

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Rehabilitation of Cognitive Deficits post Stroke: Protocol for a Systematic Review and Meta-Analysis of Randomised Controlled Trials of Non-Pharmacological Interventions
AUTHORS	O Donoghue, Mairead; Boland, Pauline; Coote, Susan; Galvin, Rose; Hayes, Sara

VERSION 1 – REVIEW

REVIEWER	Nele Demeyere & Elise Milosevich University of Oxford, UK
REVIEW RETURNED	21-May-2019

GENERAL COMMENTS	<p>The authors aim to systematically summarize RCT's of rehabilitation of cognitive deficits following stroke in effort to determine the efficacy of the existing interventions and identify an optimal approach to therapy. They have good insight into the realities of multi-domain impairments post-stroke and the fact that post-stroke cognition should not be viewed as a unitary concept. This topic has yet to be addressed through a comprehensive systematic review as the authors have highlighted and evidenced by examining existing Cochrane reviews in this field. Overall, the protocol reads well, only requiring some minor editing (punctuation), and the authors are following PRISMA guidelines, as well as pre-registering their protocol on PROSPERO. There are a few considerations that need to be addressed.</p> <p>1. Premise and structure of review</p> <p>Please can it be made explicit how the review is to be structured. Will this be by cognitive domain ? And then by complex multi domain impairments ?</p> <p>Something can be said for previous Cochrane reviews focusing on rehabilitation interventions pertaining to individual domains as, in theory, with a specific focus you can identify an optimal therapeutic strategy if an individual has a deficit in that domain (identified by domain-specific screening, rather than global cognitive scores). In that sense, this review would be replicating parts of these domain-specific reviews.</p> <p>If the intent instead is to identify the optimal type of interventions to rehab cognitive impairment post-stroke in multi-domain impairments, should the single domain impairment and rehab studies then be excluded and this review only focus on studies including patients with multi-domain impairments?</p>
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	<p>Given this review is focusing on behavioural trials only and not pharmaceuticals, this needs to be made more explicit, both in title and in search strategy.</p> <p>2. Search strategy</p> <p>In regards to the search strategy, some additions are needed. The four main concepts of terms (mesh and keywords) include randomized controlled trials, cognition, stroke and rehabilitation. The search strategy utilizes many mesh terms, but we would also recommend to include those terms and keywords also. Some terms that should be considered for inclusion in the search: rehab*, intervention*, therapy, therapeutic, neurocognit*, neuropsych*, domain specific, domain general, etc.</p> <p>Additionally, the selected adjectives following cognit* (i.e. disorder, disruption, impair*, confusion etc.) are not comprehensive – Please include further terms such as decline, deficit, deterioration, dysfunction, recovery, etc.</p> <p>As well, the alternate spelling for stroke terms should be included, such as ischaemia/ischemia, or utilize truncation, i.e. isch?emia or isch?em*.</p> <p>The domain-general and domain-specific terms selected (memory, perception, attention, executive function) need expanding to ensure all trials are captured. This would include adding further often used terminology within neuropsychology such as executive syndrome, executive dysfunction, aphasia, etc (please consider a more complete list)</p> <p>3. Data extraction</p> <p>Please include more information on how each study defines cognitive impairment, how cognition is assessed and tracked. Please make explicit how cognitive impairments will be defined. As a clinical diagnosis (dsm ?), as a score outside test norms cut off, based on a set of criteria, are dementia patients excluded ? Acute post stroke impairments only? Will delirium be excluded?</p> <p>The data extraction form only specifies severity of cognitive impairment. This will need expanding to handle the complexity of multi domain impairments.</p> <p>4. Risk of bias,</p> <p>Including both RCTs and Quasi-rcts which are not truly random, (though supported by Cochrane handbook) increases the selection bias based on studies. Ideally, there should be explicit plans on how this will be reported and discussed. Though the authors propose a sensitivity analysis to explore the impact of methodological quality on the overall findings, perhaps there should also be a cut off below which studies are not included?</p> <p>How will results be stratified, if you are not excluding based on quality?</p>
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REVIEWER	Maximilian Jonas Wessel Swiss Federal Institute of Technology (EPFL), Switzerland
REVIEW RETURNED	04-Jun-2019

GENERAL COMMENTS	<p>The authors describe their study protocol for investigating the effects of different types of interventions with the aim to enhance cognitive impairments post stroke. The protocol is well described and of interest for the field. I would have following comments/suggestions:</p> <ul style="list-style-type: none"> • The authors claim to be the first group to review post stroke cognitive interventions in a comprehensive multiple-domain approach, e.g., page 2 line 13 “No review to date has established...” or page 2 line 44 “This is the first...”. Absolute statements, as mentioned above, are difficult to make accounting for the large body of available research. Examples of two reviews, which at least partially address different post stroke cognitive interventions from a multi-domain perspective are: Paiva et al. 2015, Restor Neurol Neurosci. or Langhorne et al. 2011, Lancet. I would advise to weaken the statements on novelty a bit. • Non-invasive brain stimulation interventions (NIBS), such as rTMS, are mentioned briefly. Do the authors include studies assessing the effects of NIBS interventions on post stroke cognition or will they be excluded? In the case, NIBS interventions would be considered, it would strengthen the review, if studies applying transcranial direct current stimulation would be also discussed. • The authors point out that cognitive impairments post stroke often affect multiple domains. It would improve the quality of the manuscript if also inter-domain interactions occurring during stroke recovery would be discussed, e.g., Ramsey et al. 2017, Nat Hum Behav. • The authors state that mixed aetiology studies may be considered, how will they deal with studies also including patients with cognitive impairments prior to the stroke incidence, e.g., mixed dementia? • How will the authors deal with language-effects of the assessed cognitive tests?
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VERSION 1 – AUTHOR RESPONSE

The authors wish to thank the reviewers for their reading of the manuscript and insightful comments. Please find below a detailed point by point response to all comments (reviewers' comments in black and author comments in black and italic font). Changes to the manuscript itself have been added in bold. We have taken all the comments on board to improve and clarify the manuscript.

Reviewer 1: The authors aim to systematically summarize RCT's of rehabilitation of cognitive deficits following stroke in effort to determine the efficacy of the existing interventions and identify an optimal approach to therapy. They have good insight into the realities of multi-domain impairments post-stroke and the fact that post-stroke cognition should not be viewed as a unitary concept. This topic has yet to be addressed through a comprehensive systematic review as the authors have highlighted and evidenced by examining existing Cochrane reviews in this field. Overall, the protocol reads well, only requiring some minor editing (punctuation), and the authors are following PRISMA guidelines, as well as pre-registering their protocol on PROSPERO. There are a few considerations that need to be addressed.

Comment 1.1) Premise and structure of review

Please can it be made explicit how the review is to be structured. Will this be by cognitive domain ? And then by complex multi domain impairments ?

Response 1.1) The review will be based on randomised controlled trials evaluating interventions wherein the primary or secondary aim is to improve cognition in individuals post stroke. In order to structure the review, we will compare the effectiveness of interventions on the primary outcome of cognition, and we will also compare the effectiveness of interventions with respect to domain-specific aspects of cognition. These analyses will be completed separately in the systematic review and meta-analysis (if appropriate). We have now made this structure more explicit in the manuscript, "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". (Methods Section, Outcomes; Page 6)

Comment 1.2) Something can be said for previous Cochrane reviews focusing on rehabilitation interventions pertaining to individual domains as, in theory, with a specific focus you can identify an optimal therapeutic strategy if an individual has a deficit in that domain (identified by domain-specific screening, rather than global cognitive scores). In that sense, this review would be replicating parts of these domain-specific reviews.

Response 1.2) While the authors acknowledge that there may be inclusion of trials which have been present in previous Cochrane reviews on domain-specific cognitive intervention (a narrower focus than the proposed review here), the research question being addressed in this current review is substantially different and therefore, results of previously reported trials will be analysed and presented in a distinct manner compared to previous reviews. These existing Cochrane reviews on domain specific cognitive impairment have had narrower research questions with regard to:

- 1) Focusing on one cognitive domain e.g. attention
- 2) Focusing on "cognitive rehabilitation" interventions for that particular domain i.e. attentional treatment techniques.

In contrast, the current review aims to explore the totality of evidence with regard to the rehabilitation of cognitive deficits post stroke. This review has a more broad research question with regard to:

- 1) Focusing on general cognitive function, multi-domain cognitive impairment and cognitive deficits in the domains of attention, memory, executive function, perception, limb apraxia and neglect.
- 2) Unlike previous Cochrane reviews, this review is not centred on specific “cognitive rehabilitation” interventions, but a breadth of non-pharmacological rehabilitation interventions which mediate improvements in cognitive deficits post stroke. These interventions include, but are not restricted to self-efficacy training, physical activity interventions, neuropsychological interventions, electronic interventions, music therapy and occupational therapies etc.

Therefore, this review may identify and include a study on a particular cognitive domain such as attention, but will examine a breadth of interventions which may affect attentional deficits post stroke, as opposed to looking solely at attentional interventions, unlike previous Cochrane reviews of this type.

For instance, , the search string from the Cochrane review on “Cognitive Rehabilitation for Attention Deficits following Stroke” (Loetscher and Lincoln 2013), for example, shows the difference with regard to the breadth of interventions included:

Search terms for “Rehabilitation” in Loetscher and Lincoln (2013):

- 15.“cognitive therapy/ or cognitive rehabilitation/ or rehabilitation/
16. exp computer/ or computer assisted therapy/ or computer interface/
17. (training or re-training or retraining or therap\$ or rehabilitat\$ or neurorehabilitat\$ or treatment\$ or therapeutic\$).tw.

- Search terms for “Rehabilitation” in the planned systematic review:

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 "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" ...

(Please see full search string of CINAHL database attached as Appendix 1 in a Supplementary File).

Comment 1.3) If the intent instead is to identify the optimal type of interventions to rehab cognitive impairment post-stroke in multi-domain impairments, should the single domain impairment and rehab studies then be excluded and this review only focus on studies including patients with multi-domain impairments?

Response 1.3) With regard to excluding single domain impairment studies, respectfully, we disagree. The aim of this review is to capture the totality of evidence regarding interventions to rehabilitate cognitive deficits in individuals post stroke. While this proposed review may include studies with single domain impairments, a breadth of interventions which may mediate improvements in a particular cognitive domain will be captured, as opposed to solely “cognitive rehabilitation” interventions. This has now been more explicit in the updated manuscript in the Introduction section “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

<p>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.” (Introduction Section; Page 4).</p>
<p>Comment 1.4) Given this review is focusing on behavioural trials only and not pharmaceuticals, this needs to be made more explicit, both in title and in search strategy.</p> <p>Response 1.4) Thank you, we agree. The title of the review has now been changed to: “Rehabilitation of Cognitive Deficits post Stroke: Protocol for a Systematic Review and Meta-Analysis of Randomized Controlled Trials of non-pharmacological interventions.”</p>
<p>Comment 2.1) Search strategy</p> <p>In regards to the search strategy, some additions are needed. The four main concepts of terms (mesh and keywords) include randomized controlled trials, cognition, stroke and rehabilitation. The search strategy utilizes many MeSH terms, but we would also recommend to include those terms and keywords also. Some terms that should be considered for inclusion in the search: rehab*, intervention*, therapy, therapeutic, neurocognit*, neuropsych*, domain specific, domain general, etc.</p> <p>Response 2.1) The above MeSH terms and keywords are included in the search strings for each of the following electronic databases: PubMed, Embase, CINAHL, CENTRAL and PsycInfo. To illustrate same, please see full Pubmed search string in Appendix 1.</p>
<p>Comment 2.2) Additionally, the selected adjectives following cognit* (i.e. disorder, disruption, impair*, confusion etc.) are not comprehensive – Please include further terms such as decline, deficit, deterioration, dysfunction, recovery, etc. As well, the alternate spelling for stroke terms should be included, such as ischaemia/ischemia, or utilize truncation, i.e. isch?emia or isch?em*.</p> <p>Response 2.2) Thank you. The above adjectives have been expanded upon and included in the search string.</p>
<p>Comment 2.3) The domain-general and domain-specific terms selected (memory, perception, attention, executive function) need expanding to ensure all trials are captured. This would include adding further often used terminology within neuropsychology such as executive syndrome, executive dysfunction, aphasia, etc (please consider a more complete list)</p> <p>Response 2.3) The domain-specific terms were adopted from previous Cochrane reviews of cognitive rehabilitation of attention, memory, perception, limb apraxia, neglect and executive dysfunction [1–6]. The terms used by Cochrane were extensive and captured the terminology relating to the neuropsychological underpinnings of these cognitive domains. In addition, we have included searches of clinical trials databases to ensure all trials are captured. This has been clarified in the manuscript in the Methods section: “Clinical Trials.gov and the Vista database will be searched for potentially eligible ongoing trials.” (Methods, Search; Pg. 8.)</p>
<p>Comment 3.1) Data extraction</p> <p>Please include more information on how each study defines cognitive impairment, how cognition is assessed and tracked. Please make explicit how cognitive impairments will be defined. As a clinical diagnosis (dsm ?), as a score outside test norms cut off, based on a set of criteria?</p> <p>Response 3.1) Given the complexity and heterogeneity of post stroke cognitive impairment, no single definition or definitive neuropsychological pattern exists [7]. Individuals with a confirmed cognitive impairment post stroke as specified by the authors within each trial will be considered for inclusion. The details of how stroke was defined and identified in each trial will be recorded during data extraction and reported descriptively.</p>

<p>Within the context of this review, the construct of cognitive impairment post stroke must include:</p> <ul style="list-style-type: none"> • The presence of at least one primary deficit in the cognitive domains of: attention, memory, executive function, perception, limb apraxia and neglect, OR, a decline in general cognitive function as per cognitive assessments such as mini-mental state examination (MMSE) score, Montreal cognitive assessment scale (MoCA) score, the abbreviated mental test, AD assessment scale-cognitive (ADAS-Cog), neuropsychological test batteries etc • Diagnosis of stroke as identified from CT or MRI scans • Stroke diagnosis is the identified primary cause of cognitive impairment. <p>We will not use a pre-specified cut-off score for cognitive function.</p>
<p>Comment 3.2) Are dementia patients excluded ?</p> <p>Response 3.2) Patients with dementia will be excluded. This has been clarified in Methods section under Participants; Pg. 5</p>
<p>Comment 3.3) Acute post stroke impairments only?</p> <p>Response 3.3) Individuals in the acute, sub-acute or chronic stages post stroke will be included. This has been clarified in Methods section, Participants; Pg. 5</p>
<p>Comment 3.4) Will delirium be excluded?</p> <p>Response 3.4) Patients with delirium will be excluded. This has been clarified in Methods section, Participants; Pg. 6.</p>
<p>Comment 3.5) The data extraction form only specifies severity of cognitive impairment. This will need expanding to handle the complexity of multi domain impairments.</p> <p>Response 3.5) With regard to data relating to cognitive impairment post stroke, the data extraction form will include, where identifiable:</p> <ul style="list-style-type: none"> • Means (assessment) of formal diagnosis of cognitive impairment post stroke • Type of cognitive impairment i.e. domain(s) of cognitive function affected • Severity of cognitive impairment (mild, moderate or severe) • Neuropsychological underpinnings of cognitive impairment (where reported) <p>This has been included in the manuscript in the Methods section under Data Extraction, Pg. 9.</p>
<p>Comment 4.1) Including both RCTs and Quasi-rcts which are not truly random, (though supported by Cochrane handbook) increases the selection bias based on studies. Ideally, there should be explicit plans on how this will be reported and discussed.</p> <p>Though the authors propose a sensitivity analysis to explore the impact of methodological quality on the overall findings, perhaps there should also be a cut off below which studies are not included?</p> <p>How will results be stratified, if you are not excluding based on quality?</p> <p>Response 4.1) The authors will acknowledge study designs. The quality of these studies will be assessed using the domains identified by the Cochrane Risk of Bias Tool. Quasi randomised controlled trials will be rated high in relation to selection bias. A sensitivity analysis will also be conducted, in order to examine the evidence in the absence of studies wherein a “high” risk of bias has been identified. However, we will not exclude studies based on methodological quality, in order to capture the totality of the evidence in this field.</p>

Reviewer 2: The authors describe their study protocol for investigating the effects of different types of interventions with the aim to enhance cognitive impairments post stroke. The protocol is well described and of interest for the field. I would have following comments/suggestions:

Comment 1.1) The authors claim to be the first group to review post stroke cognitive interventions in a comprehensive multiple-domain approach, e.g., page 2 line 13 “No review to date has established...” or page 2 line 44 “This is the first...”. Absolute statements, as mentioned above, are difficult to make accounting for the large body of available research. Examples of two reviews, which at least partially address different post stroke cognitive interventions from a multi-domain perspective are: Paiva et al. 2015, Restor Neurol Neurosci. or Langhorne et al. 2011, Lancet. I would advise to weaken the statements on novelty a bit.

Response 1.1) The above statements have been amended in the manuscript and now reads as follows:

“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.” Introduction Section; Pg. 4.

Comment 1.2) Non-invasive brain stimulation interventions (NIBS), such as rTMS, are mentioned briefly. Do the authors include studies assessing the effects of NIBS interventions on post stroke cognition or will they be excluded? In the case, NIBS interventions would be considered, it would strengthen the review, if studies applying transcranial direct current stimulation would be also discussed.

Response 1.2) Studies examining the effectiveness of NIBS will be included, as per the inclusion criteria. NIBS has been added to the list of possible interventions which may be included:

“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)”

Methods Section, Interventions; Pg. 6.

Comment 2.1) The authors point out that cognitive impairments post stroke often affect multiple domains. It would improve the quality of the manuscript if also inter-domain interactions occurring during stroke recovery would be discussed, e.g., Ramsey et al. 2017, Nat Hum Behav.

Response 2.1) We thank the reviewers for recommending the work of Ramsey et al. (2017) which we have reviewed. While the authors agree that a discussion regarding interdomain interactions occurring during cognitive recovery post stroke would add to the manuscript, this is beyond the scope of this protocol and review to explore inter-domain interactions. This will be acknowledged as a limitation within the discussion of this paper.

Comment 3.1) The authors state that mixed aetiology studies may be considered, how will they deal with studies also including patients with cognitive impairments prior to the stroke incidence, e.g., mixed dementia?

Response 3.1) Studies including patients with cognitive impairments which have been identified prior to the stroke incidence will be excluded as a direct association between the cognitive impairment and stroke incidence cannot be established.

This has been clarified in the manuscript in Methods Section, Participants; Pg. 6.

Comment 4.1) How will the authors deal with language-effects of the assessed cognitive tests?

Response 4.1) The language effects of primary outcome measures, where these can be deciphered from outcome measure properties, will be extracted where this is available and reported descriptively in the results.

This has been clarified in the manuscript in the Methods section:

“In consideration of the association between language impairments and performance on cognitive assessments, the language effects of primary outcome measures will be extracted.” (Methods Section, Data Extraction; Pg. 9).

If possible, sub-group analysis will examine the potential effect of characteristics related to the cognitive outcome measures. This has been clarified in the Methods section of the manuscript:

- “Characteristics related to the cognitive outcome measures used across trials, 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.” (Methods Section, Subgroup Analysis; Page 10).

References

- 1 West C, Bowen A, Hesketh A, et al. Interventions for motor apraxia following stroke. Cochrane Database of Systematic Reviews Published Online First: 2008. doi:10.1002/14651858.CD004132.pub2
- 2 Hoffmann T, Bennett S, Koh CL, et al. Occupational therapy for cognitive impairment in stroke patients. Cochrane Database of Systematic Reviews 2010;:2–4. doi:10.1002/14651858.CD006430.pub2
- 3 Bowen A, Knapp P, Gillespie D, et al. Non-pharmacological interventions for perceptual disorders following stroke and other adult-acquired, non-progressive brain injury. Cochrane Database of Systematic Reviews 2011;:N.PAG-N.PAG.
- 4 Bowen A, Hazelton C, Pollock A, et al. Cognitive rehabilitation for spatial neglect following stroke. Cochrane Database of Systematic Reviews 2013;2013. doi:10.1002/14651858.CD003586.pub3
- 5 Loetscher T, Lincoln NB. Cognitive rehabilitation for attention deficits following stroke. Cochrane Database Syst Rev 2013;:CD002842. doi:10.1002/14651858.CD002842.pub2
- 6 das Nair R, Cogger H, Worthington E, et al. Cognitive rehabilitation for memory deficits following stroke. Cochrane Database of Systematic Reviews 2016;9:CD002293. doi:10.1002/14651858.CD002293.pub3. www.cochranelibrary.com
- 7 Lezak M, Howieson D, Loring D. Neuropsychological assessment. 5th edn Oxford University Press. Oxford, New York, ISBN 2012;10:9780195395525.

VERSION 2 – REVIEW

REVIEWER	Nele Demeyere & Elise Milosevich University of Oxford, Oxford, United Kingdom
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	<p>BMJ OPEN: Rehabilitation of cognitive deficits after stroke: Protocol for a systematic review and meta-analysis of randomized controlled trials</p> <p>We would like to thank the authors for comprehensively revising the protocol. The changes to the premise and structure of the review made the set up and planned analyses much clearer. It is now also understood that your proposed review will encompass a breadth of non-pharmacological interventions affecting both global cognition and any cognitive domain(s), which will be an extension of previous Cochrane reviews. The focus will not be on just multi-domain impairments (our initial comment/enquiry) and the review will encapsulate all non-pharmacological interventions impacting cognition (global, single-domain and multi-domain) after stroke. The updated title also makes this more transparent.</p> <p>The authors satisfactorily addressed other comments, but there are few minor remaining points that would be good to see addressed:</p> <div style="border: 1px solid black; padding: 5px; margin: 10px 0;"> <p>Original Comment - Search strategy In regards to the search strategy, some additions are needed. The four main concepts of terms (mesh and keywords) include randomized controlled trials, cognition, stroke and rehabilitation. The search strategy utilizes many MeSH terms, but we would also recommend to include those terms and keywords also. Some terms that should be considered for inclusion in the search: rehab*, intervention*, therapy, therapeutic, neurocognit*, neuropsych*, domain specific, domain general, etc.</p> <p>Response The above MeSH terms and keywords are included in the search strings for each of the following electronic databases: PubMed, Embase, CINAHL, CENTRAL and PsycInfo. To illustrate same, please see full Pubmed search string in Appendix 1.</p> </div> <p>Though your search strategy is comprehensive, particularly regarding your stroke terms, the terms mentioned in our initial comment are not included in your search strategy. The search strategy provided (“Search_strategy_for_CINAHL_COMPLETE_database”) does not contain the suggested terms we listed. For example, by including the term Neurocognit* you capture neurocognition and neurocognitive, whereas the only term you include is “neurocognitive disorders”. Similarly, with the term neuropsych*, you only include terms with neuropsychological, and you also do not include any terms pertaining to “domain-specific” or “domain-general” impairments. Additionally, you could expand on your cognitive domain terms, such as including terms regarding processing speed and aphasia. These are minor suggested additions.</p>
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	<p>Comment The domain-general and domain-specific terms selected (memory, perception, attention, executive function) need expanding to ensure all trials are captured. This would include adding further often used terminology within neuropsychology such as executive syndrome, executive dysfunction, aphasia, etc (please consider a more complete list)</p> <p>Response The domain-specific terms were adopted from previous Cochrane reviews of cognitive rehabilitation of attention, memory, perception, limb apraxia, neglect and executive dysfunction [1–6]. The terms used by Cochrane were extensive and captured the terminology relating to the neuropsychological underpinnings of these cognitive domains. In addition, we have included searches of clinical trials databases to ensure all trials are captured. This has been clarified in the manuscript in the Methods section: “Clinical Trials.gov and the Vista database will be searched for potentially eligible ongoing trials.” (Methods, Search; Pg. 8.)</p> <p>In line with your previous statement that you intend to have a much wider/more inclusive review than the previous Cochrane reviews, it would be suggested then to include more wider terms, i.e. attempt to capture more specific cognitive impairments?</p> <p>With regards to the data extraction, the changes made are good, but 2 further comments occur: It would be perhaps also good to make explicit how you will be defining acute, sub-acute and chronic? Will this be a pre-defined timeline or will you be judging based on how each author described the study cohort?</p> <p>Similarly, with regards to severity of cognitive impairment, you stated</p> <p>Response With regard to data relating to cognitive impairment post stroke, the data extraction form will include, where identifiable:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Means (assessment) of formal diagnosis of cognitive impairment post stroke <input type="checkbox"/> Type of cognitive impairment i.e. domain(s) of cognitive function affected <input type="checkbox"/> Severity of cognitive impairment (mild, moderate or severe) <input type="checkbox"/> Neuropsychological underpinnings of cognitive impairment (where reported) <p>This has been included in the manuscript in the Methods section under Data Extraction, Pg. 9.</p> <p>How will the severity of impairment be determined? If not already made explicit in each study, how will you grade severity if studies are using different definitions, assessments and criteria (as many do)?</p>
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REVIEWER	Maximilian Jonas Wessel Swiss Federal Institute of Technology (EPFL), Switzerland
REVIEW RETURNED	22-Jul-2019

GENERAL COMMENTS	All my comments have been addressed sufficiently in the revised version of the manuscript.
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1 Comments and Responses	
<p>Comment 1.1: Though your search strategy is comprehensive, particularly regarding your stroke terms, the terms mentioned in our initial comment are not included in your search strategy. The search strategy provided (“Search_strategy_for_CINAHL_COMPLETE_database”) does not contain the suggested terms we listed. For example, by including the term Neurocognit* you capture neurocognition and neurocognitive, whereas the only term you include is “neurocognitive disorders”. Similarly, with the term neuropsych*, you only include terms with neuropsychological, and you also do not include any terms pertaining to “domain-specific” or “domain-general” impairments.</p>	<p>Response 1.1: Thank you. This has been completed. Please see the search strategy for the CINAHL database attached as a supplementary file.</p>
<p>Comment 1.2: Additionally, you could expand on your cognitive domain terms, such as including terms regarding processing speed and aphasia. These are minor suggested additions.</p>	<p>Response 1.2: Thank you for your comment relating to the expansion of cognitive domain terms used. Terms such as processing speed are included within the search string as follows:</p> <p>"Cognitive Processing Speed" OR "Strategy formation*" OR planning OR organisation OR "time management" OR "problem solving" OR "decision making" OR sequencing OR "sequence of steps"</p> <p>Please see the search strategy for the CINAHL database attached as a supplementary file.</p>
<p>Comment 1.3: Additionally, you could expand on your cognitive domain terms, such as including terms regarding processing speed and aphasia. These are minor suggested additions.</p>	<p>Response 1.3: 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). Aphasia as a concept and a term will not be included. Clinical recommendations for aphasia are included in the following guidelines:</p> <ul style="list-style-type: none"> • Australian Guidelines for Stroke Management (2017) Stroke Foundation. Clinical Guidelines for Stroke Management 2017. Melbourne Australia. • Canadian Stroke Best Practice Recommendations (2014) Lindsay MP, Gubitz G, Bayley M, Hill MD, Phillips S, and Smith EE. Canadian Stroke Best Practice Recommendations Overview and Methodology. On behalf of the Canadian Stroke Best Practices Advisory Committee and Writing Groups. 2014; Ottawa, Ontario Canada: Heart and Stroke Foundation, Canada. • Royal College of Physicians National Clinical Guideline for Stroke (2016) Party, I.S.W., 2012. National clinical guideline for stroke (Vol. 20083). London: Royal College of Physicians.

- Irish Heart Foundation National Clinical Guidelines and Recommendations for the Care of People with Stroke and Transient Ischaemic Attack (2010)

Irish Heart Foundation. (2010) National Clinical Guidelines and Recommendations for the Care of People with Stroke and Transient Ischaemic Attack

Within the above guidelines, aphasia is listed as a subdomain of “communication disorders” and does not specifically relate to the term “cognition”. As aphasia is not included in these guidelines within the remit of the term cognition, we decided to exclude this term. We feel that including general cognitive status, six individual cognitive domains (attention, memory, executive function, perception, limb apraxia and neglect) and a breadth of non-pharmacological interventions, that the totality of evidence will be captured.

Comment 1.4: In line with your previous statement that you intend to have a much wider/more inclusive review than the previous Cochrane reviews, it would be suggested then to include more wider terms, i.e. attempt to capture more specific cognitive impairments?

Response 1.4: We consider the current review to be more inclusive than previous Cochrane reviews [1–6] by including multiple cognitive domains and general cognitive status within one review. We created a comprehensive search strategy in relation to the term “cognition” itself and also, in relation to each cognitive domain of “attention, memory, executive function, perception, limb apraxia and neglect”. To illustrate, please see the attached search string of the CINAHL database.

Moreover, the broader inclusivity of this review stems from the inclusion of a breadth of non-pharmacological interventions:

“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)" (Methods Section, Interventions, Pg. 6).

The inclusion of a range of non-pharmacological interventions is of a broader scope to previous Cochrane reviews which focused on specific cognitive rehabilitation interventions in relation to a single cognitive domain [1-6].

Comment 1.5: With regards to the data extraction, the changes made are good, but 2 further comments occur: It would be perhaps also good to make explicit how you will be defining acute, sub-acute and chronic? Will this be a pre-defined timeline or will you be judging based on how each author described the study cohort? How will the severity of impairment be determined? If not

already made explicit in each study, how will you grade severity if studies are using different definitions, assessments and criteria (as many do)?

Response 1.5: We have amended the manuscript to outline that we will not define acute, subacute and chronic stroke but we will descriptively report the time since stroke in each individual study. Also, we will not define stroke impairment severity. Both the stage post stroke (acute, subacute and chronic) and the severity of cognitive impairment will be considered and reported on within the context of each individual study. We will include this information in the narrative and in the descriptive characteristics table.

We have made this aspect of data extraction more explicit in the manuscript, “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.” (Methods Section, Data Extraction, Pg.9).

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VERSION 3 – REVIEW

REVIEWER	Nele Demeyere University of Oxford, UK
REVIEW RETURNED	03-Sep-2019
GENERAL COMMENTS	The authors have satisfactorily addressed my comments