Impact of short-term intensive online Grammatical Reasoning Training on cognition and function in adults over 50 (START)

Protocol v7
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Background

Cognitive decline is common amongst older adults. Whilst for many people a degree of cognitive loss is a normal and healthy part of ageing, it can also be a precursor to development of Mild Cognitive Impairment and dementia, a devastating condition characterised by the progressive loss of ability and function leading to incapacity and death. Maintenance of healthy cognition and prevention of cognitive decline and dementia is therefore a key public health issue. Development of interventions to target the underlying pathology of cognitive decline is an area of complex and highly challenging clinical research. However, the potential impact of a strategy to preserve cognition and delay the clinical onset of symptoms, rather than pathology, could be more achievable and could be extremely significant, particularly when viewed from a population perspective. The delay of symptoms of cognitive decline, even by a few months, would achieve substantial financial saving at a societal level [1].

A number of demographic and lifestyle factors impact on the development of cognitive decline [2], including a growing body of evidence that indicates a role for cognitive reserve, defined as the combined effect of education, occupation and regular completion of cognitive leisure activities, in reducing the likelihood of developing dementia and cognitive decline [3]. One systematic review reported a 46% reduction in incident dementia in people rated within a high cognitive reserve demographic [4]. A large recent epidemiological study including over 13,000 adults over 65 also reported a more favourable cognitive trajectory for people with a higher cognitive reserve score, with this group showing a lower risk of developing cognitive impairment [5].

This raises the question as to the value of specific Cognitive Training (CT) approaches. There is a large emerging evidence base supporting the use of CT in maintaining cognitive function in older adults, and its potential to reduce the risk of dementia in later life. Several studies have been conducted with in-person training programmes, of which the largest is the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study. ACTIVE investigated the effect of training in several cognitive domains, demonstrating significant improvements in key aspects of cognition such as reasoning (effect size 0.26) and memory (effect size 0.28) which were sustained for five years[6]. Of particular note, only reasoning training conferred generalizable benefits in other cognitive domains at the five-year time-point. Ten-year follow-up has also reported a sustained impact on cognition in groups receiving training in both reasoning and processing speed, but not in memory, with a significantly lower self-reported decline in the treatment groups[7]. Recently published data has also shown a reduced incidence of dementia in people who continued to participate in the ACTIVE intervention for ten years.

This is an exciting step forward, yet there is a need to consider the implementability of such an intervention in order to roll it out to on a population-wide basis. Implementation of in-person CT on a population scale is hampered by the logistics and expense, which would thereby limit the impact on public health overall. However, if similar benefits could be achieved by implementing similar interventions using online and digital channels, millions of people could benefit at a fraction of the cost. A number of computerised, online CT platforms are currently available, although there are only a small number of RCTs evaluating the impact of online CT packages on cognition. This evidence base includes our previous study which evaluated two online CT programmes in people over 50, one providing General CT, and one focussed on Reasoning CT. The study showed significant benefit to reasoning and memory, in addition to

conferring benefit to Activities of Daily Living in people over 60 when the Reasoning CT was completed over six months[8]. Further analysis of the baseline data from this trial showed a clear age-related sensitivity in performance on reasoning tasks indicating that this aspect of cognition is particularly important in age-related cognitive health[9]. Recent analysis of data from a large online longitudinal study has indicated a potential training effect when older adults complete a Grammatical Reasoning task regularly. This raises the possibility of potential benefit with short-term, intensive training is this specific domain through one focussed task.

A novel online research infrastructure is available at King's College London and Exeter University which provides the opportunity to deliver online CT interventions to large numbers of older adults. The Platform for Research Online to investigate Cognition and Genetics in Ageing (PROTECT) is an online research study and longitudinal cohort of 20,000 people over 50. Participants provide demographic and lifestyle information and complete a battery of validated cognitive and mental health assessments annually. They also provide a DNA sample to enable genetic association work to be completed. PROTECT provides a unique platform for online clinical trial delivery. The website has been designed to enable nested interventions to be embedded into it, which participants are then invited to enrol for. This will provide a ready-made platform from which to evaluate the short-term impact of intensive training in Grammatical Reasoning in older adults.

Objectives

This study seeks to establish the effectiveness of an online short-term intensive Grammatical Reasoning training (START) intervention on cognition in adults over 50

Hypothesis

The underpinning hypothesis is that adults completing the START programme regularly over six weeks will show significant improvements to their reasoning and overall cognitive ability.

Methodology

Design: Six-month randomised controlled trial with a six week intervention period. Participants will be randomised to either the START intervention or to a control group for six weeks.

Participants: 7239 adults over 50

Setting: Intervention delivered online through the PROTECT website

Inclusion Criteria: Participants will: (i) Be over 50, (ii) Have access to a computer or device (smartphone / tablet etc) and the internet (iii) Be registered as a participant on the PROTECT website

Exclusion Criteria: Participants will be excluded if they have an established diagnosis of dementia.

Intervention: The START intervention consists of a Grammatical Reasoning cognitive task delivered online by Wesnes Cognition. This task measures how well the participant can mentally reason the relationships among different shape combinations assigned to grammatical statements. The shapes are a circle and a square, on each trial the square can either be contained within the square, or vice versa. The difficulty of each problem depends on the grammatical statement presented. There are 32 trials in total, 16 being simple questions (e.g. 'the circle is bigger than the square', 'the square contains the circle') and 16 more grammatically complex questions (e.g. 'the circle is not bigger than the square; 'the square does not contain the circle'). Half of each type of trial required the answer YES, and the other

half NO. These responses are made by pressing the left keyboard arrow key for NO and the right keyboard arrow key for YES. Accuracy and speed are recorded for each trial. The task takes around three minutes to complete. Participants will be encouraged to complete the START training once a day for the six-week period of the study

The control group will complete a basic picture-matching task that will provide the same level of engagement, but without the learning effects[10].

Outcome Measures:

The primary outcome measure will be a composite measure of cognitive function, created through a combined score of each of the measures described below, as measured at six weeks. The individual measures will be included as discrete secondary outcome measures. All outcome measures will be completed online. They are sensitive to change in cognition, and validated for use in older adults to detect early changes in cognition.

1. Executive function, as measured by two tests of visual attention and task-switching, the Trailmaking B and the Switching Stroop Test which are validated measures ofr use in this population.
2. Cognitive function, as measured through the Wesnes Cognition Ltd CogTrack™ system. Individual measures are: Baddeley Logical Reasoning Task (letter sequence)[11], Digit Vigilance, Simple and Choice Reaction time, Spatial Working Memory, Numeric Working Memory, Pattern Separation, Word Recall (delayed and immediate) and Word Recognition.
3. Verbal Learning, as measured through the validated Paired Associate Learning measure, which is highly sensitive to change in cognition and has been used to predict conversion to Alzheimer's Disease in people with cognitive impairment.
4. Activities of Daily Living, as measured by the modified IADL measure which is validated for use in this population, and has been successfully used to show change in IADL in previous online brain training studies.
5. Use of cognitive training: Participants will complete a brief question regarding their use of cognitive training (computer games, crosswords, Sudoku etc) and the regularity of use at each timepoint

Participants will be directed to complete these measures at baseline, two weeks and six weeks, using their 'My Study' homepage on the PROTECT website. Prompts to complete outcome measures will be sent out as automated emails.

Justification for sample size: The sample size calculation is based on the published study of online cognitive training in adults over 50 which showed significant benefit to reasoning, memory and function[8]. Based on an effect size of 0.11, 4826 participants would be required to provide 90% power at a two-sided 0.01 significance level. Assuming a conservative drop-out rate of 50%, a total of 7326 participants will be recruited.

Recruitment and Consent: Recruitment will be achieved through the PROTECT site through promotion of the study to existing participants. Additional publicity will be coordinated to drive recruitment to the PROTECT study overall, with a focus on enrolling new participants into the START trial. This recruitment will be supported by the Royal Devon & Exeter NHS Foundation Trust and the Devon Partnership NHS Trust. This approach has been used to great success during the launch of the previous cognitive training trial, which recruited over 15,000 people over 24 hours. Participants will consent to the study through the established PROTECT online consent process, which enables an electronic records of consent to be taken. Capacity to consent will be monitored as per the approved PROTECT protocol, which involves flagging of significant cognitive decline, an informant questionnaire and regular reminders that people with a diagnosis of dementia are not eligible to continue in the study.

Randomisation: Participants will be randomly allocated to START or control groups via stratified randomisation algorithm embedded in the PROTECT website. Stratification variables will be age, gender and whether the participant was involved in a previous brain training study.

Participant Journey

1. Participants will be invited to take part in the START study via an email from the PROTECT study. Information will also be provided on the PROTECT homepage.
2. Participants will log into their PROTECT homepage and 'My Study' area. From here they will access an online version of the Participant Information Sheet, which will also be available for download.
3. Participants will provide consent to take part in the START study via the electronic consent form. This process is already in use in the PROTECT study, and requires participants to consent to each condition, and then to confirm their consent for a second time to avoid accidental consent.
4. Participants will be allocated a unique START study ID number and will be randomly allocated to either the START intervention or control
5. Participants will complete baseline assessments for cognition and Instrumental Activities of Daily Living. The cognitive test package will be provided by Wesnes Cognition, a partner website in the PROTECT study which provides validated online cognitive tests. The test batter will take up to 15 minutes to complete and will include tests of Paired Associate Learning, Pattern Separation, Simple Reaction Time, Choice Reaction Time and Digit Vigilance. The Instrumental Activities of Daily Living assessment will be completed on the PROTECT site. Participants will be prompted to complete their assessments on their individual 'My Study' web page.
6. Participants will be able to access their START training through their 'My Study' page. They will be encouraged to play the task three times a week, but they can play as often as they wish. Automated emails will encourage participants to log on and play every few days.
7. Participants will be prompted by email to log in and complete follow-up assessments after two weeks and six weeks.
8. At six weeks participants will receive an email to let them know that the training portion of the study has been completed.
9. Participants will be contacted a six months to ask them to complete the outcome assessment battery once more to evaluate long-term impacts.
10. At the end of the study participants will receive a newsletter giving them information on the findings.

Data Analysis

The analysis and presentation of the trial will be in accordance with CONSORT guidelines. Recruitment, intervention uptake, outcome completion rates and drop out will be reported (with 95% CIs) as a flow diagram and the baseline participant characteristics in the intervention and control groups compared.

The primary analysis will undertake an intention to treat between group comparison of primary and secondary outcomes at six months post-randomisation using linear regression adjusting

for baseline outcome value and stratification and minimisation variables. The primary analysis will include complete case data only.

Additional analyses of the primary outcome will take three general forms. First, the influence of missing data we be investigated. As part of our approach to missing data, we will investigate which participant characteristics (including socio-demographic characteristics and baseline clinical values) are associated with primary and secondary outcome scores, and their propensity for missingness. Second, the effect of adherence with intervention will be investigated using allocation respecting methods such as complier averaged causal effects (CACE) modelling using instrumental variable regression. Third, interaction terms will be entered into the primary regression analyses in order to conduct pre-specified subgroup analyses that will include examining impact on groups with early deficits in reasoning, memory and executive function. These will be defined as participants performing outside of one SD of age-matched norms in the reasoning, memory and executive function tasks at baseline. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, the results of these exploratory analyses will be presented using confidence intervals, as well as a global p-value for the interaction between treatment and each variable, and interpreted with due caution.

No interim analyses are planned. A full analysis plan will be developed prior to completion of data collection and agreed with the Trial Steering Committee and the Data Monitoring and Ethics Committee. All analyses will be undertaken in STATA v.14.

Data Management

All participants will be allocated a unique identifier (User ID) as part of the PROTECT study. This is stored separately from the personal data collected on the site, enabling anonymous data to be collected. All data will be stored on an encrypted online database and downloaded to secure local servers for analysis. No personal data will be used for analysis. The research team will have sole access to personal data. These individuals are the two applicants (Corbett / Ballard), the study administrator and the web developer who provides service-level support for the PROTECT study.

The PROTECT study is managed across two research sites (King's College London and Exeter University). A data transfer agreement is in place to enable transfer of anonymised data between institutions for analysis purposes. No personal details will be transferred. Participants will be given clear information that their anonymised data will be transferred between King's College London and Exeter.

Dissemination

Study outputs will be disseminated through a number of channels. Findings will be submitted for publication in a high impact peer-reviewed journal and presented at national /international conferences. They will also be reported to the funder and the research team will work with the sponsor's press office to promote the findings through these communication channels. Open dissemination to public, patient and professional audiences will be achieved through a combination of online, media and newsletter channels including the PROTECT and Exeter University websites.

References

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