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Rehabilitation of Cognitive Deficits after Stroke: Protocol for a Systematic Review and Meta-Analysis of Randomised Controlled Trials

Rehabilitation of Cognitive Deficits after Stroke: Protocol for a Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Authors' contributions:

MOD, PB and RG were major contributors in writing the manuscript. SH, PB and SC designed the overall study. MOD, PB and RG developed the search strategy. All authors critically appraised and edited the manuscript. SH is the guarantor of the review. All authors read and approved the final manuscript.

Word count: 1990 words.

Abstract

Introduction: Stroke is among the leading causes of death and disability worldwide. Post stroke cognitive impairment is a common sequela of stroke. The burden of cognitive impairment post stroke has significant impacts on the individual post stroke, their family and wider society. Despite the prevalence and associated burden of post stroke cognitive impairment, the optimal approach to rehabilitate cognitive deficits post stroke has yet to be established. A range of conservative interventions for cognitive impairment post stroke exist including self-efficacy training, physical activity interventions, neuropsychological interventions, electronic interventions, music therapy and occupational therapies. No review to date has established the efficacy of these interventions on cognitive impairment post stroke. This systematic review aims to explore the totality of evidence with regard to such interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke.

Methods and Analysis: A systematic review of randomised controlled trials which investigate the effectiveness of interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke will be conducted. The following electronic databases will be searched: PubMed, Embase, CINAHL, CENTRAL and PsycInfo. Reference lists of all identified studies will be reviewed to identify additional studies for inclusion. Titles and abstracts will be screened independently by two review authors for inclusion and exclusion. Any disagreement regarding inclusion will be resolved by discussion or by referral to a third assessor if necessary. Methodological quality will be assessed using the Cochrane Risk of Bias Tool for Randomised Controlled Trials. Meta-analyses will be performed if studies are sufficiently homogeneous. The review will be reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Ethics and Dissemination: As this systematic review will collect secondary data only, ethical approval is not required. Findings will be disseminated through presentations and peer-reviewed journals. **Registration Details:** Prospero Registration Number: CRD42019125289.

Strengths and Limitations of this study:

Strengths

- This is the first systematic review to synthesise the totality of evidence regarding interventions which improve cognitive deficits post stroke.
- Robust and transparent methods used to identify, select, appraise and synthesise findings.
- Reporting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement
- Methodological quality assessed using Cochrane Risk of Bias tool.

Limitations

- Pharmacological interventions to address cognition post stroke will not be included.

Keywords: Stroke, cognitive impairment, rehabilitation.

Introduction

Stroke is among the leading causes disability worldwide [1]. The prevalence of stroke survivors is projected to increase given advancements in acute stroke care services in conjunction with an ageing world population [2], [3]. Given the increased prevalence of individuals surviving a stroke, coupled with an increase in the number of disability-adjusted life-years (DALYs), stroke rehabilitation and the prevention of stroke-related residual disability have become increasingly important. Cognitive impairment is a common clinical feature of stroke reported in 56.6% of ischaemic stroke survivors at six months post stroke [4]. The presence of cognitive impairment post stroke is independently associated with lower quality of life at 12 months post stroke [5], higher levels of death and institutionalisation [6], increased carer burden [7] and increased healthcare costs [8].

A collaboration of stroke survivors, carers and healthcare professionals within the James Lind Alliance (UK) identified that optimum approaches to improve cognitive impairment post stroke were among the top ten research priorities with regard to life after stroke [9]. This finding is also supported by the Intercollegiate Stroke Working Party national clinical guidelines for stroke where it is acknowledged that although there have been developments within stroke rehabilitation literature; significant gaps exist in relation to cognition after stroke [10]. Furthermore, a meta-summary of qualitative studies regarding stroke survivors' experiences of rehabilitation found that individuals with stroke report an emphasis placed on the rehabilitation of physical deficits with a neglect towards non-physical needs such as social re-integration and psychological support post stroke [11].

As illustrated by the variety of neuropsychological assessments outlined by Lezak, cognition is not a unitary concept. Cognitive impairment post stroke encompasses a variety of deficits across multiple domains and typically includes memory, attention, executive function, language and visuo-perceptual ability [12]. Various cognitive domains enable complex mental processes to occur, which allow an individual to select and process information within their environment [13]. Given the complex nature of cognitive functioning, a broad range of interventions exist to improve cognitive function in individuals post stroke. Such interventions include but are not restricted to, music therapy, resistance exercise training, aerobic exercise training, repetitive transcranial magnetic stimulation (rTMS), occupational

therapies, neuropsychological interventions and cognitive strategy training [14][15][16] [17] [18] [19] [20]. No review to date has evaluated the effectiveness of all possible interventions which may mediate improvements in cognitive function post stroke. Cognitive rehabilitation is defined as "a systematic functionally orientated intervention of therapeutic cognitive activities based on the assessment and understanding of the patient's brain behaviour deficits" [13]. Six previous Cochrane reviews have explored the effectiveness of specific cognitive rehabilitation interventions on specific domains of cognitive function post stroke [18,21–25]. These previous Cochrane reviews focused on one domain of cognitive impairment despite the evidence that cognitive deficits post stroke are likely to occur across multiple cognitive domains [26][27]. To this end, there is a need to focus on a broader range of interventions other than specific cognitive rehabilitation interventions with regard to improving cognitive function post stroke. Moreover, the effectiveness of interventions across multiple domains of cognitive function needs to be investigated given the diffuse nature of cognitive impairment post stroke.

This review aims to examine the totality of evidence with regard to interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke.

Methods

Study Design

The current systematic review protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[28]. In accordance with the PRISMA-P guidelines, this protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 13 February 2019.

Prospero Registration Number: CRD42019125289

Eligibility Criteria

Types of study

Randomised controlled trials and quasi-randomised control trials will be included, as defined by the Cochrane Handbook for Systematic Reviews of Interventions [29]. The pre-cross-over component of randomised and quasi-randomised cross-over trials will also be included, as

will cluster trials. While methodological quality will be assessed, given the breadth of interventions considered, no studies will be excluded on this basis.

Participants

Adults aged 18 years of age or older with a clinical diagnosis of ischaemic or haemorrhagic stroke are eligible for inclusion. Individuals with a confirmed cognitive impairment post stroke as specified by the authors within each trial will be included. Mixed aetiology studies (e.g. traumatic brain injury and stroke mix) will be included if separate data is reported on individuals with stroke which can be clearly extracted for review. Participants post transient ischaemic attack will be excluded.

Patient and Public Involvement

No patient involved.

Interventions

Interventions where the primary or secondary aim is to improve cognitive function after stroke will be included. Interventions may be of any type or duration or time since stroke. Some anticipated interventions may include, but are not restricted to:

- Cognitive rehabilitation interventions
- Exercise interventions: aerobic training, resistance training, flexibility training, balance training, Tai Chi
- Neuropsychological interventions
- Electronic interventions e.g. use of iPads, mobile phone apps
- Self-efficacy training
- Patient education interventions

Controls

Eligible control groups include:

Passive controls:

- Usual/Standard care control
- No treatment control
- Wait list control

Active controls:

- Comparing different forms of interventions which are hypothesised to mediate improvements in cognitive function post stroke.

Outcomes

The primary outcome is change in cognitive function post intervention in individuals with post stroke cognitive impairment. Outcome measures may focus on a domain-specific aspect of cognition such as executive function, attention, memory, perception, limb apraxia and neglect. Outcome measures may also cover a range of different cognitive functions in a single measure or give a measure of general cognitive status also.

Secondary outcome measures include quality of life, functional abilities, physical fitness, mobility, mood, participation and return to work.

Anticipated outcome measures include, but are not restricted to:

- Standardised tests or cognitive screening tools which provide a cognitive function score e.g. Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA).
- Subjective cognitive function e.g. cognitive failures questionnaire
- Performance tests e.g. the Trail-Making Test, the Clock Drawing Test.
- Functional Assessments e.g. Personal/ domestic ADL's, community-based tasks, assessment of Motor and Process Skills (AMPS), Functional Independence Measure (FIM) or Functional Assessment Measure (FAM).

Pharmacological interventions (including over-the-counter medications) will be excluded.

Search

The following electronic databases will be searched: PubMed, , Embase, CENTRAL, PsycInfo and CINAHL. The search strategy was developed in consultation with an academic librarian (LD, University of Limerick). The search strategy includes search terms relating to the population of interest (individuals post stroke), the intervention (breadth of rehabilitation

interventions as described) and the primary outcome of interest (cognitive improvement post stroke). The Pubmed search strategy is detailed in *Appendix 1.* Reference lists of included studies will be searched to identify potentially eligible studies and authors of key texts may be contacted as appropriate. Forward citations on included studies will be checked.

Data selection

The search results from each individual database will be saved in a master reference management library (EndnoteX7) and duplicates will be removed. Titles and abstracts of the citations retrieved by the literature search will be screened independently by two review authors (MOD, RG) for inclusion or exclusion using Rayyan QCRI. The full text of potentially relevant studies will be selected for further assessment and two independent authors will ascertain and agree on eligibility based on the full article (RG, MOD). Any disagreement regarding inclusion will be resolved by discussion, or by referral to a third assessor (PB) if necessary.

Results of the screening process will be detailed within a PRISMA flow diagram.

Data Extraction

Data will be extracted and entered into a standardised recording data extraction form. Data including author, country and year of publication, study design, details of the population (age, type of stroke, severity of stroke, severity of cognitive impairment, time since stroke), intervention, comparison group, primary and secondary outcomes measures will be extracted. Description of the interventions as well as the mechanisms by which these interventions mediated cognitive improvement will also be documented.

Risk of Bias

The internal and external validity of studies will be assessed by two independent reviewers (MOD, SH) using the Cochrane Risk of Bias Tool in accordance with the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and any other sources of bias[29]. Disagreements will be resolved by consensus among two other reviewers (RG, PB). Disagreements among the review authors on the methodological quality of the identified studies will be discussed and resolved by group consensus.

Strategy for data synthesis

We will perform separate analyses for trials comparing interventions to reduce cognitive impairment with 'treatment as usual', or with a 'placebo' control intervention, and trials comparing two active interventions. The Cochrane Review Manager software (RevMan) will be used to conduct statistical analyses to determine the treatment effect. For continuous data we will calculate the treatment effect using mean differences (SMD) and 95% CI where different studies used different scales to assess the same outcome, and calculate standardised mean differences (SMD) and 95% CI where studies have all used the same method of measuring outcome.

Due to the breadth of both interventions and cognitive outcome measures, it may be difficult to synthesise the data across studies. The impact of heterogeneity on results will be assessed using the I^2statistic. When the I^2 is < 30% there is little concern about statistical heterogeneity [29]If there is statistical heterogeneity ≥50% we will use random- effects models to take account of the between-study variation in our findings [29].
If meta-analysis is not possible as a result of substantial heterogeneity, a narrative synthesis of findings from the included studies will be provided.

Subgroup Analysis
If a sufficient number of RCTs are identified, subgroup analyses will be conducted to establish the effect of the following subgroups on overall outcomes:

- Participant-related characteristics e.g. age of individuals with stroke (<65 vs >65); type and severity of stroke; time since stroke onset; severity of cognitive impairment; effect of depression and/ or fatigue on cognitive function; adherence to intervention;
- Intervention-related characteristics e.g. type of intervention: individual vs group training, self-efficacy training vs aerobic exercise training; impact of healthcare professionals on intervention outcomes; frequency, intensity, time and type of intervention

A sensitivity analysis will also be conducted to explore the impact of methodological quality on the overall findings.

Discussion

This systematic review and meta-analysis will use a rigorous methodology to provide up to date evidence regarding the effectiveness of all types of non-pharmacological interventions on cognitive function post-stroke. Given the breadth of interventions shown to have an effect on post stroke cognitive impairment, there is a need to investigate all interventions, not solely cognitive rehabilitation interventions, which may mediate improvements in cognitive function post stroke. Previous research has taken a domain-specific approach to evaluating the effectiveness of interventions on cognitive deficits post stroke. These reviews have failed to capture the true clinical presentation of cognitive impairment post stroke with their focus on domain-specific cognitive deficits. Given the diffuse nature of post stroke cognitive impairment which typically affects more than one cognitive domain, the effectiveness of all interventions across multiple cognitive domains post stroke needs to be investigated. A rigorous review of the effectiveness of all non-pharmacological interventions with regard to cognitive impairment post stroke is therefore needed.

The results of this review will inform the optimal type of interventions to rehabilitate cognitive impairment post stroke including information on frequency, intensity, type and delivery of interventions. This information will inform the development of an optimal intervention to rehabilitate cognitive impairment post stroke. In addition, if data proves to be sufficiently homogenous to conduct a meta-analysis, information regarding the expected effect size associated with each intervention may be made available to healthcare professionals. This will be of use to clinicians and policy makers in their design and evaluation of rehabilitation services aimed at improving cognitive impairment post stroke.

Footnotes

Ethics and Dissemination

Findings will be disseminated through publication in peer-reviewed journals and through conferences. The rigorous scrutiny of primary studies will identify the strengths and limitations of current research and will provide recommendations for future research within this area.

Authors' Contributions: MOD, PB and RG were major contributors in writing the manuscript. SH, PB and SC designed the overall study. MOD, PB and RG developed the

search strategy. All authors critically appraised and edited the manuscript. SH is the guarantor of the review. All authors read and approved the final manuscript.

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Competing Interests Statement: None declared

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Appendix 1

Pubmed search strategy, modified accordingly for use in other databases.

(((((Randomised[Title/Abstract] OR randomized[Title/Abstract] OR Control*[Title/Abstract] OR experiment*[Title/Abstract] OR treatment*[Title/Abstract] OR conservative*[Title/Abstract])))) OR ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial"[Publication Type]))) AND (("Rehabilitation"[Mesh] OR "Rehabilitation Nursing"[Mesh] OR "Rehabilitation, Vocational"[Mesh] OR "Rehabilitation of Speech and Language Disorders"[Mesh] OR "Physical and Rehabilitation Medicine"[Mesh] OR "Hospitals, Rehabilitation"[Mesh] OR "Cardiac Rehabilitation"[Mesh] OR "Stroke Rehabilitation"[Mesh] OR "Psychiatric Rehabilitation"[Mesh] OR "Neurological Rehabilitation"[Mesh] OR "Telerehabilitation"[Mesh] OR "Exercise Therapy"[Mesh] OR "Treatment Outcome"[Mesh])) AND ((((((("Cognition"[Mesh] OR "Cognition Disorders"[Mesh])) OR ((Cognition[Title/Abstract] OR cogniti*[Title/Abstract] OR "cogniti* disorder*"[Title/Abstract] OR cogniti* AND disruption* AND "[Title/Abstract] OR " AND cogniti* AND impair* AND "[Title/Abstract] OR impairment*[Title/Abstract] OR " AND cogniti* AND disorder* AND "[Title/Abstract] OR confusion[Title/Abstract]))) OR (" AND Executive Function AND "[Mesh] OR " AND Neuropsychological Tests AND "[Mesh])) OR (" AND Memory AND "[Mesh] OR " AND Spatial Memory AND "[Mesh] OR " AND Memory, Episodic AND "[Mesh] OR " AND Memory, Long-Term AND "[Mesh] OR " AND Memory, Short-Term AND "[Mesh] OR " AND Memory Disorders AND "[Mesh] OR " AND Metacognition AND "[Mesh])) OR (" AND Perception AND "[Mesh] OR " AND Touch Perception AND "[Mesh] OR " AND Olfactory Perception AND "[Mesh] OR " AND Visual Perception AND "[Mesh] OR " AND Time Perception AND "[Mesh] OR " AND Speech Perception AND "[Mesh] OR " AND Social Perception AND "[Mesh] OR " AND Size Perception AND "[Mesh] OR " AND Motion Perception AND "[Mesh] OR " AND Pitch Perception AND "[Mesh] OR " AND Distance Perception AND "[Mesh] OR " AND Depth Perception AND "[Mesh] OR " AND Form Perception AND "[Mesh] OR " AND Color Perception AND "[Mesh])) OR " AND Apraxias AND "[Majr]) OR ((Neglect[Title/Abstract] OR perception*[Title/Abstract] OR attention[Title/Abstract] OR hemineglect[Title/Abstract] OR " AND hemi-neglect AND "[Title/Abstract] OR " AND unilateral neglect AND "[Title/Abstract] OR " AND spatial neglect AND "[Title/Abstract] OR " AND spatial-neglect AND "[Title/Abstract] OR " AND hemi-attention AND "[Title/Abstract] OR " AND hemi attention AND "[Title/Abstract] OR visuospatial[Title/Abstract])))) OR (" AND Attention AND "[Mesh] OR " AND Attentional Bias AND "[Mesh])))) OR ((((" AND Stroke AND "[Mesh] OR " AND Stroke, Lacunar AND "[Mesh] OR " AND Infarction, Middle Cerebral Artery AND "[Mesh] OR " AND Brain Stem Infarctions AND "[Mesh] OR " AND Infarction, Posterior Cerebral Artery AND "[Mesh])) OR ((((((Stroke*[Title/Abstract] OR poststroke*[Title/Abstract] OR post-stroke*[Title/Abstract] OR " AND cerebrovascular disorder* AND "[Title/Abstract] OR cerebrovascular*[Title/Abstract] OR " AND cerebral vascular AND "[Title/Abstract] OR " AND cerebrovascular disease* AND "[Title/Abstract] OR " AND basal ganglia cerebral vascular disease AND "[Title/Abstract] OR CVA*[Title/Abstract] OR " AND cerebrovascular accident* AND "[Title/Abstract])) OR (Ischaemia*[Title/Abstract] OR " AND brain ischemia AND "*[Title/Abstract] OR " AND ischaemic attack* AND

"[Title/Abstract] OR " AND ischaemic event* AND "[Title/Abstract] OR " AND carotid artery disease* AND "[Title/Abstract] OR " AND intracranial arterial disease* AND "[Title/Abstract] OR infarct*[Title/Abstract] OR " AND brain infarct* AND "[Title/Abstract] OR " AND cerebral infarct* AND "[Title/Abstract] OR thrombo*[Title/Abstract] OR emboli*[Title/Abstract])) OR (Cerebral[Title/Abstract] OR cerebellar[Title/Abstract] OR vertbrobailar[Title/Abstract] OR " AND cerebellar disorder* AND "[Title/Abstract] OR " AND cerebellar dysfunction* AND "[Title/Abstract] OR intracranial[Title/Abstract] OR intracerebral[Title/Abstract])) OR (subarachnoid[Title/Abstract] OR haemorrhag*[Title/Abstract] OR hemorrhag*[Title/Abstract] OR " AND intracranial haemorrhag* AND "[Title/Abstract] OR " AND intracranial hemorrhag* AND "[Title/Abstract] OR " AND cerebral haemorrhag* AND "[Title/Abstract] OR " AND cerebral hemorrhag* AND "[Title/Abstract] OR " AND subarachnoid haemorrhag* AND "[Title/Abstract] OR subarachnoid hemorrhag*"[Title/Abstract] OR "intracerebral haemorrhag*"[Title/Abstract] OR "intracerebral hemorrhag*"[Title/Abstract] OR "subdural haemorrhage*"[Title/Abstract] OR "subdural hemorrhag*"[Title/Abstract] OR extradural haemorrhage* AND "[Title/Abstract] OR " AND extradural hemorrhag* AND "[Title/Abstract] OR haematoma*[Title/Abstract] OR bleed*[Title/Abstract] OR " AND brain bleed* AND "[Title/Abstract] OR " AND acquired brain injur* AND Title/Abstract)) OR (hemiplegia*[Title/Abstract] OR hemiparesis*[Title/Abstract] OR paresis*[Title/Abstract])))))

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Sources	#5a	Indicate sources of financial or other support for the review	10

Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study	7

		level, or both; state how this information will be used in data synthesis	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	7
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

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Rehabilitation of Cognitive Deficits post Stroke: Protocol for a Systematic Review and Meta-Analysis of Randomised Controlled Trials of Non-Pharmacological Interventions

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Rehabilitation of Cognitive Deficits post Stroke: Protocol for a Systematic Review and Meta-Analysis of Randomised Controlled Trials of Non-Pharmacological Interventions

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Authors' contributions:

MOD, PB and RG were major contributors in writing the manuscript. SH, PB and SC designed the overall study. MOD, PB and RG developed the search strategy. All authors critically appraised and edited the manuscript. SH is the guarantor of the review. All authors read and approved the final manuscript.

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Abstract

Introduction: Stroke is among the leading causes of death and disability worldwide. Post stroke cognitive impairment is a common sequela of stroke. The burden of cognitive impairment post stroke has significant impacts on the individual post stroke, their family and wider society. Despite the prevalence and associated burden of post stroke cognitive impairment, the optimal approach to rehabilitate cognitive deficits post stroke has yet to be established. A range of conservative interventions for cognitive impairment post stroke exist including self-efficacy training, physical activity interventions, neuropsychological interventions, electronic interventions, music therapy and occupational therapies. This systematic review aims to explore the totality of evidence with regard to non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke.

Methods and Analysis: A systematic review of randomised controlled trials which investigate the effectiveness of interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke will be conducted. The following electronic databases will be searched: PubMed, Embase, CINAHL, CENTRAL and PsycInfo. Reference lists of all identified studies will be reviewed to identify additional studies for inclusion. Titles and abstracts will be screened independently by two review authors for inclusion and exclusion. Any disagreement regarding inclusion will be resolved by discussion or by referral to a third assessor if necessary. Methodological quality will be assessed using the Cochrane Risk of Bias Tool for Randomised Controlled Trials. Meta-analyses will be performed if studies are sufficiently homogeneous. The review will be reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Ethics and Dissemination: As this systematic review will collect secondary data only, ethical approval is not required. Findings will be disseminated through presentations and peer-reviewed journals.

Registration Details: Prospero Registration Number: CRD42019125289.

Strengths and Limitations of this study:

Strengths

- This is the first systematic review to synthesise the totality of evidence regarding non-pharmacological rehabilitation interventions which improve cognitive deficits post stroke.
- Robust and transparent methods used to identify, select, appraise and synthesise findings.
- Reporting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement
- Methodological quality assessed using Cochrane Risk of Bias tool.

Limitations

- Pharmacological interventions to address cognition post stroke will not be included.

Keywords: Stroke, cognitive impairment, rehabilitation.

Introduction

Stroke is among the leading causes disability worldwide [1]. The prevalence of stroke survivors is projected to increase given advancements in acute stroke care services in conjunction with an ageing world population [2]. Given the increased prevalence of individuals surviving a stroke, coupled with an increase in the number of disability-adjusted life-years *(*DALYs), stroke rehabilitation and the prevention of stroke-related residual disability have become increasingly important. Cognitive impairment is a common clinical feature of stroke reported in 56.6% of ischaemic stroke survivors at six months post stroke [3]. The presence of cognitive impairment post stroke is independently associated with lower quality of life at 12 months post stroke [4], higher levels of death and institutionalisation [5], increased carer burden [6] and increased healthcare costs [7].

A collaboration of stroke survivors, carers and healthcare professionals within the James Lind Alliance (UK) identified that optimum approaches to improve cognitive impairment post stroke were among the top ten research priorities with regard to life after stroke [8]. This finding is also supported by the Intercollegiate Stroke Working Party national clinical guidelines for stroke where it is acknowledged that although there have been developments within stroke rehabilitation literature; significant gaps exist in relation to cognition after stroke [9]. Furthermore, a meta-summary of qualitative studies regarding stroke survivors' experiences of rehabilitation found that individuals with stroke report an emphasis placed on the rehabilitation of physical deficits with a neglect towards non-physical needs such as social re-integration and psychological support post stroke [10].

As illustrated by the diversity and range of neuropsychological assessments, cognition is not a unitary concept [11]. Cognitive impairment post stroke encompasses a variety of deficits across multiple domains and typically includes memory, attention, executive function, language and visuo-perceptual ability [12]. Various cognitive domains enable complex mental processes to occur, which allow an individual to select and process information within their environment [13]. Given the complex nature of cognitive functioning, a broad range of interventions exist to improve cognitive function in individuals post stroke. Such interventions include, but are not restricted to, music therapy, resistance exercise training, aerobic exercise training, repetitive transcranial magnetic stimulation (rTMS), occupational therapies, neuropsychological interventions, cognitive strategy training, self-efficacy training,

virtual reality training, cognitive computerised training and electroacupuncture interventions [14]. Much of the previous research in this area has examined specific cognitive rehabilitation interventions on single domains of cognition post stroke. Six Cochrane reviews have explored the effectiveness of specific cognitive rehabilitation interventions on specific domains of cognitive function post stroke [15–20]. Cognitive rehabilitation is defined as "a systematic functionally orientated intervention of therapeutic cognitive activities based on the assessment and understanding of the patient's brain behaviour deficits" [13]. There is a need to capture a broader range of interventions other than specific cognitive rehabilitation interventions with regard to improving cognitive function post stroke. Moreover, the effectiveness of interventions across multiple domains of cognitive function needs to be investigated, given the diffuse nature of cognitive impairment post stroke [21]. Studies focusing on the rehabilitation of single cognitive domains fail to capture the interrelated and highly overlapping nature of cognitive domains [11].

In consideration of the effect of interventions other than specific cognitive rehabilitation interventions on cognitive impairment post stroke, “cognitive rehabilitation” is arguably too narrow a term to use regarding the remediation cognitive impairment post stroke. Rather, there should be a focus on the broader picture of the rehabilitation of cognitive deficits post stroke. The efficacy of all types of non-pharmacological rehabilitation interventions on cognitive deficits post stroke needs to be investigated. The breadth of interventions identified will capture the totality of evidence with regard to all types of non-pharmacological rehabilitation interventions to rehabilitate cognitive deficits in individuals post stroke. Furthermore, given the diffuse nature of cognitive deficits post stroke, there is a need to investigate the effects of interventions across all domains of cognition post stroke as opposed to focusing on domain-specific cognitive deficits.

In contrast with previous literature which has focused on specific single-domain cognitive rehabilitation interventions, this review will include all forms of non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function post stroke. Randomised controlled trials of interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke will be evaluated. In the context of this review, cognition will include general cognitive function as assessed by a standardised cognitive screening assessment. The review will also capture deficits across the domains of attention, memory, executive function, perception, limb apraxia and neglect

as outlined in the latest Australian Clinical Guidelines for Stroke (2017). To this end, this review aims to examine the totality of evidence with regard to non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke.

Methods

Study Design

The current systematic review protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[22]. In accordance with the PRISMA-P guidelines, this protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 13 February 2019.

Prospero Registration Number: CRD42019125289

Eligibility Criteria

Types of study

Randomised controlled trials and quasi-randomised control trials will be included, as defined by the Cochrane Handbook for Systematic Reviews of Interventions [23]. The pre-cross-over component of randomised and quasi-randomised cross-over trials will also be included, as will cluster trials. Studies published in the English language with full text available will be included.

Participants

Adults aged 18 years of age or older with a clinical diagnosis of ischaemic or haemorrhagic stroke are eligible for inclusion. Individuals with a confirmed cognitive impairment post stroke as specified by the authors within each trial will be included. Individuals may be in the acute, subacute or chronic stage post stroke.

Mixed aetiology studies (e.g. traumatic brain injury and stroke mix) will be included if separate data is reported on individuals with stroke which can be clearly extracted for review. Participants post transient ischaemic attack will be excluded, as will patients with dementia and patients with delirium. Individuals with cognitive impairment diagnosed before stroke onset will also be excluded.

Interventions

Interventions of which the primary or secondary aim is to improve cognitive function after stroke will be included. Interventions may focus on general cognitive function as assessed by a standardised cognitive screening assessment such as mini-mental state examination (MMSE) score, Montreal cognitive assessment scale (MoCA) score, the Addenbrooke Cognitive Examination (ACE). Interventions may also focus on cognitive in relation to the following cognitive domains: executive function, attention, memory, perception, limb apraxia and neglect as outlined in the Australian Clinical Guidelines for Stroke Management (2017).

Interventions may be of any type or duration or time since stroke. Some anticipated interventions may include, but are not restricted to:

- Neuropsychological interventions
- Exercise interventions: aerobic training, resistance training, flexibility training, balance training, Tai Chi
- Electronic interventions e.g. use of iPads, mobile phone apps
- Self-efficacy training
- Patient education interventions
- Cognitive rehabilitation interventions
- Virtual reality training
- Cognitive computerised training
- Acupuncture/ electroacupuncture interventions
- Non-invasive Brain Stimulation (NIBS)

Controls

Eligible control groups include:

Passive controls:

- Usual/Standard care control
- No treatment control
- Wait list control

Active controls:

- Comparing different forms of interventions which are hypothesised to mediate improvements in cognitive function post stroke.

Outcomes

The primary outcome is change in cognitive function post intervention in individuals with post stroke cognitive impairment. Outcome measures may focus on a domain-specific aspect of cognition such as executive function, attention, memory, perception, limb apraxia and neglect as outlined in the Australian Clinical Guidelines for Stroke Management (2017). Outcome measures may also cover a range of different cognitive functions in a single measure or give a measure of general cognitive status also.

Secondary outcome measures include quality of life, functional abilities, physical fitness, mobility, mood, participation and return to work.

Anticipated outcome measures include, but are not restricted to:

- Standardised tests or cognitive screening tools which provide a general cognitive function score e.g. Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), Addenbrooke Cognitive Examination (ACE).
- Subjective cognitive function e.g. cognitive failures questionnaire
- Neuropsychological Test Batteries
- Performance tests e.g. the Trail-Making Test, the Clock Drawing Test.
- Functional Assessments e.g. Personal/ domestic ADL's, community-based tasks, assessment of Motor and Process Skills (AMPS), Functional Independence Measure (FIM) or Functional Assessment Measure (FAM).

Pharmacological interventions (including over-the-counter medications) will be excluded.

Public and Patient Involvement

No patient involved.

Search

The following electronic databases will be searched: PubMed, , Embase, CENTRAL, PsycInfo and CINAHL. The search strategy was developed in consultation with an academic librarian (LD, University of Limerick). The search strategy includes search terms relating to the population of interest (individuals post stroke), the intervention (breadth of rehabilitation interventions as described), study type (randomised controlled trials) and the primary outcome of interest (change in cognitive function post stroke). To illustrate, the full electronic database search string for the CINAHL database is detailed in *Appendix 1.*

Reference lists of included studies will be searched to identify potentially eligible studies and authors of key texts may be contacted as appropriate. Forward citations on included studies will be checked. Clinical Trials.gov and the Vista database will be searched for potentially eligible ongoing trials.

Data selection

The search results from each individual database will be saved in a master reference management library (EndnoteX7) and duplicates will be removed. Titles and abstracts of the citations retrieved by the literature search will be screened independently by two review authors (MOD, RG) for inclusion or exclusion using Rayyan QCRI. The full text of potentially relevant studies will be selected for further assessment and two independent authors will ascertain and agree on eligibility based on the full article (RG, MOD). Any disagreement regarding inclusion will be resolved by discussion, or by referral to a third assessor (PB) if necessary.

Results of the screening process will be detailed within a PRISMA flow diagram.

Data Extraction

Data will be extracted and entered into a standardised recording data extraction form. Data including author, study design, population characteristics (age, gender, type of stroke, severity of stroke), intervention characteristics (intervention type, intervention content, duration of intervention, method of delivery, setting of intervention, length of follow-up), control group (passive, active), primary and secondary outcomes at post-interventions and follow-up, when available, will be extracted.

Data including the severity of cognitive impairment, type of cognitive impairment (i.e. domain(s) of cognition affected), neuropsychological underpinnings of cognitive impairment,

means(assessment) of formal diagnosis of cognitive impairment, definition of cognition/ cognitive impairment post stroke within each study, where available, will be extracted. The theoretical basis of the intervention/ mechanisms by which these interventions mediated cognitive improvement post stroke will also be documented. In consideration of the association between language impairments and performance on cognitive assessments, the language effects of primary outcome measures will be extracted.
Study authors will be contacted for missing data if necessary.

Risk of Bias

The internal and external validity of studies will be assessed by two independent reviewers (MOD, SH) using the Cochrane Risk of Bias Tool in accordance with the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and any other sources of bias[23]. Disagreements will be resolved by consensus among two other reviewers (RG, PB). Disagreements among the review authors on the methodological quality of the identified studies will be discussed and resolved by group consensus.

Strategy for data synthesis

We will perform separate analyses for trials comparing interventions to reduce cognitive impairment with 'treatment as usual', or with a 'placebo' control intervention, and trials comparing two active interventions. The Cochrane Review Manager software (RevMan) will be used to conduct statistical analyses to determine the treatment effect. For continuous data we will calculate the treatment effect using mean differences (SMD) and 95% CI where different studies used different scales to assess the same outcome, and calculate standardised mean differences (SMD) and 95% CI where studies have all used the same method of measuring outcome.

Due to the breadth of both interventions and cognitive outcome measures, it may be difficult to synthesise the data across studies. The impact of heterogeneity on results will be assessed using the I^2statistic. When the I^2 is < 30% there is little concern about statistical heterogeneity [23]. If there is statistical heterogeneity ≥50% we will use random- effects models to take account of the between-study variation in our findings [23].
If meta-analysis is not possible as a result of substantial heterogeneity, a narrative synthesis of findings from the included studies will be provided.

Subgroup Analysis

If a sufficient number of RCTs are identified, subgroup analyses will be conducted to establish the effect of the following subgroups on overall outcomes:

- Participant-related characteristics e.g. age of individuals with stroke (<65 vs >65); type and severity of stroke; time since stroke onset; severity of cognitive impairment; effect of depression and/ or fatigue on cognitive function; adherence to intervention;
- Intervention-related characteristics e.g. type of intervention: individual vs group training, self-efficacy training vs aerobic exercise training; impact of healthcare professionals on intervention outcomes; frequency, intensity, time and type of intervention
- Outcome-related characteristics, e.g. type of cognitive outcome assessed [including potential effects of language impairment on performance of the test], global cognitive outcome versus domain-specific outcome.

Discussion

This systematic review and meta-analysis will use a rigorous methodology to provide up to date evidence regarding the effectiveness of all types of non-pharmacological rehabilitation interventions on cognitive function post-stroke. Given the breadth of interventions shown to have an effect on post stroke cognitive impairment, there is a need to investigate all interventions, not solely cognitive rehabilitation interventions, which may mediate improvements in cognitive function post stroke. Previous research has taken a domain-specific approach to evaluating the effectiveness of cognitive rehabilitation interventions on cognitive deficits post stroke. Given the diffuse nature of post stroke cognitive impairment , the effectiveness of all types of non-pharmacological rehabilitation interventions across multiple domains of cognitive functioning post stroke needs to be investigated. A rigorous review of the effectiveness of all non-pharmacological rehabilitation interventions with regard to cognitive impairment post stroke is therefore needed.

The results of this review will inform the optimal type of interventions to rehabilitate cognitive impairment post stroke including information on frequency, intensity, type and delivery of interventions. This information will inform the development of an optimal intervention to rehabilitate cognitive impairment post stroke. In addition, if data proves to be

sufficiently homogenous to conduct a meta-analysis, information regarding the expected effect size associated with each intervention may be made available to healthcare professionals. This will be of use to clinicians and policy makers in their design and evaluation of rehabilitation services aimed at improving cognitive impairment post stroke.

Footnotes

Ethics and Dissemination

Findings will be disseminated through publication in peer-reviewed journals and through conferences. The rigorous scrutiny of primary studies will identify the strengths and limitations of current research and will provide recommendations for future research within this area.

Authors' Contributions: MOD, PB and RG were major contributors in writing the manuscript. SH, PB and SC designed the overall study. MOD, PB and RG developed the search strategy. All authors critically appraised and edited the manuscript. SH is the guarantor of the review. All authors read and approved the final manuscript.

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Competing Interests Statement: None declared.

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Search Strategy for CINAHL COMPLETE database

Appendix 1

S1) TI (Stroke* OR poststroke* OR post-stroke* OR “cerebrovascular disorder*” OR cerebrovascular* OR “cerebral vascular” OR “cerebrovascular disease*” OR “basal ganglia cerebral vascular disease” OR CVA* OR “cerebrovascular accident*”) OR AB (Stroke* OR poststroke* OR post-stroke* OR “cerebrovascular disorder*” OR cerebrovascular* OR “cerebral vascular” OR “cerebrovascular disease*” OR “basal ganglia cerebral vascular disease” OR CVA* OR “cerebrovascular accident*”) OR TI (Ischaemia* OR “brain ischemia”* OR “ischaemic attack*” OR “ischaemic event*” OR “carotid artery disease*” OR “intracranial arterial disease*” OR infarct* OR “brain infarct*” or “cerebral infarct*” OR thrombo* OR emboli*) OR AB (Ischaemia* OR “brain ischemia”* OR “ischaemic attack*” OR “ischaemic event*” OR “carotid artery disease*” OR “intracranial arterial disease*” OR infarct* OR “brain infarct*” or “cerebral infarct*” OR thrombo* OR emboli*) OR TI (Cerebral OR cerebellar OR vertbrobailar OR “cerebellar disorder*” OR “cerebellar dysfunction*” OR intracranial OR intracerebral) OR AB (Cerebral OR cerebellar OR vertbrobailar OR “cerebellar disorder*” OR “cerebellar dysfunction*” OR intracranial OR intracerebral) OR TI (subarachnoid OR haemorrhag* OR hemorrhag* OR “intracranial haemorrhag*” OR “intracranial hemorrhag*” OR “cerebral haemorrhag*” OR “cerebral hemorrhag*” OR “subarachnoid haemorrhag*” OR subarachnoid hemorrhag*” OR “intracerebral haemorrhag*” OR “intracerebral hemorrhag*” OR “subdural haemorrhage*” OR “subdural hemorrhag*” OR extradural haemorrhage*” OR “extradural hemorrhag*” OR haematoma* OR bleed* OR “brain bleed*” OR “acquired brain injur*”) OR AB (subarachnoid OR haemorrhag* OR hemorrhag* OR “intracranial haemorrhag*” OR “intracranial hemorrhag*” OR “cerebral haemorrhag*” OR “cerebral hemorrhag*” OR “subarachnoid haemorrhag*” OR subarachnoid hemorrhag*” OR “intracerebral haemorrhag*” OR “intracerebral hemorrhag*” OR “subdural haemorrhage*” OR “subdural hemorrhag*” OR extradural haemorrhage*” OR “extradural hemorrhag*” OR haematoma* OR bleed* OR “brain bleed*” OR “acquired brain injur*”) OR TI (hemiplegia* OR hemiparesis* OR paresis*) OR AB (hemiplegia* OR hemiparesis* OR paresis*)

S2) DE "Cerebrovascular Accidents" OR DE "Cerebrovascular Disorders" OR DE "Cerebral Arteriosclerosis" OR DE "Cerebral Hemorrhage" OR DE "Cerebral Ischemia" OR DE "Cerebral Small Vessel Disease"

S3) S1 OR S2

S4) TI (Cognition OR cogniti* OR “cogniti* disorder*” OR cogniti* disruption*” OR “cogniti* impair*” OR impairment* OR “cogniti* disorder*” OR confusion OR “neurobehavioural manifestation*” OR neurobehavioural disorder *” “cogniti* abilil*” OR “neurobehavioural disruption*”) OR AB (Cognition OR cogniti* OR “cogniti* disorder*” OR cogniti* disruption*” OR “cogniti* impair*” OR impairment* OR “cogniti* disorder*” OR confusion OR “neurobehavioural manifestation*” OR neurobehavioural disorder *” “cogniti* abilil*” OR “neurobehavioural disruption*”)

S5) DE "Cognition" OR DE "Cognitive Processes" OR DE "Cognitive Impairment"

S6) DE "Cognitive Ability" OR DE "Cognitive Impairment" OR DE "Spatial Ability" OR DE "Cognitive Processing Speed" OR DE "Executive Function" OR DE "Neurocognitive Disorders"

S7) S4 OR S5 OR S6

S8) TI (“Executive function*” OR “executive dysfunction*” OR “dysexecutive syndrome*” OR “dysexecutive function*”) OR AB (“Executive function*” OR “executive dysfunction*” OR “dysexecutive syndrome*” OR “dysexecutive function*”) OR TI (“Goal management” OR “goal selection*” OR “goal setting*”) OR AB (“Goal management” OR “goal selection*” OR “goal setting*”) OR TI (“Strategy formation*” OR planning OR organisation OR “time management” OR “problem solving” OR “decision making” OR sequencing OR “sequence of steps”) OR AB (“Strategy formation*” OR planning OR organisation OR “time management” OR “problem solving” OR “decision making” OR sequencing OR “sequence of steps”)

S9) DE "Executive Function" OR DE "Cognitive Processes" OR DE "Dysexecutive Syndrome" OR DE "Executive Functioning Measures"

S10) S8 OR S9

S11) TI (Attention OR arousal OR concentration OR alert* OR vigilance OR inattention OR distract*) OR AB (Attention OR arousal OR concentration OR alert* OR vigilance OR inattention OR distract*)

S12) DE "Attention" OR DE "Awareness" OR DE "Divided Attention" OR DE "Focused Attention" OR DE "Selective Attention" OR DE "Sustained Attention" OR DE "Visual Attention" OR DE "Attention Span" OR DE "Concentration"

S13) S11 OR S12

S14) TI (memory OR “computer assisted therap*” OR “computer-assisted therap*”) OR AB (memory OR “computer assisted therap*” OR “computer-assisted therap*”)

S15) DE "Memory" OR DE "Forgetting" OR DE "Episodic Memory" OR DE "Explicit Memory" OR DE "Implicit Memory" OR DE "Long Term Memory" OR DE "Short Term Memory" OR DE "Cognitive Aging" OR DE "Memory Training"

S16) S14 OR S15

S17) TI (Perception* OR “perceptual disorder*” OR “visual perception*” OR “visual construct*” OR agnosia* OR prosopagnosia* OR stereognosis) OR AB (Perception* OR “perceptual disorder*” OR “visual perception*” OR “visual construct*” OR agnosia* OR prosopagnosia* OR stereognosis)

S18) DE "Perception" OR DE "Auditory Perception" OR DE "Perceptual Distortion" OR DE "Perceptual Motor Processes" OR DE "Time Perception" OR DE "Visual Perception" OR DE "Perceptual Disturbances" OR DE "Sensory Integration Dysfunction"

S19) S17 OR S18

S20) TI (“limb apraxia*” OR “motor apraxia*” OR Apraxia* OR psychomotor OR “psychomotor performance*” OR “psychomotor disorder*” OR psychomotor disruption*”) OR AB (“limb apraxia*” OR “motor apraxia*” OR Apraxia* OR psychomotor OR “psychomotor performance*” OR “psychomotor disorder*” OR psychomotor disruption*”)

S21) DE "Apraxia" OR DE "Movement Disorders"

S22) S20 OR S21

S23) TI (Neglect OR perception* OR attention OR hemineglect OR “hemi-neglect” OR “unilateral neglect” OR “spatial neglect” OR “spatial-neglect” OR “hemi-attention” OR “hemi attention” OR visuospatial) OR AB (Neglect OR perception* OR attention OR hemineglect OR “hemi-neglect” OR “unilateral neglect” OR “spatial neglect” OR “spatial-neglect” OR “hemi-attention” OR “hemi attention” OR visuospatial)

S24) DE "Sensory Neglect" OR DE "Receptive Fields"

S25) TI (Rehabilitation* OR rehab* OR recover* OR recovery* OR “re-establishment*” OR vocational OR retraining OR re-training OR remediation) OR AB (Rehabilitation* OR rehab* OR recover* OR recovery* OR “re-establishment*” OR vocational OR retraining OR re-training OR remediation) OR TI (intervention* OR therap* OR “cogniti* intervention*” OR “cogniti* therap*” OR “cogniti” behaviour* therap*” OR “cogniti* training” OR “cognitive rehab*” OR “cognit* stimulation” OR “cogniti* program*”) OR AB (intervention* OR therap* OR “cogniti* intervention*” OR “cogniti* therap*” OR “cogniti” behaviour* therap*” OR “cogniti* training” OR “cognitive rehab*” OR “cognit* stimulation” OR “cogniti* program*”) OR TI (neuropsychological OR “neuropsychological rehab*”) OR AB (neuropsychological OR “neuropsychological rehab*”) OR TI (“computer-assisted therap*” OR “internal strategy*” OR “external strategy*” OR “time pressure management” OR “self-monitoring” OR

“stimulus control” OR “vanishing cue*” OR “self-instruction” OR “errorless learning” OR “psychological intervention*” OR “psychological rehab*” OR “psychological retraining”) OR AB (“computer-assisted therap*” OR “internal strategy*” OR “external strategy*” OR “time pressure management” OR “self-monitoring” OR “stimulus control” OR “vanishing cue*” OR “self-instruction” OR “errorless learning” OR “psychological intervention*” OR “psychological rehab*” OR “psychological retraining”)

S26) DE "Rehabilitation" OR DE "Cognitive Rehabilitation" OR DE "Neuropsychological Rehabilitation" OR DE "Neurorehabilitation" OR DE "Occupational Therapy" OR DE "Physical Therapy" OR DE "Psychosocial Rehabilitation" OR DE "Rehabilitation Centers" OR DE "Telerehabilitation" OR DE "Activities of Daily Living" OR DE "Adaptive Behavior" OR DE "Animal Assisted Therapy" OR DE "Deinstitutionalization" OR DE "Independent Living Programs" OR DE "Intervention" OR DE "Rehabilitation Counseling" OR DE "Self-Care Skills" OR DE "Support Groups"

S27) S25 OR S26

S28) S23 OR S24

S29) S7 OR S10 OR S13 OR S16 OR S19 OR S22 OR S28

S30) S3 AND S29

S31) S27 AND S30

S32) TI (Control* OR experiment* OR treatment* OR conservative) OR AB (Control* OR experiment* OR treatment* OR conservative) OR TI (Treatment* OR therapy* OR procedure* OR manage*) OR AB (Treatment* OR therapy* OR procedure* OR manage*) OR TI (“singl* blind" OR "doubl* blind" OR "tripl* blind") OR AB (“singl* blind" OR "doubl* blind" OR "tripl* blind") OR TI (" singl* blind" OR "doubl* mask*" OR "tripl* mask*" OR "trebl* mask*") OR AB (" singl* blind" OR "doubl* mask*" OR "tripl* mask*" OR "trebl* mask*") OR TI (Random* OR "controlled trial*" OR "controlled stud*" OR "clinical trial*" OR "clinical stud*" OR "therapeutic trial*" OR "therapeutic stud*") AND AB (Random* OR "controlled trial*" OR "controlled stud*" OR "clinical trial*" OR "clinical stud*" OR "therapeutic trial*" OR "therapeutic stud*"

S33) DE "Randomized Clinical Trials" OR DE "Randomized Controlled Trials" OR DE "Experimental Subjects" OR DE "Placebo" OR DE "Random Sampling"

S34) S32 OR S33

S35) S31 AND S34

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Sources	#5a	Indicate sources of financial or other support for the review	11
Sponsor	#5b	Provide name for the review funder and / or sponsor	11
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	11
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-7
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such	5

		as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9-10

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

Rehabilitation of Cognitive Deficits post Stroke: Protocol for a Systematic Review and Meta-Analysis of Randomised Controlled Trials of Non-Pharmacological Interventions

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Rehabilitation of Cognitive Deficits post Stroke: Protocol for a Systematic Review and Meta-Analysis of Randomised Controlled Trials of Non-Pharmacological Interventions

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Authors' contributions:

MOD, PB and RG were major contributors in writing the manuscript. SH, PB and SC designed the overall study. MOD, PB and RG developed the search strategy. All authors critically appraised and edited the manuscript. SH is the guarantor of the review. All authors read and approved the final manuscript.

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Abstract

Introduction: Stroke is among the leading causes of death and disability worldwide. Post stroke cognitive impairment is a common sequela of stroke. The burden of cognitive impairment post stroke has significant impacts on the individual post stroke, their family and wider society. Despite the prevalence and associated burden of post stroke cognitive impairment, the optimal approach to rehabilitate cognitive deficits post stroke has yet to be established. A range of conservative interventions for cognitive impairment post stroke exist including self-efficacy training, physical activity interventions, neuropsychological interventions, electronic interventions, music therapy and occupational therapies. This systematic review aims to explore the totality of evidence with regard to non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke.

Methods and Analysis: A systematic review of randomised controlled trials which investigate the effectiveness of interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke will be conducted (August 2019). The following electronic databases will be searched: PubMed, Embase, CINAHL, CENTRAL and PsycInfo. Reference lists of all identified studies will be reviewed to identify additional studies for inclusion. Titles and abstracts will be screened independently by two review authors for inclusion and exclusion. Any disagreement regarding inclusion will be resolved by discussion or by referral to a third assessor if necessary. Methodological quality will be assessed using the Cochrane Risk of Bias Tool for Randomised Controlled Trials. Meta-analyses will be performed if studies are sufficiently homogeneous. The review will be reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Ethics and Dissemination: As this systematic review will collect secondary data only, ethical approval is not required. Findings will be disseminated through presentations and peer-reviewed journals.

Registration Details: Prospero Registration Number: CRD42019125289.

Strengths and Limitations of this study:

Strengths

- This is the first systematic review to synthesise the totality of evidence regarding non-pharmacological rehabilitation interventions which improve cognitive deficits post stroke.
- Robust and transparent methods used to identify, select, appraise and synthesise findings.
- Reporting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement
- Methodological quality assessed using Cochrane Risk of Bias tool.

Limitations

- Pharmacological interventions to address cognition post stroke will not be included.

Keywords: Stroke, cognitive impairment, rehabilitation.

Introduction

Stroke is among the leading causes disability worldwide [1]. The prevalence of stroke survivors is projected to increase given advancements in acute stroke care services in conjunction with an ageing world population [2]. Given the increased prevalence of individuals surviving a stroke, coupled with an increase in the number of disability-adjusted life-years *(*DALYs), stroke rehabilitation and the prevention of stroke-related residual disability have become increasingly important. Cognitive impairment is a common clinical feature of stroke reported in 56.6% of ischaemic stroke survivors at six months post stroke [3]. The presence of cognitive impairment post stroke is independently associated with lower quality of life at 12 months post stroke [4], higher levels of death and institutionalisation [5], increased carer burden [6] and increased healthcare costs [7].

A collaboration of stroke survivors, carers and healthcare professionals within the James Lind Alliance (UK) identified that optimum approaches to improve cognitive impairment post stroke were among the top ten research priorities with regard to life after stroke [8]. This finding is also supported by the Intercollegiate Stroke Working Party national clinical guidelines for stroke where it is acknowledged that although there have been developments within stroke rehabilitation literature; significant gaps exist in relation to cognition after stroke [9]. Furthermore, a meta-summary of qualitative studies regarding stroke survivors' experiences of rehabilitation found that individuals with stroke report an emphasis placed on the rehabilitation of physical deficits with a neglect towards non-physical needs such as social re-integration and psychological support post stroke [10].

As illustrated by the diversity and range of neuropsychological assessments, cognition is not a unitary concept [11]. Cognitive impairment post stroke encompasses a variety of deficits across multiple domains and typically includes memory, attention, executive function, language and visuo-perceptual ability [12]. Various cognitive domains enable complex mental processes to occur, which allow an individual to select and process information within their environment [13]. Given the complex nature of cognitive functioning, a broad range of interventions exist to improve cognitive function in individuals post stroke. Such interventions include, but are not restricted to, music therapy, resistance exercise training, aerobic exercise training, repetitive transcranial magnetic stimulation (rTMS), occupational therapies, neuropsychological interventions, cognitive strategy training, self-efficacy training,

virtual reality training, cognitive computerised training and electroacupuncture interventions [14]. Much of the previous research in this area has examined specific cognitive rehabilitation interventions on single domains of cognition post stroke. Six Cochrane reviews have explored the effectiveness of specific cognitive rehabilitation interventions on specific domains of cognitive function post stroke [15–20]. Cognitive rehabilitation is defined as "a systematic functionally orientated intervention of therapeutic cognitive activities based on the assessment and understanding of the patient's brain behaviour deficits" [13]. There is a need to capture a broader range of interventions other than specific cognitive rehabilitation interventions with regard to improving cognitive function post stroke. Moreover, the effectiveness of interventions across multiple domains of cognitive function needs to be investigated, given the diffuse nature of cognitive impairment post stroke [21]. Studies focusing on the rehabilitation of single cognitive domains fail to capture the interrelated and highly overlapping nature of cognitive domains [11].

In consideration of the effect of interventions other than specific cognitive rehabilitation interventions on cognitive impairment post stroke, “cognitive rehabilitation” is arguably too narrow a term to use regarding the remediation cognitive impairment post stroke. Rather, there should be a focus on the broader picture of the rehabilitation of cognitive deficits post stroke. The efficacy of all types of non-pharmacological rehabilitation interventions on cognitive deficits post stroke needs to be investigated. The breadth of interventions identified will capture the totality of evidence with regard to all types of non-pharmacological rehabilitation interventions to rehabilitate cognitive deficits in individuals post stroke. Furthermore, given the diffuse nature of cognitive deficits post stroke, there is a need to investigate the effects of interventions across all domains of cognition post stroke as opposed to focusing on domain-specific cognitive deficits.

In contrast with previous literature which has focused on specific single-domain cognitive rehabilitation interventions, this review will include all forms of non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function post stroke. Randomised controlled trials of interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke will be evaluated. In the context of this review, cognition will include general cognitive function as assessed by a standardised cognitive screening assessment. The review will also capture deficits across the domains of attention, memory, executive function, perception, limb apraxia and neglect

as outlined in the latest Australian Clinical Guidelines for Stroke (2017). To this end, this review aims to examine the totality of evidence with regard to non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function in individuals post stroke.

Methods

Study Design

The current systematic review protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[22]. In accordance with the PRISMA-P guidelines, this protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 13 February 2019.

Prospero Registration Number: CRD42019125289

Eligibility Criteria

Types of study

Randomised controlled trials and quasi-randomised control trials will be included, as defined by the Cochrane Handbook for Systematic Reviews of Interventions [23]. The pre-cross-over component of randomised and quasi-randomised cross-over trials will also be included, as will cluster trials. Studies published in the English language with full text available will be included.

Participants

Adults aged 18 years of age or older with a clinical diagnosis of ischaemic or haemorrhagic stroke are eligible for inclusion. Individuals with a confirmed cognitive impairment post stroke as specified by the authors within each trial will be included. Individuals may be in the acute, subacute or chronic stage post stroke.

Mixed aetiology studies (e.g. traumatic brain injury and stroke mix) will be included if separate data is reported on individuals with stroke which can be clearly extracted for review. Participants post transient ischaemic attack will be excluded, as will patients with dementia and patients with delirium. Individuals with cognitive impairment diagnosed before stroke onset will also be excluded.

Interventions

Interventions of which the primary or secondary aim is to improve cognitive function after stroke will be included. Interventions may focus on general cognitive function as assessed by a standardised cognitive screening assessment such as mini-mental state examination (MMSE) score, Montreal cognitive assessment scale (MoCA) score, the Addenbrooke Cognitive Examination (ACE). Interventions may also focus on cognitive in relation to the following cognitive domains: executive function, attention, memory, perception, limb apraxia and neglect as outlined in the Australian Clinical Guidelines for Stroke Management (2017).

Interventions may be of any type or duration or time since stroke. Some anticipated interventions may include, but are not restricted to:

- Neuropsychological interventions
- Exercise interventions: aerobic training, resistance training, flexibility training, balance training, Tai Chi
- Electronic interventions e.g. use of iPads, mobile phone apps
- Self-efficacy training
- Patient education interventions
- Cognitive rehabilitation interventions
- Virtual reality training
- Cognitive computerised training
- Acupuncture/ electroacupuncture interventions
- Non-invasive Brain Stimulation (NIBS)

Controls

Eligible control groups include:

Passive controls:

- Usual/Standard care control
- No treatment control
- Wait list control

Active controls:

- Comparing different forms of interventions which are hypothesised to mediate improvements in cognitive function post stroke.

Outcomes

The primary outcome is change in cognitive function post intervention in individuals with post stroke cognitive impairment. Outcome measures may focus on a domain-specific aspect of cognition such as executive function, attention, memory, perception, limb apraxia and neglect as outlined in the Australian Clinical Guidelines for Stroke Management (2017). Outcome measures may also cover a range of different cognitive functions in a single measure or give a measure of general cognitive status also.

Secondary outcome measures include quality of life, functional abilities, physical fitness, mobility, mood, participation and return to work.

Anticipated outcome measures include, but are not restricted to:

- Standardised tests or cognitive screening tools which provide a general cognitive function score e.g. Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), Addenbrooke Cognitive Examination (ACE).
- Subjective cognitive function e.g. cognitive failures questionnaire
- Neuropsychological Test Batteries
- Performance tests e.g. the Trail-Making Test, the Clock Drawing Test.
- Functional Assessments e.g. Personal/ domestic ADL's, community-based tasks, assessment of Motor and Process Skills (AMPS), Functional Independence Measure (FIM) or Functional Assessment Measure (FAM).

Pharmacological interventions (including over-the-counter medications) will be excluded.

Public and Patient Involvement

No patient involved.

Search

The following electronic databases will be searched: PubMed, , Embase, CENTRAL, PsycInfo and CINAHL (August 2019). The search strategy was developed in consultation with an academic librarian (LD, University of Limerick). The search strategy includes search terms relating to the population of interest (individuals post stroke), the intervention (breadth of rehabilitation interventions as described), study type (randomised controlled trials) and the primary outcome of interest (change in cognitive function post stroke). To illustrate, the full electronic database search string for the CINAHL database is detailed in *Appendix 1*.

Reference lists of included studies will be searched to identify potentially eligible studies and authors of key texts may be contacted as appropriate. Forward citations on included studies will be checked. Clinical Trials.gov and the Vista database will be searched for potentially eligible ongoing trials.

Data selection

The search results from each individual database will be saved in a master reference management library (EndnoteX7) and duplicates will be removed. Titles and abstracts of the citations retrieved by the literature search will be screened independently by two review authors (MOD, RG) for inclusion or exclusion using Rayyan QCRI. The full text of potentially relevant studies will be selected for further assessment and two independent authors will ascertain and agree on eligibility based on the full article (RG, MOD). Any disagreement regarding inclusion will be resolved by discussion, or by referral to a third assessor (PB) if necessary.

Results of the screening process will be detailed within a PRISMA flow diagram.

Data Extraction

Data will be extracted and entered into a standardised recording data extraction form. Data including author, study design, population characteristics (age, gender, type of stroke, severity of stroke), intervention characteristics (intervention type, intervention content, duration of intervention, method of delivery, setting of intervention, length of follow-up), control group (passive, active), primary and secondary outcomes at post-interventions and follow-up, when available, will be extracted.

Data including the severity of cognitive impairment, type of cognitive impairment (i.e. domain(s) of cognition affected), neuropsychological underpinnings of cognitive impairment,

means(assessment) of formal diagnosis of cognitive impairment, definition of cognition/ cognitive impairment post stroke within each study, where available, will be extracted.

Both the stage post stroke (acute, subacute and chronic) and the severity of cognitive impairment (mild, moderate, severe) will be considered within the context of each individual study and reported descriptively. The theoretical basis of the intervention/ mechanisms by which these interventions mediated cognitive improvement post stroke will also be documented. In consideration of the association between language impairments and performance on cognitive assessments, the language effects of primary outcome measures will be extracted.

Study authors will be contacted for missing data if necessary.

Risk of Bias

The internal and external validity of studies will be assessed by two independent reviewers (MOD, SH) using the Cochrane Risk of Bias Tool in accordance with the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and any other sources of bias[23]. Disagreements will be resolved by consensus among two other reviewers (RG, PB). Disagreements among the review authors on the methodological quality of the identified studies will be discussed and resolved by group consensus.

Strategy for data synthesis

We will perform separate analyses for trials comparing interventions to reduce cognitive impairment with 'treatment as usual', or with a 'placebo' control intervention, and trials comparing two active interventions. The Cochrane Review Manager software (RevMan) will be used to conduct statistical analyses to determine the treatment effect. For continuous data we will calculate the treatment effect using mean differences (SMD) and 95% CI where different studies used different scales to assess the same outcome, and calculate standardised mean differences (SMD) and 95% CI where studies have all used the same method of measuring outcome.

Due to the breadth of both interventions and cognitive outcome measures, it may be difficult to synthesise the data across studies. The impact of heterogeneity on results will be assessed using the I^2statistic. When the I^2 is < 30% there is little concern about statistical heterogeneity

[23]. If there is statistical heterogeneity ≥50% we will use random- effects models to take account of the between-study variation in our findings [23].

If meta-analysis is not possible as a result of substantial heterogeneity, a narrative synthesis of findings from the included studies will be provided.

Subgroup Analysis

If a sufficient number of RCTs are identified, subgroup analyses will be conducted to establish the effect of the following subgroups on overall outcomes:

- Participant-related characteristics e.g. age of individuals with stroke (<65 vs >65); type and severity of stroke; time since stroke onset; severity of cognitive impairment; effect of depression and/ or fatigue on cognitive function; adherence to intervention;
- Intervention-related characteristics e.g. type of intervention: individual vs group training, self-efficacy training vs aerobic exercise training; impact of healthcare professionals on intervention outcomes; frequency, intensity, time and type of intervention
- Outcome-related characteristics, e.g. type of cognitive outcome assessed [including potential effects of language impairment on performance of the test], global cognitive outcome versus domain-specific outcome.

Discussion

This systematic review and meta-analysis will use a rigorous methodology to provide up to date evidence regarding the effectiveness of all types of non-pharmacological rehabilitation interventions on cognitive function post-stroke. Given the breadth of interventions shown to have an effect on post stroke cognitive impairment, there is a need to investigate all interventions, not solely cognitive rehabilitation interventions, which may mediate improvements in cognitive function post stroke. Previous research has taken a domain-specific approach to evaluating the effectiveness of cognitive rehabilitation interventions on cognitive deficits post stroke. Given the diffuse nature of post stroke cognitive impairment , the effectiveness of all types of non-pharmacological rehabilitation interventions across multiple domains of cognitive functioning post stroke needs to be investigated. A rigorous review of the effectiveness of all non-pharmacological rehabilitation interventions with regard to cognitive impairment post stroke is therefore needed.

The results of this review will inform the optimal type of interventions to rehabilitate cognitive impairment post stroke including information on frequency, intensity, type and delivery of interventions. This information will inform the development of an optimal intervention to rehabilitate cognitive impairment post stroke. In addition, if data proves to be sufficiently homogenous to conduct a meta-analysis, information regarding the expected effect size associated with each intervention may be made available to healthcare professionals. This will be of use to clinicians and policy makers in their design and evaluation of rehabilitation services aimed at improving cognitive impairment post stroke.

Footnotes

Ethics and Dissemination

Findings will be disseminated through publication in peer-reviewed journals and through conferences. The rigorous scrutiny of primary studies will identify the strengths and limitations of current research and will provide recommendations for future research within this area.

Authors' Contributions: MOD, PB and RG were major contributors in writing the manuscript. SH, PB and SC designed the overall study. MOD, PB and RG developed the search strategy. All authors critically appraised and edited the manuscript. SH is the guarantor of the review. All authors read and approved the final manuscript.

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Competing Interests Statement: None declared.

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23 Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**. doi:10.1136/bmj.d5928

TI (Stroke* OR poststroke* OR post-stroke* OR “cerebrovascular disorder*” OR cerebrovascular* OR “cerebral vascular” OR “cerebrovascular disease*” OR “basal ganglia cerebral vascular disease” OR CVA* OR “cerebrovascular accident*”) OR AB (Stroke* OR poststroke* OR post-stroke* OR “cerebrovascular disorder*” OR cerebrovascular* OR “cerebral vascular” OR “cerebrovascular disease*” OR “basal ganglia cerebral vascular disease” OR CVA* OR “cerebrovascular accident*”) OR TI (Ischaemia* OR “brain ischemia”* OR “ischaemic attack*” OR “ischaemic event*” OR “carotid artery disease*” OR “intracranial arterial disease*” OR infarct* OR “brain infarct*” or “cerebral infarct*” OR thrombo* OR emboli*) OR AB (Ischaemia* OR “brain ischemia”* OR “ischaemic attack*” OR “ischaemic event*” OR “carotid artery disease*” OR “intracranial arterial disease*” OR infarct* OR “brain infarct*” or “cerebral infarct*” OR thrombo* OR emboli*) OR TI (Cerebral OR cerebellar OR vertbrobailar OR “cerebellar disorder*” OR “cerebellar dysfunction*” OR intracranial OR intracerebral) OR AB (Cerebral OR cerebellar OR vertbrobailar OR “cerebellar disorder*” OR “cerebellar dysfunction*” OR intracranial OR intracerebral) OR TI (subarachnoid OR haemorrhag* OR hemorrhag* OR “intracranial haemorrhag*” OR “intracranial hemorrhag*” OR “cerebral haemorrhag*” OR “cerebral hemorrhag*” OR “subarachnoid haemorrhag*” OR subarachnoid hemorrhag*” OR “intracerebral haemorrhag*” OR “intracerebral hemorrhag*” OR “subdural haemorrhage*” OR “subdural hemorrhag*” OR extradural haemorrhage*” OR “extradural hemorrhag*” OR haematoma* OR bleed* OR “brain bleed*” OR “acquired brain injur*”) OR AB (subarachnoid OR haemorrhag* OR hemorrhag* OR “intracranial haemorrhag*” OR “intracranial hemorrhag*” OR “cerebral haemorrhag*” OR “cerebral hemorrhag*” OR “subarachnoid haemorrhag*” OR subarachnoid hemorrhag*” OR “intracerebral haemorrhag*” OR “intracerebral hemorrhag*” OR “subdural haemorrhage*” OR “subdural hemorrhag*” OR extradural haemorrhage*” OR “extradural hemorrhag*” OR haematoma* OR bleed* OR “brain bleed*” OR “acquired brain injur*”) OR TI (hemiplegia* OR hemiparesis* OR paresis*) OR AB (hemiplegia* OR hemiparesis* OR paresis*)

DE "Cerebrovascular Accidents" OR DE "Cerebrovascular Disorders" OR DE "Cerebral Arteriosclerosis" OR DE "Cerebral Hemorrhage" OR DE "Cerebral Ischemia" OR DE "Cerebral Small Vessel Disease"

S1 OR S2

TI (Cognition OR cogniti* OR “cogniti* disorder*” OR cogniti* disruption*” OR “cogniti* impair*” OR impairment* OR “cogniti* disorder*” OR confusion OR “neurobehavioural manifestation*” OR neurobehavioural disorder *” “cogniti* abilil*” OR “neurobehavioural disruption*”) OR AB (Cognition OR cogniti* OR “cogniti* disorder*” OR cogniti* disruption*” OR “cogniti* impair*” OR impairment* OR “cogniti* disorder*” OR confusion OR “neurobehavioural manifestation*” OR neurobehavioural disorder *” “cogniti* abilil*” OR “neurobehavioural disruption*”) OR “domain-specific” OR “domain-general”

DE "Cognition" OR DE "Cognitive Processes" OR DE "Cognitive Impairment"

DE "Cognitive Ability" OR DE "Cognitive Impairment" OR DE "Spatial Ability" OR DE "Cognitive Processing Speed" OR DE "Executive Function" OR DE "Neurocognitive Disorders" OR neurocognit* OR neuropsych* OR “neurocognit* disorder*” OR “neuropsych* disorder*”

S4 OR S5 OR S6

TI (“Executive function*” OR “executive dysfunction*” OR “dysexecutive syndrome*” OR “dysexecutive function*”) OR AB (“Executive function*” OR “executive dysfunction*” OR “dysexecutive syndrome*” OR “dysexecutive function*”) OR TI (“Goal management” OR “goal selection*” OR “goal setting*”) OR AB (“Goal management” OR “goal selection*” OR “goal setting*”) OR TI (“Strategy formation*” OR planning OR organisation OR “time management” OR “problem solving” OR “decision making” OR sequencing OR “sequence of steps”) OR AB (“Strategy formation*” OR planning OR organisation OR “time management” OR “problem solving” OR “decision making” OR sequencing OR “sequence of steps”)

DE "Executive Function" OR DE "Cognitive Processes" OR DE "Dysexecutive Syndrome" OR DE "Executive Functioning Measures"

S8 OR S9

TI (Attention OR arousal OR concentration OR alert* OR vigilance OR inattention OR distract*) OR AB (Attention OR arousal OR concentration OR alert* OR vigilance OR inattention OR distract*)

DE "Attention" OR DE "Awareness" OR DE "Divided Attention" OR DE "Focused Attention" OR DE "Selective Attention" OR DE "Sustained Attention" OR DE "Visual Attention" OR DE "Attention Span" OR DE "Concentration"

S11 OR S12

TI (memory OR “computer assisted therap*” OR “computer-assisted therap*”) OR AB (memory OR “computer assisted therap*” OR “computer-assisted therap*”)

S14 OR S15

TI (Perception* OR “perceptual disorder*” OR “visual perception*” OR “visual construct*” OR agnosia* OR prosopagnosia* OR stereognosis) OR AB (Perception* OR “perceptual disorder*” OR “visual perception*” OR “visual construct*” OR agnosia* OR prosopagnosia* OR stereognosis)

DE "Perception" OR DE "Auditory Perception" OR DE "Perceptual Distortion" OR DE "Perceptual Motor Processes" OR DE "Time Perception" OR DE "Visual Perception" OR DE "Perceptual Disturbances" OR DE "Sensory Integration Dysfunction"

S17 OR S18

TI (“limb apraxia*” OR “motor apraxia*” OR Apraxia* OR psychomotor OR “psychomotor performance*” OR “psychomotor disorder*” OR psychomotor disruption*”) OR AB (“limb apraxia*” OR “motor apraxia*” OR Apraxia* OR psychomotor OR “psychomotor performance*” OR “psychomotor disorder*” OR psychomotor disruption*”)

DE "Apraxia" OR DE "Movement Disorders"

S20 OR S21

TI (Neglect OR perception* OR attention OR hemineglect OR “hemi-neglect” OR “unilateral neglect” OR “spatial neglect” OR “spatial-neglect” OR “hemi-attention” OR “hemi attention” OR visuospatial) OR AB (Neglect OR perception* OR attention OR hemineglect OR “hemi-neglect” OR “unilateral neglect” OR “spatial neglect” OR “spatial-neglect” OR “hemi-attention” OR “hemi attention” OR visuospatial)

DE "Sensory Neglect" OR DE "Receptive Fields"

TI (Rehabilitation* OR rehab* OR recover* OR recovery* OR “re-establishment*” OR vocational OR retraining OR re-training OR remediation) OR AB (Rehabilitation* OR rehab* OR recover* OR recovery* OR “re-establishment*” OR vocational OR retraining OR re-training OR remediation) OR TI (intervention* OR therap* OR “cogniti* intervention*” OR “cogniti* therap*” OR “cogniti” behaviour* therap*” OR “cogniti* training” OR “cognitive rehab*” OR “cognit* stimulation” OR “cogniti* program*”) OR AB (intervention* OR therap* OR “cogniti* intervention*” OR “cogniti* therap*” OR “cogniti” behaviour* therap*” OR “cogniti* training” OR “cognitive rehab*” OR “cognit* stimulation” OR “cogniti* program*”) OR TI (neuropsychological OR “neuropsychological rehab*”) OR AB (neuropsychological OR “neuropsychological rehab*”) OR TI (“computer-assisted therap*” OR “internal strategy*” OR “external strategy*” OR “time pressure management” OR “self-monitoring” OR “stimulus control” OR “vanishing cue*” OR “self-instruction” OR “errorless learning” OR “psychological intervention*” OR “psychological rehab*” OR “psychological retraining”) OR AB (“computer-assisted therap*” OR “internal strategy*” OR “external strategy*” OR “time pressure management” OR “self-monitoring” OR “stimulus control” OR “vanishing cue*” OR “self-instruction” OR “errorless learning” OR “psychological intervention*” OR “psychological rehab*” OR “psychological retraining”)

DE "Rehabilitation" OR DE "Cognitive Rehabilitation" OR DE "Neuropsychological Rehabilitation" OR DE "Neurorehabilitation" OR DE "Occupational Therapy" OR DE "Physical Therapy" OR DE "Psychosocial Rehabilitation" OR DE "Rehabilitation Centers" OR DE "Telerehabilitation" OR DE "Activities of Daily Living" OR DE "Adaptive Behavior" OR DE "Animal Assisted Therapy" OR DE "Deinstitutionalization" OR DE "Independent Living Programs" OR DE "Intervention" OR DE "Rehabilitation Counseling" OR DE "Self-Care Skills" OR DE "Support Groups"

S25 OR S26

S23 OR S24

S7 OR S10 OR S13 OR S16 OR S19 OR S22 OR S28

S3 AND S29

S27 AND S30

TI (Control* OR experiment* OR treatment* OR conservative) OR AB (Control* OR experiment* OR treatment* OR conservative) OR TI (Treatment* OR therapy* OR procedure* OR manage*) OR AB (Treatment* OR therapy* OR procedure* OR manage*) OR TI (“singl* blind" OR "doubl* blind" OR "tripl* blind") OR AB (“singl* blind" OR

"doubl* blind" OR "tripl* blind") OR TI (" singl* blind" OR "doubl* mask*" OR "tripl* mask*" OR "trebl* mask*") OR AB (" singl* blind" OR "doubl* mask*" OR "tripl* mask*" OR "trebl* mask*") OR TI (Random* OR "controlled trial*" OR "controlled stud*" OR "clinical trial*" OR "clinical stud*" OR "therapeutic trial*" OR "therapeutic stud*") AND AB (Random* OR "controlled trial*" OR "controlled stud*" OR "clinical trial*" OR "clinical stud*" OR "therapeutic trial*" OR "therapeutic stud*")

DE "Randomized Clinical Trials" OR DE "Randomized Controlled Trials" OR DE "Experimental Subjects" OR DE "Placebo" OR DE "Random Sampling"

S32 OR S33

S31 AND S34

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Sources	#5a	Indicate sources of financial or other support for the review	11
Sponsor	#5b	Provide name for the review funder and / or sponsor	11
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	11
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-7
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such	5

		as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9-10

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9