each trial. For AT participants, difficulty of the training tasks is progressively increased in response to task performance, in order to adaptively increase environmental demands. For NA participants, however, task difficulty is fixed at a relatively low level across all sessions. Training of the MU task lasts between 25-30 minutes while the KT training lasts between 20-25 minutes. The WMU training sessions will last between one hour to one hour and fifteen minutes taking into consideration time to provide instructions and practice.

ix. Post-intervention Feedback

After the end of the intervention all participants will have the opportunity to rate the perceived usefulness and experience of the interventions including any adverse effects using Likert scales (for further details please see the feedback form). This information will be used to guide the possible development of a future full-scale trial. This will be carried together with the immediate follow-up session after the end of the intervention (i.e. visit 12) by the PhD researcher.

x. Outline of Study Visits

Visit 1: Baseline Neuropsychological and Functional Assessment and Introductory GMT session

Full details of baseline assessment is given in section V: *Baseline neuropsychological and functional assessments.* Following completion of the assessments, the PhD researcher will then proceed with the introductory GMT session where the idea behind the intervention as well as its usefulness in people with ABI will be presented. Emphasis will be given on the importance of having goals in everyday life and a few key concepts central to GMT will be mentioned. In addition, the PhD researcher will discuss the expectations clients should have from this intervention, i.e. learn strategies, practice relaxation techniques, take control by stopping and thinking about their goals when performing a task. The overall duration of Visit 1 will be around three hours (approximately one to one and half hours for the neuropsychology assessment, half an hour for a break and one hour for the first introductory GMT session).

There is a very small possibility the PhD student might be required to make a few home visits as an exception (assuming the participant has a great difficulty travelling themselves on a day) in order to complete neuropsychological assessments, which carry a potential personal safety risk. To minimise these risks, all home visits will be carried out during office hours and the PhD student will be required to carry mobile phones and to let a member of the research team (or if not possible, a member of staff at their usual place of work) know when and where their appointments are and when they have finished. Hence, the University of Glasgow lone

study policy will be followed. Please follow this link for further information https://www.gla.ac.uk/media/Media_500540_smxx.pdf

Visits 2 and 11: Time 1 and Time 2 fMRI sessions

There will be two fMRI sessions, Time 1 (T1) and Time 2 (T2), to measure functional brain activity pre and post intervention respectively. These sessions will last approximately two hours in total. The PhD researcher together with one of the qualified radiographers at the CRIF will first perform the MRI screening form. Then the PhD researcher will give a detailed description of the scanning procedure and answer any potential questions; this step will last approximately half hour. The PhD researcher together with the radiographer will then move the participant to the scanner area. At both T1 and T2, participants will perform three tasks inside the scanner: (1) Matrix Updating serving as the criterion task, i.e. scanner version of visuospatial WMU training task, (2) Spatial N-Back task assessing transfer of learning to a closely related untrained task, i.e. near transfer, and (3) Object-Location Association, a visual episodic memory task assessing transfer of learning to an unrelated untrained task, i.e. far transfer. In each task run, a gradient-echo EPI sequence will be used to obtain functional images sensitive to BOLD contrast. One of the radiographers at the CRIF will conduct the scanning sessions together with the PhD researcher at all times.

Spatial N-Back is selected as a scanned task representing near transfer, based on the prediction that it and the WMU training tasks engage overlapping processing components and brain areas. Based on the scanned N-Back paradigm used by Flegal and colleagues (2019), stimuli will appear in one of eight locations and the task is to respond by pressing one button when the current location matches the location presented n trials earlier and pressing a second button when there is not a match.

Object-Location association is a measure of visual episodic memory, selected as a scanned task representing far transfer. Based on a paired associate learning paradigm adapted for fMRI testing as in Flegal et al. (2019), the task consists of blocks of trials arranged into an encoding phase followed by a retrieval phase. During encoding, a sequence of stimuli will appear in different locations, then during retrieval, each one of the locations will be cued and the task is to respond by pressing a button corresponding to one of three stimuli choices which had appeared in that location.

At both T1 and T2 the task runs will be followed by a T1-weighted sequence to obtain high-resolution anatomical images. In conducting fMRI data analysis the functional images will be spatially realigned using a six-parameter rigid body transformation and coregistered to their T1-weighted anatomical image. In total, visits 2 and 11 will take around two hours to complete, i.e. thirty minutes for the safety procedure prior to the scan and another one hour and a half for the scanning procedure itself. Comparisons in scanned task performance between T1 and T2 will allow us to examine how much benefit is gained due to the training intervention and if there is evidence of generalisation to other untrained tasks. In addition, we will examine neural changes in terms of task-related brain activity.

The procedure and tasks will be identical at T1 and T2, with the exception of three structural imaging sequences acquired only at T1, in addition to the T1-weighted anatomical image, for the purposes of a comprehensive, accurate and detailed neuroradiologist report (please see sections 6 and 7 below). These additional sequences are: 1. Axial T2-weighted, 2. Axial T2-weighted fluid attenuation recovery (FLAIR), and 3. A haemosiderin sensitive sequence.

For both fMRI sessions, the participants will spend no more than one hour inside the scanner.

Visits 3- 10: GMT+WMU Intervention sessions

There will be 8 weeks of a combined GMT and WMU intervention. Each GMT session will be two hours long while the WMU session will last between one hour and one hour and fifteen minutes. There will be a break between the training sessions allowing participants to have a rest and relax lasting between thirty minutes to an hour. The intervention visits will be conducted either at the Psychology department, University of Glasgow or at the CTCBI. Both GMT and WMU sessions will be administered by the PhD researcher undertaking the project. These will be conducted weekly on a group level at the same day; that means each intervention visit will last approximately three hours and forty-five minutes to four hours including the break in between. If attending both intervention sessions at the same day is not feasible for some participants, due to reasons such as getting easily fatigued or not being able to commit this long on the same day, the following guidelines will be implemented:

1. The option of coming for the two interventions separately within the same week will be offered, i.e. arranging the GMT and WMU interventions at two different times.
2. The option of conducting the WMU intervention in one's own time at home will be offered after the PhD researcher makes sure the necessary requirements are in place, i.e. the participant has a laptop at home to perform the training tasks, they have fully understood the tasks and are practicing according to the guidelines. Under these conditions, task performance will be monitored from encrypted anonymised data files (logging trial accuracy and response time) transmitted to the PhD researcher via e-mail at the end of each at-home training session.

Visit 12: T3, Immediate follow-up: neuropsychological and functional assessments

All standardised measures that were administered at baseline (Visit 1) will be re-administered after the end of the intervention (please see table 1) by the PhD researcher. An acceptable period between the end of the intervention and neuropsychology assessment will be within three weeks. In addition, a feedback form will be given to the participants to rate the perceived usefulness and experience of the interventions. This final visit will last around one and a half hours.

The PhD researcher will have access to supervision and will be given advice regarding what steps to take, including sharing relevant information, if they become concerned about the welfare of the participant at any stage during the study.

xi. *COVID-19 mitigation plan- Online option for study visits 1, 3-10 and 12.*

An online alternative will be offered to run the study visits remotely in order to minimise the risk of infection due to COVID-19. As a result, no unnecessary travelling nor physical group sessions will be taking place. In more detail:

- *Neuropsychology assessment - Visits 1 and 12*

The assessments listed in section 4vii will be adapted to be conducted remotely through an NHS approved software. Those tests that cannot be adapted for online use will be discarded and no further assessments will be used in their place, or, where feasible, these assessments may be adapted for delivery with social distancing when people come to CRIF for the scanning sessions, i.e. visits 2 and 11. After each participant, the test materials will be disinfected for use with the next individual. Another alternative is the use of a validated software via a secure web-based, GDPR compliant platform such as CANTAB, which is

designed and validated by Cambridge Cognition: https://www.cambridgecognition.com/cantab .

GMT- Visits 3-10

The GMT sessions will be conducted remotely via NHS IT systems to ensure security and data protection and the PhD researcher will use an NHS approved software (please see further information below). The session duration will remain the same while more regular breaks will be introduced. The PhD researcher will provide practice sessions, so participants familiarise themselves and feel comfortable using the software prior to starting the intervention. These will be part of visit 1 or any other time that is suitable for participants. The material, content and duration of the GMT will remain unchanged as described earlier. The PhD researcher will additionally record a brief five-minute video providing: 1. a recap for each session, 2. a brief summary of the key concepts explored and 3. a reminder of the homework for the next session. The video recording will be provided at the end of each GMT session only to those participants that were in attendance.

- *WMU Training - Visits 3-10*

The WMU training sessions will take place remotely. A computer with Windows Vista/7/8/10 is required to run the WMU training tasks using the Presentation software by Neurobehavioural Systems specifically designed for secure remote management of stimulus delivery in experimental research https://www.neurobs.com/ . If participants have no personal computer access, then the research team is able to provide the necessary equipment for the duration of the intervention depending on numbers and availability. The PhD researcher will be offering individual practice sessions and detailed step-by-step guidance for using the presentation software prior to starting the training sessions. The training tasks, session duration and content will remain unchanged as originally planned. All devices will be disinfected before given to a new participant using alcohol based sanitising products, i.e. 60-80% alcohol, as recommended per NHS guidelines https://coronavirusexplained.ukri.org/en/article/pub0006/

- *Scanning sessions – Visits 2 and 11*

The scanning sessions at CRIF will adhere to COVID-19 related NHS regulations and guidelines. Consequently, the sessions will be conducted as originally planned while ensuring the necessary precautions are taken to protect participant's health and safety. If participants feel uncomfortable taking part in the scanning sessions for reasons relating to COVID-19, then those people will only participate in the intervention component of the study.

- *NHS-approved software*

The online version of the intervention will be conducted using NHS approved software, such as Attend anywhere, Microsoft Teams and National Video Conferencing Service (NVCS) Cisco Meeting Server (CMS) which have already been adopted by the NHS to run their service remotely, i.e. one to one sessions and group meetings. These are ideal for sharing content, e.g. GMT module slides, for taking part in a group chat as well as support larger size group meetings effectively. The softwares will be accessed remotely through NHS networks to ensure data security and protection.

5. Randomisation and Bias prevention

Stratified randomisation in conjunction with permuted block random allocation will be used to allocate participants to one of two study groups of equal size. The sample will be stratified

by the following factor: aetiology of brain injury (two strata, i.e. TBI or stroke. Participants will be blinded to study allocation.

The sample will be randomised by Dr Kristin Flegal, a member of the PhD researcher's supervisory team. Dr Flegal is a neuroscience researcher with an expertise in fMRI methodology and thus she is less likely to come in direct contact with the participants through the clinical domain. The randomisation procedure will be conducted in a computerised manner. A code for randomisation will be created using Matlab programming software. Two databases will be created: 1. a patient's database that lists basic information such as participant ID, recruitment site, age, aetiology of brain injury and 2. a "randomisation" database that holds data on which participants have been registered and their treatment allocation. The participants' database will be password protected and accessed only by Dr Flegal. The PhD researcher will have no way of knowing which participant is allocated into which intervention arm prior to the individual starting the trial or change it afterwards. For the purposes of the present project stratified randomisation with blocking will be used and thus several participants will be randomised at once. Alternatively, if Dr Flegal is unable to perform the randomisation for any reason Dr Viveka Biswas will conduct the procedure instead.

1. Sample size

Thirty-two participants will be randomised (16 per group) to estimate recruitment, adherence and retention rates, and the variance of outcome measures. The sample size was based upon what could be feasibly expected to be recruited as part of a small-scale PhD feasibility research study whilst accounting for eligibility restrictions especially in regards to MRI contra-indications as well as the duration of the study. i.e. committing to the study for 12 weeks. Given that one of the primary aims is examining feasibility and acceptability of the novel intervention, the study is not designed to be powered to detect differences in outcomes between the two groups.

2. Neuroradiologist Report of Structural Scans

Dr Natasha Fullerton is the collaborator Neuro-radiologist in this study. She will review structural brain images acquired with the following sequences: 1. T1-weighted, 2. Axial T2-weighted, 3. Axial T2-weighted FLAIR, and 4. a haemosiderin sensitive sequence (e.g., gradient-echo or susceptibility-weighted). These scans will be transferred to NHS PACS in order to be linked to each participant's medical record. This way Dr Fullerton will be able to produce a comprehensive report in CRIS for each participant to:

1. Discern between the pre-existing brain injury and any new potential incidental finding, as per protocol (please see section 6 below).
2. Comment on the location and size of lesion as well as nature of injury, presence of atrophy or diffuse axonal injury.
3. Compare the current anatomical images with earlier ones if available and comment on the differences.

In addition to being recorded in PACS, the neuroradiologist's report containing information on exact anatomical location, size, and number of lesions will facilitate accurate and high quality fMRI data analysis, i.e. coregistration and spatial normalisation steps, accounting for abnormalities in the participants' T1-weighted anatomical images resulting from their brain injury.

The participants' anatomical scans will be automatically transferred to NHS PACS through the direct link between the CRIF and NHS PACS.

3. Incidental Findings Report

Incidental finding generally refers to the unlikely event where an abnormality is detected, by chance, in the scan of a volunteer by the radiographer or one of the investigators. Because participants in this study all will have an existing brain injury, a modified approach will be taken to allow for the expectation of some abnormality. In this study, Dr Natasha Fullerton will examine the anatomical brain scan for each participant and provide a report (please see section 6 above). In cases of an incidental finding extending beyond the existing brain injury the following procedure will be implemented:

1. The participant's GP will be informed
2. The participant will be referred to an appropriate clinician for further investigation

The procedure will be outlined in the study information sheet (please see the participant information form for further details).

4. Statistical methods

Quantitative behavioural data will be analysed using SPSS 21 software or equivalent. Data on recruitment, adherence and retention rates will be summarised as percentages with 95% confidence interval (CI). Baseline characteristics of the sample will be presented using descriptive statistics. Measures of cognition (overall and domain specific composite scores) and psychological and functional constructs will be summarised by group and overall with 95% CI, and analysed using correlational analyses and t-tests or their non-parametric equivalents to estimate effect sizes (ES). The estimated ES, Cohen's d (Sullivan & Feinn, 2012), will be calculated using linear regressing adjusted for baseline and factors. The sample means, SD and change scores on these outcome measures will form the basis of sample size calculations for a further full-scale study, if indicated.

fMRI BOLD responses will be analysed using the general linear model implemented in SPM12 developed at the Wellcome Center for Human Neuroimaging, UCL (www.fil.ion.ucl.ac.uk/spm). Data preprocessing will include each participant's functional images being realigned using a six-parameter rigid body transformation and coregistered to their anatomical image. Covariates of interest will be constructed by convolving vectors of predicted neural activity with a canonical hemodynamic response function. To account for residual variance because of head movement, motion parameters will be estimated at the realignment stage of pre-processing and motion spikes will be identified using the ArtRepair toolbox (cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) and included in each model as covariates of no interest. For group analysis, functional images will be normalised to MNI (Montreal Neurological Institute) space using affine and nonlinear transformations, and spatially smoothed.

5. Data Storage & Sharing

All sensitive information such as participants' names, addresses, phone numbers etc will remain on NHS systems. All electronic anonymised data will be stored on secure University

of Glasgow networked drives accessed via password-protected university (laptop) computers to ensure that the data is automatically backed-up. All participants will be assigned a study ID and all electronic data will be anonymised using this unique identification number. Physical data will be stored in locked filing cabinets in locked offices on University of Glasgow premises. The index of ID codes and identities will be stored separately from the study data. A secure University network drive will be used for the purpose of sharing raw data between the PhD researcher and investigators. If the data were to be shared, it would be completely anonymous (i.e. the link between participant name and study ID would be broken and a random ID number would be given instead). Please see **further details on the data management plan document).**

6. PhD student training

The PhD student, Katerina Pappa, has attended the following training opportunities to ensure she can produce high quality research, perform the Goal Management Intervention and conduct the fMRI scanning sessions together with the qualified radiographer at the CRIF, QEUH.

1. **Research Data Management** (October 2018), University of Glasgow
2. **Ethical Approval for People Working with Human Subjects** (November 2018), University of Glasgow
3. **Good Clinical Practice** (November 2018), NHS Greater Glasgow and Clyde
4. **MRI Safety Training,** (November 2018), University of Glasgow
5. **Goal Management Training** online attendance (December 2018), organised by Baycrest, University of Toronto, http://goalmanagementtraining.weebly.com/
6. **Applied Statistics for Postgraduate Students** (January 2019), University of Glasgow
7. **Writing a Data Management Plan** (May 2019), University of Glasgow
8. **Statistical Parametric Mapping (SPM)** Course, Wellcome Centre for Human Neuroimaging (May 2019), University College London
9. **Visceral Mind Neuroanatomy Course,** (September 2019), University of Bangor

7. Dissemination plan

The study participants will not be debriefed of the randomisation they underwent. However, they will be notified when the study results are published and the journal article will be shared with them. Findings from this study will be further disseminated to the funder and the wider research community via presentation at conferences and publication in peer reviewed journal(s) in line with the Neurosciences Foundation (NSF) open access policy (or in line with the University of Glasgow policy in the absence of NSF policy). The findings will also be shared with individuals with ABI and their families via local networks. No personally identifiable information about participants will be included in these reports and presentations. If the novel intervention is shown to be feasible and acceptable, we plan to arrange workshops for healthcare professionals in conjunction with patient, care and public involvement (PCPI) with a view to apply for postdoctoral funding after completion of the PhD research project.

8. Timeline

The duration of the study is 18 months and it is anticipated that recruitment will commence on Autumn 2019. A summary of the study timetable is given in Figure 1.

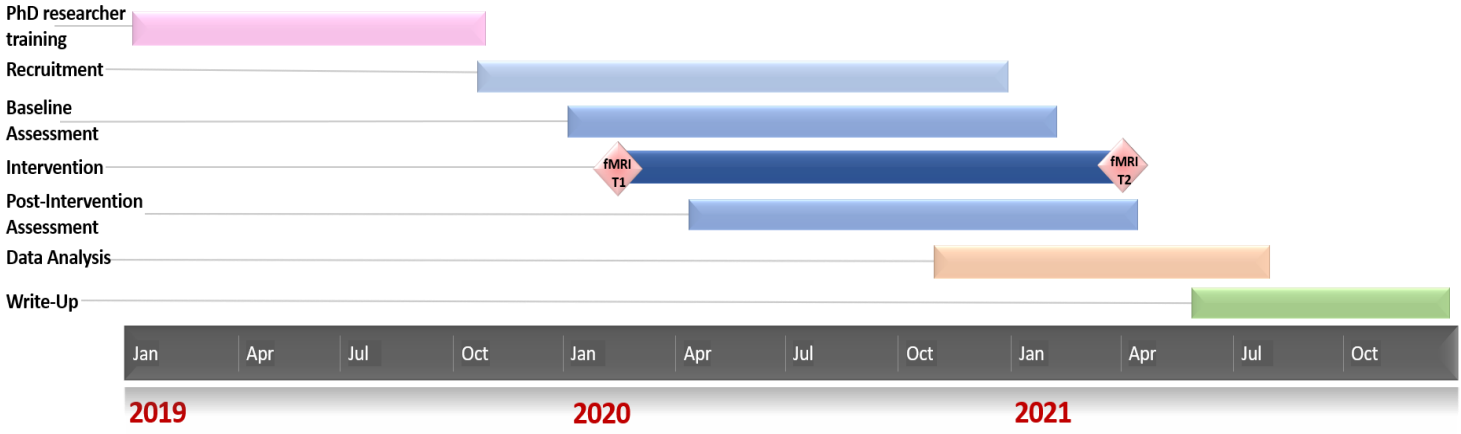

Figure 1: Study Timeline

- *COVID-19 mitigating circumstances – delay in study timeline*

Due to the significant delay in starting data collection for this research project, the study timeline has been amended as depicted in Figure 2 below. The study comprising Katerina Pappa's PhD research project will reach its end around late 2021. However, data collection for the overall project will continue for another year to allow study completion.

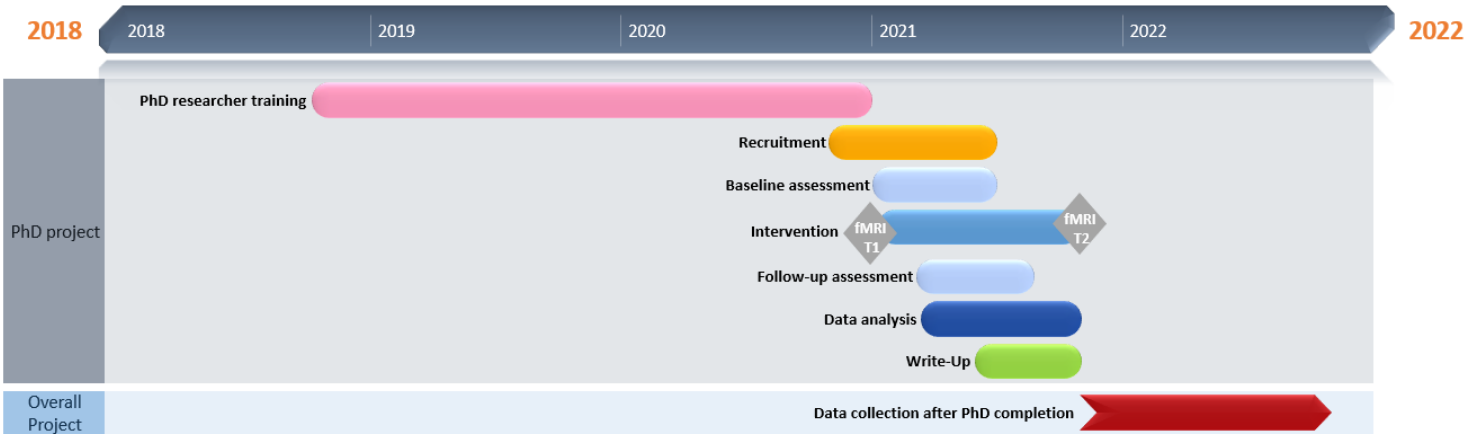

Figure 2: Updated study Timeline

9. Outcomes and Outputs

Results from this work will contribute new knowledge that may improve outcomes for patients with ABI long term, and will lay the groundwork for further research extending the adjunctive cognitive training approach to other clinical populations with cognitive deficits. Additionally, by establishing a new interdisciplinary research collaboration and strengthening the links between cognitive neuroscientists and clinical psychologists in the west of Scotland, this study will facilitate further development of the pipeline for translation of basic cognitive neuroscience research into clinical applications. Potential funding sources for subsequent

grant applications include Brain Research UK, the Medical Research Council and the Wellcome Trust.

10. Funding Arrangements

This study is supported by a Neurosciences Foundation/ Sackler Foundation PhD studentship (2018-2021, £75,000) awarded to Professor Jonathan Evans and Drs Kristin Flegal and Satu Baylan. In addition, an NHS GG&C Endowment Research Funding (£14,960) has been awarded to further support with MRI scanning costs.

References

Bahar-Fuchs, A., Clare, L., & Woods, B. (2013). Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *The Cochrane Database of Systematic Reviews, 6:* CD003260.

Baylan, S., & Evans, J. (2016). Development of a paradigm for studying the effects of brief Goal Management Training with Implementation Intentions. Neuropsychological Rehabilitation, 1-17.

Brehmer, Y., Kalpouzos, G., Wenger, E., & Lövdén, M. (2014). Plasticity of brain and cognition in older adults. Psychological Research, 78(6), 790-802. doi:10.1007/s00426-014-0587-z

Buschkuehl, M., Hernandez-Garcia, L., Jaeggi, S. M., Bernard, J. A., & Jonides, J. (2014). Neural effects of short-term training on working memory. Cognitive, affective & behavioral neuroscience, 14(1), 147-60.

Cicerone, K.D. et al. (2011). Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. Archives of Physical Medicine and Rehabilitation, 92, 519-530.

Constantinidis, C., & Klingberg, T. (2016). The neuroscience of working memory capacity and training. Nat Rev Neurosci, 17(7), 438-449. doi:10.1038/nrn.2016.43

Dahlin, E., Neely, A. S., Larsson, A., Bäckman, L., & Nyberg, L. (2008). Transfer of Learning After Updating Training Mediated by the Striatum. Science, 320(5882), 1510. doi:10.1126/science.1155466

Dahlin, E., Backman, L., Neely, A. S., & Nyberg, L. (2009). Training of the executive component of working memory: subcortical areas mediate transfer effects. Restor Neurol Neurosci, 27(5), 405-419. doi:10.3233/RNN-2009-0492

Flegal, K.E., Ragland, D.J., & Ranganath. C. (2019). Adaptive Task Difficulty Influences Neural Plasticity and Transfer of Training. NeuroImage, 188: 111-21. https://doi.org/10.1016/j.neuroimage.2018.12.003

Hallock, H., Collins, D., Lampit, A., Deol, K., Fleming, J., & Valenzuela, M. (2016). Cognitive training for post-acute traumatic brain injury: A systematic review and meta-analysis. Frontiers in Human Neuroscience, 10: 537.

Hsu, N.S., Novick, J.M., & Jaeggi, S.M. (2014). The development and malleability of executive control abilities. Frontiers in Behavioral Neuroscience, 8.

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. Proceedings of the National Academy of Sciences of the UnitedStates of America, 105, 6829–6833. doi:10.1073/pnas.0801268105.

Jolles, D. D., Grol, M. J., Van Buchem, M. A., Rombouts, S. A. R. B., & Crone, E. A. (2010). Practice effects in the brain: Changes in cerebral activation after working memory practice depend on task demands. Neuroimage, 52(2), 658-668. doi:https://doi.org/10.1016/j.neuroimage.2010.04.028

Klingberg, T. (2010). Training and plasticity of working memory. Trends in Cognitive Sciences, 14(7): 317-324.

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., & Schmiedek, F. (2010). A theoretical framework for the study of adult cognitive plasticity. Psychological Bulletin, 136(4): 659-676.

Melby-Lervag, M., & Hulme, C. (2013). Is working memory training effective? A meta-analytic review. Dev Psychol, 49(2), 270-291. doi:10.1037/a0028228

Nordvik, J.E., Walle, K.M., Nyberg, C.K., Fjell, A.M., Walhovd, K.B., Westlye, L.T., & Tornas, S. (2014). Bridging the gap between clinical neuroscience and cognitive rehabilitation: The role of cognitive training, models of neuroplasticity and advanced neuroimaging in future brain injury rehabilitation. NeuroRehabilitation, 34(1): 81-85.

Sullivan, G. M., & Feinn, R. (2012). Using Effect Size-or Why the P Value Is Not Enough. Journal of graduate medical education, 4(3), 279-82.

Tornås, S., Løvstad, M., Solbakk, A.-K., Evans, J., Endestad, T., Hol, P. K., Schanke, A.-K. and Stubberud, J. (2016) Rehabilitation of executive functions in patients with chronic acquired brain injury with goal management training, external cuing, and emotional regulation: a randomized controlled trial. Journal of the International Neuropsychological Society, 22(4): 436-452.

van de Ven, R.M., Murre, J.M., Veltman, D.J., & Schmand, B.A. (2016). Computer-based cognitive training for executive functions after stroke: A systematic review. Frontiers in Human Neuroscience, 10: 150.

Westerberg, H., & Klingberg, T. (2007). Changes in cortical activity after training of working memory — a single-subject analysis. Physiology & Behavior, 92(1), 186-192. doi:https://doi.org/10.1016/j.physbeh.2007.05.041