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Active Control-Group Designs in Cognitive Rehabilitation Trials: A Qualitative Review of Computer -Based Rehabilitation in Patients with Acquired Brain Injury

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Abstract

Background and Objectives: To outline experimental variables of relevance to clinical trials employing active control condition (ACC) designs within cognitive rehabilitation after Acquired Brain Injury (ABI), and to qualitatively review the current methodology of trials within this field.

Method: Firstly, experimental variables which evidently impact rehabilitation outcome were outlined, based on the authors' joint knowledge of the research field. Secondly, clinical trials within cognitive rehabilitation after ABI that employed ACC designs were identified and qualitatively evaluated based on the outlined variables. Due to the breadth of this research field, a focus on computer-based cognitive rehabilitation (CBCR) was chosen. Trials were identified through a systematic search in prespecified scientific databases using prespecified inclusion criteria.

Results: 10 experimental variables were identified. Nine trials were included in this review. None of the included trials accounted for all experimental variables in their study design.

Conclusion: There are methodological shortcomings in the design of trials using ACC's within the field of CBCR after ABI. Although this methodological review is limited to a subfield within cognitive rehabilitation research, the conclusions drawn here are believed to generalize to the overall field. The experimental variables outlined here may aid researchers in the design phase of future trials using ACC's.

Keywords

Active control-group design, Cognitive rehabilitation, Computer-based cognitive rehabilitation, Acquired brain injury, Qualitative review

Abbreviations

ABI: Acquired Brain Injury; **ACC:** Active Control Condition; **CBCR:** Computer-Based Cognitive Rehabilitation; **EC:** Experimental Condition; **PCC:** Passive Control Condition

Introduction

Research in cognitive rehabilitation after acquired brain injuries (ABI) explores the efficacy of various rehabilitation interventions for specific injury-related cognitive deficits [1, 2]. To minimize potential bias from placebo effects in

clinical trials, it is essential that any experimental intervention is compared with an active control condition, and that both participants, researchers and outcome-assessors are kept blind if possible [3-6]. As such, as many variables as possible should be identical between the intervention group and the active control group [7, 8], and ideally only the variable(s) of scientific interest should differ.

The fact that these methodological standards are intrinsically more difficult to accomplish in studies of psychological interventions in comparison with pharmacological interventions is an issue raised several times before [3, 7]. It is arguably easier to isolate the expected effective components of a drug and mask whether a given drug contains it or not, than it is to design an equally well-matched active control condition in a psychological intervention study.

Identifying and removing the active components of a given treatment and blinding as many of the involved parties to the experimental conditions as possible thus poses a great methodological challenge within the field of cognitive rehabilitation. Although this challenge may be impossible to overcome completely [7, 9], studies in cognitive rehabilitation should nevertheless strive to incorporate an active control condition in order to obtain the highest quality of evidence possible [3]. To promote this, researchers must have sufficient knowledge of the experimental variables thought to influence the outcome of cognitive rehabilitation. Furthermore, when blinding of intervention allocation is not possible, researchers should take the accompanying biases into account when they interpret their findings.

An intervention that contains several interactive components within the experimental and control condition is often referred to as a 'complex intervention' [10]. Within the research field of complex interventions this challenge has led to a discussion of whether a design similar to that of a drug-trial is even desirable, or if separate standards of methodological quality should be developed for complex intervention trials [11, 12]. This discussion has led to a framework for researchers to recognize and adopt when designing complex intervention trials, described in depth elsewhere [11, 12]. Even though methodological quality within complex interventions needs to be assessed by the field's own standards, a rigorous approach to design and methodology is still essential [10]. A key element in the design phase of a complex intervention trial is to define the components of the intervention [10]. Building on this, the first aim of this paper is to outline known experimental variables of relevance to clinical trials employing active control group designs within cognitive rehabilitation after ABI. These known experimental variables are identified based on the authors' joint knowledge of variables that evidently impact rehabilitation outcome. It is the hope of the authors that this overview provides a tool to identify and account for important intervention components in the design phase of future trials within cognitive rehabilitation. The second aim is to identify clinical trials within cognitive rehabilitation after ABI (defined as stroke, brain tumors, traumatic brain injuries and surgery sequelae) that have included an active control group, and qualitatively evaluate the methodological quality of these based on the previously identified variables.

Because cognitive rehabilitation after ABI is a broad research field, the scope of this paper is delineated to cover the described methodological challenges within a specific subfield: Computer based cognitive rehabilitation (CBCR). CBCR is an increasingly used intervention within cognitive rehabilitation that has recently received critique for its lack of active control designs in clinical trials [13]. It thus serves as a relevant example to illustrate some of the overall challenges within the research field. Furthermore, the issues raised within this subfield are believed to generalize to the broader field of cognitive rehabilitation research. This review is reported in accordance with the PRISMA-guidelines for reporting systematic reviews [14].

Section One: Experimental Variables to Account for in Active Control Group Designs of Computer Based Cognitive Rehabilitation after Acquired Brain Injury

This section outlines experimental variables to account for when conducting clinical trials on the effects of CBCR after ABI. The variables outlined here are also relevant to consider when conducting trials within the broader research field of cognitive rehabilitation. Although clinical trials can (and often do) use multiple group designs, for methodological clarity this section will focus on a trial-design with just one experimental group and one active control group. However, the issues raised here generalize to trials with more complicated designs. The outlined experimental variables have been identified through the authors' joint knowledge of variable which evidently impact the effects of cognitive rehabilitation interventions.

All the outlined variables can be manipulated depending on the specific research question of a given trial. All variables should be equal between the experimental condition and the active control condition, except for the variable(s) of scientific interest. Therefore, all the identified experimental variables outlined below should only be equal between groups when they do not constitute the variable being researched.

Demographics and other individual-related variables

As many demographic variables as realistically possible should be equalized between the experimental group and the active control group to ensure that these do not constitute confounding variables in the rehabilitation outcome. Demographic variables include information such as age, gender and level of education [15]. In studies of cognitive rehabilitation after various types of ABI, variables such as the nature, location and size of the brain damage [16], the type and severity of cognitive symptoms [17] and the timing of the intervention relative to the onset of ABI [18] also constitute relevant individual-related variables that should preferably be equalized between groups.

Intensity of the intervention

Both preclinical studies [19] and clinical trials with humans [20, 21] suggest that the intensity of an intervention is of great importance to the outcome: The more intensive the

intervention, the better the rehabilitation outcome. Krakauer et al. [22] state that the intensity of the rehabilitation which patients currently undergo after ABI is often sparse compared to the amount of rehabilitation shown to be effective in preclinical studies. Based on this they suggest intensifying the amount of rehabilitation training in humans to increase the presumed positive outcome. Since the intensity of a rehabilitation intervention seems highly influential for the outcome, the amount of training ought not to differ between the experimental group and the active control group in a clinical trial. Differences in training intensity between the two groups can, on their own, cause significant differences in rehabilitation outcome.

Expectations of intervention effects

Boot et al. [3] point out that:

“Although active control groups are superior to “no-contact” controls, only when the active control group has the same expectation of improvement as the experimental group can we attribute differential improvements to the potency of the treatment. Despite the need to match expectations between treatment and control groups, almost no psychological interventions do so.” (p. 445).

Proper blinding of whether participants receive a real- or a sham-intervention is crucial, because it assures that any differences in rehabilitation outcome between the groups can be attributed to the intervention [3]. As Boot and colleagues [3] point out, proper blinding is not achieved by simply implementing an active control condition. Since expectations can themselves have significant impact on the rehabilitation outcome, differences in outcome can only be attributed to the intervention when the two groups have similar expectations [3]. However, as Bavalier and Davidson [7] state: *“Placebo controls are not possible, so optimal designs probably involve having several comparison groups, including an active gameplaying comparison and perhaps other, more typical interventions”* (p. 426)

Although proper blinding of active control groups within cognitive rehabilitation is more challenging than for pharmacological studies, it is no excuse not to take the variable of outcome expectations into account [3]. Therefore, researchers should ask participants directly or apply quantifiable measures of outcome expectations to account for the possible confounding effects of this variable.

Interest value of intervention and patient motivation

Just as it is necessary to minimize differences in expectations regarding the effectiveness of the intervention, researchers should be aware of any motivational differences that may exist between groups [3]. One of the main reasons for this may seem rather obvious: If only one group is motivated to engage in an intervention or to perform well on a set of tests, it is impossible to know whether any differences in outcome between groups is simply due to differences in motivation. It is pointed out by Boot et al. [3] that although differences in expectations may affect the participant’s motivation, it is important not to conflate these two terms. An important distinction is that whereas differences in overall motivation may influence participant’s performance on all tasks, differences in

expectations may lead to more specific improvements. In other words, if one group is more motivated overall, they will likely perform better in all aspects of a task, whereas if they expect a certain effect (e.g. improvements in memory after memory-training tasks), their improvement in performance should be limited to that one domain. Therefore, it is important to assess and control for potential differences in motivation between groups. During the intervention period, the perceived interest value of the intervention could have a significant effect on patient motivation: if the experimental condition is provided with an intervention that is generally perceived as interesting, engaging and motivating, while the active control condition is provided with an intervention perceived as tedious and boring, this could in itself cause significant difference in compliance with the intervention [3]. Researchers should therefore ask participants directly or apply quantifiable measures to assess the perceived interest value of the intervention to account for possible confounding effects of this variable.

Setting

According to Mogensen and Wulf-Andersen [23] training in the home environment allows for a better utilization of cognitive strategies acquired pre-traumatically and a more direct transfer of training results from formalized training to activities of daily living of the patient - compared to institutionalized rehabilitation. On the other hand, rehabilitation in an institutionalized setting often provides continuous training support from a health professional, possibly increasing training compliance. Thus, the setting in which a rehabilitation-intervention is carried out possibly impacts its efficacy. If one group receives a home-based intervention while the other group receives an intervention at a hospital, rehabilitation institution or experimental laboratory, this can by itself impact post-intervention results. Therefore, both the experimental condition and the active control condition should train in the same environment with or without the same amount of support from health professionals.

Continuous adjustment of task difficulty

If your physical condition allows you to run a certain distance within a given timeframe and you repeatedly do so, you will sustain your physical condition, but you are unlikely to improve it to the same extent as if you increased the difficulty continuously to match your current level of fitness [24]. The same principle seems to apply in rehabilitation after ABI. Nudo [25] conducted a study of motoric rehabilitation in squirrel monkeys to illustrate how primates do not simply improve performance by sheer use of affected limbs in repetitive motoric tasks. Significant increases in performance does not occur until task demands are amplified to a degree that matches the primate’s current motoric abilities and is continuously adjusted to match the new ability level [25]. The above example outlines motoric rehabilitation in non-human primates, but according to Green and Bavalier [26] continuous adjustments to match the task difficulty to a patient’s current abilities is equally important in cognitive rehabilitation of humans. Consequently, cognitive rehabilitation interventions should strive to increase the level of difficulty as the patient’s level of ability increases to ensure continuous improvement.

It thus constitutes a confounding variable if the experimental group receives continuous training adjustments to match their current ability level while the active control condition does not.

Side-effects of the intervention

To reduce the risk of unblinding, pharmacological trials sometimes make use of active placebo control groups in which a control group is purposefully given a placebo drug designed to mimic the known side effects of the experimental drug [27]. Little has currently been written regarding potential side effects of CBCR interventions, but known possible side-effects include mental fatigue, headaches and eye-irritability directly after training [28]. It could make sense to try to create an active control condition which were likely to produce the same side-effects as the experimental condition to control for the impact of various side-effects.

Variability in training material

While continuous adjustment of task-difficulty seems to be crucial for improvement within the trained task, the variability of available training material is a strong predictor of both near- and far transfer effects of training. Near transfer effects refer to transferability of the trained task to cognitively similar and related tasks, while far transfer effects refer to transferability of the trained task to cognitively dissimilar and unrelated tasks [29]. The greater the diversity of available training material, the greater the generalizability of the training to untrained tasks [30]. Near transfer effects of training are usually significantly greater than far transfer effects but increases in the variability of training material also expands the possibility of transferability to both near and far transfer tasks [30]. Building on this, Mogensen and Wulf-Andersen [23] suggest that variation of training should be as great as possible to ensure as much transferability as possible. It is therefore essential to ensure equal variability in available training material between the intervention group and the active control group to ensure variability in training material does not constitute a confounding variable.

Load on the cognitive function of interest

A patient with executive impairments who engages in interventions with a high executive load executes near transfer training, whereas a patient with executive impairments engaged in interventions with a relatively low executive load such as visuospatial function training executes far transfer training [26]. Several studies suggest that near transfer training elicits larger training effects on the cognitive function of interest than far transfer training [26, 29, 31]. For all studies included in this review, load on the cognitive function of interest differed between the experimental condition and the active control condition, and this particular variable is expected to be an experimental variable for most studies on cognitive rehabilitation. However, in study designs in which the load on specific cognitive functions is not an experimental variable, this variable should be held equal between the experimental condition and the active control condition.

The type of medium used for the intervention

Converting the same training paradigm from one medium

to another produces surprisingly large differences in the effects of the intervention. Wilms and Mala [32] conducted a study of prism adaptation therapy in patients with visuospatial neglect in which patients had to point to various predefined targets with and without wearing prism-glasses. The patients either received direct visual feedback on their performance in the form of seeing their own fingertip, or indirect visual feedback via icons on a computer-screen. The feedback medium had a significant impact on the patients' performance [32], which subsequently led Wilms and Mogensen [33] to state that:

“In the study of the brain and how it adapts to changes or injury, researchers sometimes come across situations where apparently similar types of tests or training do not achieve similar outcome results. This is true, in particular, within the field of computer-based rehabilitation where paper-and-pencil tests and training is converted to a computer.” (p. 221).

As such, variations in the rehabilitation medium between the experimental condition and the active control condition can produce confounding experimental effects. It is therefore relevant to consider the intervention-medium as an experimental variable to account for in CBCR studies using active control designs.

Section Two: A Qualitative Review of Computer Based Cognitive Rehabilitation Studies using Active Control Designs for Patients with Acquired Brain Injury

Methods

Eligibility criteria:

Studies were eligible for this review if they met the following PICOS criteria [34]:

- *Population:* Studies were eligible if the study-population consisted of patients with one or more of the following common types of acquired brain injury (ABI): Stroke, traumatic brain injury, brain tumors or surgery sequela. Studies were eligible if they included adults aged 18 years and above. Gender, time since ABI, education level or any other demographic variables besides age and ABI pathology did not constitute exclusion criteria. However, the matching of demographic variables between groups were registered.

- *Intervention:* Studies examining the effect of computer based cognitive rehabilitation (CBCR) were eligible. In this review CBCR is defined as any computer-software consisting of various cognitive exercises which can be performed on a standard computer, which excludes Virtual Reality interventions and other interventions requiring more advanced electronic equipment. Studies were eligible if the CBCR targeted one or more cognitive functions. Therefore, trials of computer-based interventions for motoric symptoms and similar non-cognitive computer-based interventions were excluded. Studies were not eligible if CBCR was used as part of a larger multidisciplinary intervention without any isolated CBCR conditions.

• *Comparison:* Studies comparing the effects of CBCR with one or more active control conditions of any type were eligible. As such, studies which compared multiple interventions were eligible if at least one CBCR-group and one or more active control-conditions were present. Because of the methodological scope of this review, studies were not eligible if they compared the effects of multiple interventions without any specified active control condition.

• *Outcome measures:* Because of the methodological nature of this review, there were no inclusion or exclusion criteria regarding the outcome measures of studies, and relevant study protocols were also eligible. However, the primary outcome measures and the results provided by these (if available) were registered for each study.

• *Setting:* Studies were eligible regardless of which setting the CBCR intervention was carried out in. This includes hospitals, rehabilitation clinics, the patients' own homes, experimental laboratories and so forth. However, the intervention-settings of both the experimental condition and the active control condition were registered.

• *Other eligibility criteria:* The earliest case studies of CBCR for cognitive symptoms after ABI appeared in the 1980s [35]. Therefore, this review only searched for studies from 1980 and onward. Furthermore, only studies written in English were eligible. Because of the methodological nature of this review, both study protocols for clinical trials and papers describing results of clinical trials were eligible.

Information sources and search:

Studies were identified through a systematic search of the following scientific databases: Pubmed/Medline, Psycinfo and Embase. All electronic searches were completed on September 16, 2018. Furthermore, lists of references of papers included in the review were screened for further relevant papers. The full search strategy and a full search string is provided in [appendix 1](#).

Study selection:

Two authors were involved in the entire process of study selection from initial searches and screening for relevant titles to final inclusion in the review. The authors selected studies for each step individually before checking if the chosen studies for each step were identical. When this was not the case, a third author was involved in the discussion about further inclusion. For details of the stages of the inclusion process, see flow diagram in [figure 1](#).

Data collection process:

All data were extracted from included studies by use of a pre-designed coding table. Data were extracted independently by two review authors, before checking if the coded variables were identical for each study. Any disagreements were solved by a third review author.

Data items:

The following data items were collected for each study:

General study information:

- Study design
- Sample size

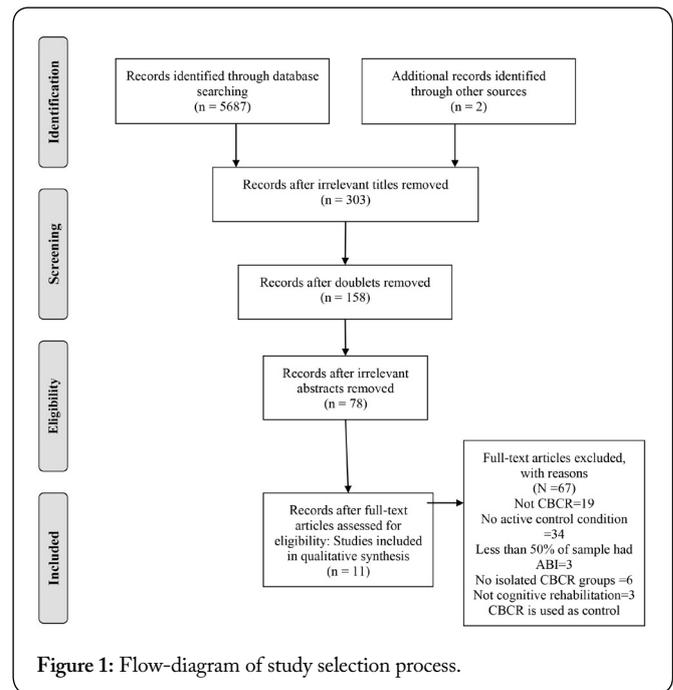


Figure 1: Flow-diagram of study selection process.

- Randomization procedure
- Blinding procedure
- Type of acquired brain injury
- Average time since acquired brain injury
- Cognitive domains targeted by the intervention
- Experimental condition (EC)
- Active control condition (ACC)
- Intervention period
- Primary outcome measures
- Results of the interventions on primary outcome measures

Experimental variables:

- Matching of demographic and individual-related variables between EC and ACC
- Intensity of the interventions
- Expectations of the intervention effects
- Interest value of the interventions and patient motivation
- Intervention setting
- Continuous adjustment of task-difficulty
- Side-effects of interventions
- Variations in training material
- Type of medium used for the interventions
- Cognitive load on cognitive function of interest

Reflections on choice of active control condition:

- Did the study report any reflections on the choice of ACC, and if yes, which?

Appendix 1: Systematic Search String for Active Control Conditions in Trials Exploring the Effects of Computer Based Cognitive Rehabilitation for Cognitive Symptoms after Acquired Brain Injury

Databases:

Pubmed, Embase & Psycinfo

Target Words:

String Number	A-String: Type of Acquired Brain Injury (Abi)	And	B-String: Intervention
	Cerebral tumor	AND	Computer based cognitive rehabilitation (CBCR)
	Stroke	AND	
	Post operative sequelae	AND	
	Traumatic Brain Injury	AND	

Synonyms for stroke based on: Bowen A, Hazelton C, Pollock A, Lincoln NB (2013) Cognitive Rehabilitation for Spatial Neglect Following Stroke, Cochrane Stroke Group

Synonyms for post-operative sequelae based on: Thesaurus synonyms

Synonyms for cerebral tumor based on: Tremont-Lukast IW, Ratilal BO, Armstrong T, Gilbert MR (2008) Antiepileptic drugs for preventing seizures in people with brain tumors, Cochrane Epilepsy Group

Synonyms for TBI based on: Langham J, Goldfrad C, Teasdale G, Shaw D, Rowan K (2003) Calcium channel blockers for acute traumatic brain injury, Cochrane injuries Group

Synonyms for CBCR based on: Bowen A, Hazelton C, Pollock A, Lincoln NB (2013) Cognitive Rehabilitation for Spatial Neglect Following Stroke, Cochrane Stroke Group

Stroke Search:

Apoplexia	AND	Computer based cognitive rehabilitation
Anterior cerebral artery embolism, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		Cognitive intervention, rehabilitation, training, therapy
Anterior circulation embolism, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		Computer intervention, rehabilitation, training, therapy
Apoplectic attack, insult		Computer assisted intervention, rehabilitation, training, therapy
Arteriovenous malformation		Computer assisted cognitive intervention, rehabilitation, training, therapy
Basal ganglia accident, bleed, disease, disorder, embolism, event, haematoma, haemorrhage, hematoma, hemorrhage, hypoxia, infarct, injury, insult, ischemia, obstruction, occlusion, thrombosis, trauma, vasculopathy, vasospasm		Computer based intervention, rehabilitation, training, therapy
Basilar aneurysm		Computer based cognitive intervention, rehabilitation, training, therapy
Basilar artery arteriosclerosis, ischemia, insufficiency, occlusion, stenosis		Computerized intervention, rehabilitation, training, therapy
Berry aneurysm		Computerized cognitive intervention, rehabilitation, training, therapy
Brain accident, aneurysm, angioma, disease, disorder, embolism, event, haemangioma, hemangioma, hypoxia, infarct, injury, insult, ischemia, obstruction, occlusion, thrombosis, trauma, vascular malformation, vasculopathy, vasospasm		Internet intervention, rehabilitation, training, therapy
Cerebral aneurysm, angioma, bleed, embolism, haemangioma, haematoma, haemorrhage, hemangioma, hematoma, hemorrhage, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		Internet based intervention, rehabilitation, training, therapy
Cerebellar bleed, embolism, haematoma, haemorrhage, hematoma, hemorrhage, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		Internet based cognitive intervention, rehabilitation, training, therapy
Cerebral artery arteriosclerosis, disease, ischemia, insufficiency, occlusion, stenosis		Online intervention, rehabilitation, training, therapy
Cerebral vein thrombosis		Online cognitive intervention, rehabilitation, training, therapy
Cerebral venous thrombosis		
Communication aneurysm		
Cortical embolism, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		
Giant aneurysm		
Hemispheric embolism, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		
Infratentorial bleed, embolism haematoma, haemorrhage, hematoma, hemorrhage, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		
intracerebral bleed, EMBOLISM, haematoma, haemorrhage, hematoma, hemorrhage, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		

Intracranial accident, aneurysm, bleed, disease, disorder, embolism, event, haematoma, haemorrhage, hematoma, hemorrhage, hypoxia, infarct, injury, insult, ischemia, obstruction, occlusion, thrombosis, trauma, vasculopathy, vasospasm		
Intraventricular bleed, haematoma, haemorrhage, hematoma, hemorrhage		
Ischemic attack, insult		
Lacunar infarct		
Lenticulostriate accident, disease, disorder, event, injury, insult, trauma		
Medial cerebral artery embolism, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		
Medial circulation embolism, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		
Parenchymal bleed, haematoma, haemorrhage, hematoma, hemorrhage		
Posterior cerebral artery embolism, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		
Posterior circulation embolism, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		
Posterior fossa bleed, haemorrhage, hemorrhage, haematoma, hematoma		
Poststroke/Post-stroke		
Putamen bleed, haemorrhage, hemorrhage, haematoma, hematoma		
Putaminal bleed, haemorrhage, hemorrhage, haematoma, hematoma		
Ruptured aneurysm		
Saccular aneurysm		
Sagittal thrombosis		
Sinus thrombosis		
Stroke		
Subarachnoid bleed, haemorrhage, hemorrhage, haematoma, hematoma		
Supratentorial bleed, embolism haematoma, haemorrhage, hematoma, hemorrhage, hypoxia, infarct, ischemia, obstruction, occlusion, thrombosis, vasculopathy, vasospasm		
Venous malformation		
Vertebral artery aneurysm, arteriosclerosis, dissection, ischemia, insufficiency, occlusion, stenosis		
Vertebral basilar arteriosclerosis, ischemia, insufficiency, occlusion, stenosis		
Vertebrobasilar arteriosclerosis, embolism, hypoxia, infarct, insufficiency, ischemia, obstruction, occlusion, thrombosis, stenosis, vasculopathy, vasospasm		

Post Operative Sequelae Search:

Post-operative sequelae	AND	Computer based cognitive rehabilitation
Aciurgy consequence, corollary, emanation, ramification, residual, residuum, sequela, sequelae, swelling		Cognitive intervention, rehabilitation, training, therapy
Incision consequence, corollary, emanation, ramification, residual, residuum, sequela, sequelae, swelling		Computer intervention, rehabilitation, training, therapy
Operation consequence, corollary, emanation, ramification, residual, residuum, sequela, sequelae, swelling		Computer assisted intervention, rehabilitation, training, therapy
Operative consequence, corollary, emanation, ramification, residual, residuum, sequela, sequelae, swelling		Computer assisted cognitive intervention, rehabilitation, training, therapy
Postoperative consequence, corollary, emanation, ramification, residual, residuum, sequela, sequelae, swelling		Computer based intervention, rehabilitation, training, therapy
Resection consequence, corollary, emanation, ramification, residual, residuum, sequela, sequelae, swelling		Computer based cognitive intervention, rehabilitation, training, therapy
Surgery consequence, corollary, emanation, ramification, residual, residuum, sequela, sequelae, swelling		Computerized intervention, rehabilitation, training, therapy
		Computerized cognitive Intervention, rehabilitation, training, therapy
		Internet intervention, rehabilitation, training, therapy

		Internet based intervention, rehabilitation, training, therapy
		Internet based cognitive intervention, rehabilitation, training, therapy
		Online intervention, rehabilitation, training, therapy
		Online cognitive intervention, rehabilitation, training, therapy

CEREBRAL TUMOR SEARCH:

Cerebral tumor	AND	Computer based cognitive rehabilitation
Astrocytoma		Cognitive intervention, rehabilitation, training, therapy
Brain cancer, carcinoma, cyst, lump, swelling, metastases, neoplasm, sarcoma, tumefaction, tumor		Computer intervention, rehabilitation, training, therapy
Cerebral cancer, carcinoma, cyst, lump, swelling, metastases, neoplasm, sarcoma, tumefaction, tumor		Computer assisted intervention, rehabilitation, training, therapy
Cerebellar cancer, carcinoma, cyst, lump, swelling, metastases, neoplasm, sarcoma, tumefaction, tumor		Computer assisted cognitive intervention, rehabilitation, training, therapy
Ependymoma		Computer based intervention, rehabilitation, training, therapy
Glial tumor		Computer based cognitive intervention, rehabilitation, training, therapy
Glioblastoma		Computerized intervention, rehabilitation, training, therapy
Glioma		Computerized cognitive intervention, rehabilitation, training, therapy
Intracranial cancer, carcinoma, cyst, lump, swelling, metastases, neoplasm, sarcoma, tumefaction, tumor		Internet intervention, rehabilitation, training, therapy
Intracerebral cancer, carcinoma, cyst, lump, swelling, metastases, neoplasm, sarcoma, tumefaction, tumor		Internet based intervention, rehabilitation, training, therapy
Meningeoma		Internet based cognitive intervention, rehabilitation, training, therapy
Oligodendroglioma		Online intervention, rehabilitation, training, therapy
Primary brain tumor		Online cognitive intervention, rehabilitation, training, therapy
Secondary brain tumor		Computer based visuospatial intervention, rehabilitation, training, therapy
Subarachnoid cancer, carcinoma, cyst, lump, swelling, neoplasm, sarcoma, tumefaction, tumor		

TRAUMATIC BRAIN INJURY SEARCH:

Traumatic brain injury	AND	Computer based cognitive rehabilitation
Brain damage, fracture, injury, laceration, swelling, trauma, wound		Cognitive intervention, rehabilitation, training, therapy
Cerebral damage, fracture, injury, laceration, swelling, trauma, wound		Computer intervention, rehabilitation, training, therapy
Cerebellar damage, fracture, injury, laceration, swelling, trauma, wound		Computer assisted intervention, rehabilitation, training, therapy
Cranio cerebral trauma		Computer assisted cognitive intervention, rehabilitation, training, therapy
Cranial damage, fracture, injury, laceration, swelling, trauma, wound		Computer based intervention, rehabilitation, training, therapy
Diffuse axonal injury		Computer based cognitive intervention, rehabilitation, training, therapy
Diffuse brain damage, fracture, injury, laceration, swelling, trauma, wound		Computerized intervention, rehabilitation, training, therapy
Encephalopathy		Computerized cognitive intervention, rehabilitation, training, therapy
Penetrating head injury		Internet intervention, rehabilitation, training, therapy
Pneumocephalus		Internet based intervention, rehabilitation, training, therapy
Skull fracture		Internet based cognitive intervention, rehabilitation, training, therapy
Traumatic brain injury		Online intervention, rehabilitation, training, therapy
		Online cognitive intervention, rehabilitation, training, therapy

Analysis of methodological strengths and limitations of each study:
 Methodological strengths and limitations regarding the

design of each included study was qualitatively analyzed by use of the identified relevant experimental variables outlined

in section one.

Results

Study characteristics

A total of 11 papers were included in this review. Nine which were final publications of results from clinical trials, and two which were clinical trial protocols. Two final publications [36-38] referred to the same clinical trial. Therefore, these three papers are jointly discussed here. Overall results of individual studies are outlined below, and a detailed description of all variables can be found in table 1.

Gray, Robertson, Pentland, & Anderson [39]

Methods: This randomized clinical trial explored the effects of CBCR on attention and working memory in 55 patients with traumatic and non-traumatic ABI in a parallel design with three conditions: an experimental condition (EC), an active control condition (ACC) and a passive control condition, which will not be discussed further here. The EC consisted of five different computerized attention and working memory exercises using unspecified computer software. The ACC consisted of a non-specified number of computerized recreational games. The intervention period lasted three to nine weeks depending on the individual subject, but overall there was no significant difference in total training time between groups. The authors have not explicitly stated the setting in which the trial took place.

Results: The study found beneficial effects of the EC intervention compared to the ACC intervention on the primary outcome measures of attention and working memory, but not on the primary outcome of general health. According to the paper, the ACC was designed to control for any non-specific effects of computer use.

Strengths and limitations of study design: This study designed the EC intervention to be continuously more challenging and targeted the cognitive domains of scientific interest with very domain-specific exercises which presumably had a high load on the targeted functions. The ACC received general computerized cognitive stimulation exercises instead of domain-specific exercises without continuous adjustment of task difficulty. As the groups trained with equal intensity with the same type of intervention medium, similar side-effects can be expected between groups. This study design allows for comparisons between domain-specific and continuously adjusted training which targets specific cognitive functions with general cognitive stimulation in which the level of difficulty is kept constant. However, the study neither accounts for differences in the variation of training material between the two groups, nor for differences in expectations or interest value between the interventions. As such, these variables are possible confounders that reduce the certainty of the interpretation of study-results.

Katz & Werts [40]

Methods: This study was a randomized clinical trial of the effects of CBCR on aphasia in 55 stroke patients. The study consisted of two parallel groups: The EC, which completed

32 computerized visual matching and reading comprehension exercises with a non-commercial software developed for the study, and the ACC, which completed an unspecified number of nonverbal exercises using a cognitive rehabilitation software, along with computerized recreational games without language stimuli. Both groups trained for an approximate total of 78 hours over a period of 26 weeks. Participants mostly made use of computers located in the speech-language pathology department at which the trial was carried out (although two subjects occasionally had a computer brought to their homes).

Results: The EC improved significantly more than the ACC during the intervention period on the primary outcome measures of language. The paper states that the ACC was designed to provide general cognitive stimulation with little to no language stimulation or use.

Strengths and limitations of study design: The ACC used general cognitive stimulation with low load on the targeted function on the same intervention medium as EC. EC used domain specific exercises with high load on the targeted function. As the groups trained with equal intensity with the same intervention medium, similar side-effects can be expected between groups. The study is thus able to explore differences between specific versus general cognitive stimulation on symptoms of aphasia. The study states that the EC can assess different difficulty levels of the cognitive rehabilitation software, but whether this is also possible for the ACC is not specified. It is therefore not possible to determine if both of the two groups were able to adjust difficulty level continuously. Furthermore, the study does not state if the two groups had the same variability in training material, and potential differences in the interest value and expectations of the two interventions are not measured. As such, several variables are not controlled for and thus constitute possible confounders for the interpretation of the study results.

Kerner & Acker [35]

Methods: This randomized, clinical trial with a parallel three group design (EC, ACC and a passive control group; PCC) explored the effects of four and a half weeks of memory-CBCR on 24 patients with traumatic brain injuries. The EC completed two computerized memory-exercises, and the ACC completed one computerized drawing exercise. Both groups trained for an average of nine hours. All participants made use of computers located at the clinic in which the trial took place.

Results: The study reports a significant improvement of the EC compared to the ACC on the primary outcome measure of memory. Regarding the design of the ACC, the study states that the Sham-intervention was designed to not deliver memory retraining.

Strengths and limitations of study design: In contrast to the abovementioned studies which compare domain specific training with general cognitive stimulation, this study compares a specific memory intervention with a specific visuospatial intervention on the same intervention medium. As the groups trained with equal intensity with the same intervention medium, similar side-effects can be expected between groups. This study thus explores whether near-transfer

Table 1: Characteristics of included studies

Study Name	Gray et al. (1992)	Katz & Wertz (1997)	Kerner et al. (1985)	Niemann, Ruff & Baser (1990)	Palmer et al. (2015)	Robertson et al. (1990)	Van de Ven et al. (2015, 2017 & 2017)	Wentink et al. (2016)	Zucchella et al. (2014)
General Study Information									
Design	Parallel, two groups: EC and ACC	Parallel, three groups: EC, ACC and PCC	Parallel, three groups: EC, ACC and PCC	Parallel, two groups: EC and ACC	Parallel, three groups: EC, ACC and PCC	Parallel, two groups: EC and ACC	Parallel trial, three groups: EC, ACC and PCC	Parallel trial, two groups: EC and ACC	Parallel, two groups: EC and ACC
Sample size	N=31 (EC=17, ACC=14)	N=55 (EC= 21, ACC= 19, PCC=15)	N=24 (EC=12, ACC=6, PCC=6)	N=26 (EC=13, ACC=13)	N=285 expected. (No information of group allocation yet, paper is a study protocol)	N=36 (EC=20, ACC=16)	N=120 (EC=38, ACC=35, PCC=24)	N=110 (EC=53, ACC=57)	N=87 (EC=42, ACC=45)
Randomization	Cluster randomization based on symptom severity	Study states that group assignment is randomized, but the method is not specified	Randomization by drawing notes with names from a hat	Study states that group assignment is randomized, but the method is not specified	Computerized randomization administered by a clinical trial unit	Semi-randomized: Partial random allocation of subjects within blocks of severe vs. mild neglect patients.	Computerized randomization with Minimpy software	Randomization by a third party not otherwise involved in the study using a random digit generator in Microsoft Excel	Computerized randomization with random number generator
Blinding	The study does not state anything about blinding of any parties	The study does not state anything about blinding of any parties	The study does not state anything about blinding of any parties	The study does not state anything about blinding of any parties	Follow-up assessment blinded to group allocation of patients	Follow-up assessment blinded to group allocation of patients	Double blind: Both patients and outcome-assessors are blind. Assessors of computer tasks were not blinded as they provided the training instructions	Follow-up assessment blinded to group allocation of patients	Follow-up assessment blinded to group allocation of patients
Type of acquired brain injury	Patients with traumatic or non-traumatic brain injuries	Patients with Stroke	Patients with traumatic brain injuries	Patients with traumatic brain injuries	Patients with Stroke	Patients with stroke, traumatic brain injuries and brain tumors	Patients with stroke	Patients with stroke	Patients with stroke
Average time since ABI	~1,5 years	~7 years	~1,3 years	~3,3 years	No information, paper is a study protocol	~1,5 months	~2,4 years	~2,1 years	Average not stated, but inclusion criteria that onset was within the last 4 weeks
Cognitive domains targeted	Attention and working memory	Language (aphasia)	Memory	Attention	Language (aphasia)	Visuospatial (neglect)	Attention, reasoning and working memory	Attention, speed, memory, flexibility and problem solving	Time and spatial orientation, visual attention, logical reasoning, memory and executive functions
Experimental condition (EC)	5 different computerized attention and working memory exercises, name of used software not stated	32 computerized visual matching and reading comprehension exercises with non-commercial software developed for the study	Two computerized memory exercises with software developed by Rosamond Gianutsos (1981).	Computerized exercises of three domains of attention: Visual, auditory and divided attention. Name of software and number of exercises not stated.	Computerized practice of communicating 100 personally relevant words using the software 'StepbyStep'	5 computerized visual scanning and visual attention exercises, name of used software not stated	9 computerized exercises of attention, reasoning and working memory with the software 'Braingymmer'	16 computerized exercises of attention, speed, memory, flexibility and problem solving with the software 'Lumosity'	Computerized exercises of time and spatial orientation, visual attention, logical reasoning, memory and executive functions carried out with a psychologist with the software 'Una PALESTRA per la mente' and 'Training di riabilitazione cognitiva'. Number of exercises not stated

Active control condition (ACC)	Computerized recreational games like noughts and crosses, puzzles and reds and greens. Number of exercises not stated	Nonverbal exercises in CBCR software and computerized recreational games without language stimuli. Number of exercises not stated	1 Computerized exercise: Makes drawings on the computer screen using 'LOGO' software	Computerized memory exercises with 'Einstein memory trainer' software. Number of exercises not stated	Completing puzzle-books (not computerized) with word searches, sudoku, spotting differences between pictures and so forth. Number of exercises not stated.	Computerized recreational games like word games, anagram tasks, quizzes and reds and greens. Number of exercises not stated.	4 computerized exercises of visuospatial functions and visual attention	Uses homepage (computerized) to receive information about the brain once a week	Spending time with a psychologist discussing general topics, news and their recent activities
Intervention period	3-9 weeks depending on subject	26 weeks	4,5 weeks	9 weeks	26 weeks	7 weeks	12 weeks	8 weeks	4 weeks
Primary outcome measures	Paced Auditory Serial Addition Test (PASAT), Wais-R arithmetic, General Health Questionnaire-28 (GHQ-28)	Porch Index of Communicative ability (PICA) and Western Aphasia Battery (WAB)	New York University Memory Test (NYUMT) overall score	D2-test, PASAT-R, Divided attention test, trail making B	Change in number of words named correctly, change in functional communication (blinded video recordings)	Behavioral Inattention Test (BIT), Rey-Osterrieth Complex Figure Copy, (ROCF), Neale Reading Test (NRT), Letter Cancellation (LC), WAIS-R Picture completion (WAIS-R-PC) and WAIS-R Block Design (WAIS-R BD)	Number-Letter Switching from D-Kefs (NLS-DK), Category Fluency (CL), Letter Fluency (LF), Tower of London (TL), Letter-Number sequencing from WAIS-III (LN-WAIS-III)	Block Span Task forward and backward (BST-f & BST-b), Digit Span forward and backward (DS-f & DS-b) Trail Making A and B (TMT-A & TMT-B), Flanker Task congruent and incongruent (FT-c & FT-ic)	Mini mental state examination (MMSE), Digit span, Corsi's test, Rey Auditory Verbal Learning Test (RAVLT), Logical memory (LM), Frontal Assessment Battery (FAB), Trail Making A and B (TMT-A & TMT B), progressive matrices 47 (PM47), phonological and semantic fluency (PF & SF), Rey Osterrieth Complex Figure Copy (ROCF), Functional Independence Measure (FIM)
Primary study results	T-test between pre- and post-intervention for each group: PASAT: EC: p=0.004, ACC: Non-significant, p-value not provided. Wais-R arithmetic: EC: p=0.005, ACC: Non-significant, p-value not provided. GHQ-28: Non-significant for both groups, p-values not provided.	T-test of difference between the improvement in the EC and ACC group: EC improved significantly more than ACC on all tests: PICA overall: (p<0.003), PICA verbal percentile: (p<0.001), WAB Aphasia Quotient: (p<0.008), WAB repetition subtest: (p<0.02)	T-test of difference between the improvement in the EC and ACC group: EC improved significantly more than ACC on NYUMT overall score: (p=0.006)	Wilks's lambda test of difference between the improvement in the EC and ACC group on all 4 primary outcome measures: EC improved significantly more than ACC: (p<0.025)	No results yet, paper is a study protocol	T-test of difference between the improvement in the EC and ACC group: There were no significant differences between EC and ACC on any primary outcome measures: BIT, ROCFC, NRT, LC, WAIS-R-PC, WAIS-R-BD: (p>0.10)	A Manova analysis showed that both EC, ACC and PCC improved during between pre- and post-intervention testing: NLS-DK: (p<0.001), LN-WAIS-III: (p<0.01) CL: (p=0.61), LF: (p=0.20), TL: (p<0.01). However, there were no time group interaction: (p=0.65)	Unspecified statistical analysis of primary outcome measures between pre- and post-intervention test (both parametric and nonparametric tests used, but not specified where): BST-f: (p=0.02), BST-b: (p=0.45), DS-f: (p=0.23), DS-b: (p=0.28), TMT-A: (0.54), TMT-B: (p=0.10), FT-c: (p=0.08), FT-ic: (p= 0.00).	Mann-Whitney U test of difference between the improvement of the EC and ACC: No significant differences on: Digit span, Corsi's test, RAVLT, FAB, PF, SF, ROCFC, FIM. P-values not stated. Significant differences on: MMSE: (p=0.05), LM: (p=0.005), TMT-A: (P=0.03), TMT-B: (p=0.01)
Variables									

Matcing of demographic variables between groups	Yes	Yes	Yes	Yes	No information, paper is a study protocol	Training time not matched, all other demographic variables matched	Yes	Randomization is stratified for age and educational level, but no post-hoc analysis of significant differences in demographics between groups	Yes
Intensity of the intervention	15,35 hours for EC and 12,7 hours for ACC - no significant difference between EC and ACC	78 hours for both EC and ACC - no significant difference between EC and ACC	9 hours for both EC and ACC -no significant difference between EC and ACC	18 hours for both EC and ACC – no significant difference between EC and ACC	No information, paper is a study protocol	EC trained for 15,5 hours, ACC trained for 11,4 hours. This is a statistically significant difference (p<0.003)	29 hours for both EC and ACC	10 hours for EC and 1 hour and 10 minutes for ACC	16 hours of computerized exercises for EC and 16 hours of general discussion with a psychologist for ACC
Expectations of intervention effects	Not measured	Not measured	Not measured	Not measured	Not measured	Not measured	Not measured	Not measured	Not measured
Interest value of intervention and patient motivation	The study states no reflections on differences in interest value between the EC and ACC intervention	The study states no reflections on differences in interest value between the EC and ACC intervention	The study states no reflections on differences in interest value between the EC and ACC intervention	The study states no reflections on differences in interest value between the EC and ACC intervention	The study states no reflections on differences in interest value between the EC and ACC intervention	The study states no reflections on differences in interest value between the EC and ACC intervention	According to the protocol the two interventions were designed to have the same interest value, and the patients in both groups register their daily motivation, but the result papers do not state if the patients in the different groups registered equal levels of interest and motivation for their interventions	The study states no reflections on differences in interest value between the EC and ACC intervention	Satisfaction with the intervention is measured on a scale from 1-4. EC are significantly more satisfied with their intervention than ACC. EC average: 3.19, ACC average: 2.57. Mann-Whitney U test of significance: (p=0.000)
Setting	Setting not explicitly stated	All participants used computers located in the speech-language pathology departments. Two subjects occasionally used a computer brought to their homes when problems with transportation occurred. Participants in the no-treatment group did not receive computer training.	All participants used "computers located in the Educational Diagnostic Clinic De Anza College. Participants sat in either a wheelchair or a wooden desk chair. The room was not closed off from other parts of the Educational Diagnostic Clinic; however, the structure of the carrels cut off visual contact with everything outside of the carrel itself. The Clinic is considered a library so the noise level is very low and there were no other distractions."	Setting not explicitly stated. Authors simply state the means of delivery (computer and cassette tapes) and that patients "were seen twice per week on a one-to-one basis."	Self-managed computerized intervention group: "The majority of the practice time involved in the intervention is self-managed by the participant through regular use of the aphasia computer software." Attention and activity control arm: "Participants completes puzzle books by themselves and are contacted by phone or email once a month."	Setting not explicitly stated.	"Participants in the training groups trained at home five times per week during half an hour for 12 weeks. The waiting list group received care as usual which most often meant they did not receive any treatment; they were not contacted by phone."	"Intervention and control condition is administered online. Participants receive contact details of a research assistant to contact in case of difficulties using the website or software" (thus, although not explicitly stated, it is implied that participants access the website from their home environment).	Setting is not explicitly stated.

Continuous adjustment of task-difficulty	For EC yes (on the dimension time pressure). For ACC no	For EC yes (8 difficulty levels with different dimensions of difficulty), not stated for ACC	The study states nothing about this variable	For EC yes (on dimensions such as number of distractors and similarity between target and distractors), not stated for ACC	Study states that software used by EC is personally tailored for the patient, but not if the software continuously adjusts to the patient's current ability. ACC gets more difficult puzzle-books everytime they finish current puzzle-books	For EC yes (on dimensions such as time pressure, amount and visibility of helping cues). For ACC no	For EC yes (Patients can increase difficulty level from 1-20 at any time) For ACC to a smaller degree (difficulty level increases from 1-9 at fixed times during the intervention period)	For EC yes (software adjusts difficulty level based on latest previous performance). For ACC no: They do not use any exercises	For EC yes (level 1-3 depending on patients latest previous performance). For ACC no: They do not use any exercises
Side-effects of intervention	The study states nothing about this variable, but both EC and ACC gets an intervention expected to create similar side-effects	The study states nothing about this variable, but both EC and ACC gets an intervention expected to create similar side-effects	The study states nothing about this variable, but both EC and ACC gets an intervention expected to create similar side-effects	The study states nothing about this variable, but both EC and ACC gets an intervention expected to create similar side-effects	The study states nothing about this variable, and EC and ACC gets interventions that might produce different side-effects	The study states nothing about this variable, but both EC and ACC gets an intervention expected to create similar side-effects	The study states nothing about this variable, but both EC and ACC gets an intervention expected to create similar side-effects	The study states nothing about this variable, and EC and ACC gets interventions that might produce different side-effects	The study states nothing about this variable, and EC and ACC gets interventions that might produce different side-effects
Variation in training material	EC does 4 exercises. It is not stated how many ACC does, but 3 exercises are used as examples	EC does 32 exercises. It is not stated how many ACC does, but 3 tasks are used as examples	EC does 2 exercises and ACC does 1	The study does not state how many exercises EC and ACC use	EC trains a 100 words. It is not stated how many exercises ACC does	EC does 5 exercises. It is not stated how many ACC does, but 4 exercises are used as examples	EC does 9 exercises, ACC does 4	EC does 16 exercises, ACC does 1	EC trains 6 sub-fields of cognition, but number of exercises not stated. ACC does not use any exercises
Type of medium used for the intervention	Both EC and ACC uses computer software	Both EC and ACC uses computer software	Both EC and ACC uses computer software	Both EC and ACC uses computer software	EC uses computer software, ACC uses puzzle-books	Both EC and ACC uses computer software	Both EC and ACC uses computer software	Both EC and ACC uses computer software	EC uses computer software, ACC gets conversations on general topics with a psychologist
Cognitive load on targeted function	EC gets high load on targeted functions (Attention and working memory). ACC gets general cognitive stimulation with presumed low load on targeted function, although recreational gaming must be expected to have some impact on visual attention	EC gets high load on targeted function (language), ACC gets general cognitive stimulation with presumed low load on targeted function	EC gets high load on targeted function (memory), ACC gets visuospatial cognitive stimulation with presumed low load on targeted function	EC gets high load on targeted function (attention), ACC gets memory training with presumed low load on targeted function, although the ACC intervention must be expected to have some impact on attention	EC gets high load on targeted function (language), ACC gets general cognitive stimulation with presumed low load on the targeted function	EC gets high load on targeted function (visuospatial functioning), ACC gets general cognitive stimulation with presumed low load on targeted function, although recreational gaming must be expected to have some impact on visual attention	EC gets high load of targeted functions (attention, reasoning and working memory), ACC gets high load on visuospatial functions and visual attention with presumed low load on targeted function, although the ACC intervention must be expected to have some impact on attention	EC gets high load of targeted functions (attention, speed, memory, flexibility and problem solving), ACC gets psychoeducation with presumed low load on targeted functions, although the ACC intervention must be expected to have some impact on attention	EC gets high load on targeted functions (time and spatial orientation, visual attention, logical reasoning, memory and executive functions) ACC gets general conversations with a psychologist with presumed low load on targeted functions

<p>Reflections on choice of ACC</p>	<p>“Recreational computing was used as the control procedure, rather than, for example, no treatment or psychotherapy, to control for any non-specific effects of using micro-computers” (p. 99)</p>	<p>“Any language stimulation or use (in ACC, red.) was unstructured and incidental. Thus, the game and CR software were very different from the focused and intentional language activities provided by the computer reading treatment software” (Stimulation software section, line: 6-9)</p>	<p>The programme used by the ACC is designed for: “drawing one’s own trees, houses, and so on, but does not deliver memory retraining.” (p. 69)</p>	<p>“To control for nonspecific treatment effects, the control group received a memory training of equivalent duration and intensity.” (p.811)</p>	<p>“(…) intends to control for the potential impact of elements of the intervention which of themselves do not provide or require speech and language intervention.” (p. 8)</p>	<p>“The subjects (in ACC, red.) be exposed to plausible computer activities, but that there should be no potential neuropsychologic mechanism by which these activities could improve cognitive function. (...) The main exclusion criteria for such programmes were if they included any speed component (...) or if they included tasks with a large component of visual search.” (p. 666)</p>	<p>“The active control group received a non-adaptive mock training consisting of four computer tasks, which in our view were not likely to improve executive functioning. (...) The control training was designed to have the same amount of feedback, motivational instructions, visual stimulation, and use of mouse as the intervention training.” (Van de Ven et al., 2015, p.6)</p>	<p>The study states no reflections about the choice of the ACC intervention</p>	<p>The study states no reflections about the choice of the ACC intervention</p>
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EC: Experimental condition, ACC: Active control condition, PCC: Passive control condition, CR: Cognitive rehabilitation.

specific memory training is more beneficial for memory than far-transfer training of another specific cognitive domain. As the study does not report whether the software made use of continuous adjustment of task-difficulty for any of the groups, it is not possible to comment on this variable. However, the study does state that the EC and ACC do not have access to the same number of exercises. Furthermore, the study does not measure the impact of participants’ expectations regarding the interventions or the interest value of the interventions. It is therefore not possible to rule out that the interpretations of the study-results may be confounded by these unaccounted-for variables.

Niemann, Ruff & Baser [41]

Methods: 26 patients with traumatic brain injuries were enrolled in this randomized, parallel trial with two groups (EC and ACC), to explore the effects of CBCR on attention. The EC performed computerized exercises of three domains of attention (visual, auditory and divided attention) whereas the ACC performed computerized memory exercises. Both groups trained for approximately 18 hours within the nine-week intervention period. The authors have not explicitly stated the setting in which the trial took place.

Results: The EC improved significantly more on the primary outcome variables of attention than the ACC during the intervention period. The study states that the ACC was designed to control for nonspecific training effects, and should thus be of equal length and intensity as the EC.

Strengths and limitations of study design: This study compares a specific attention intervention with a specific memory

intervention. As the groups trained with equal intensity with the same intervention medium, similar side-effects can be expected between groups. The study is therefore able to explore whether near-transfer specific attention training is more beneficial for attention than far-transfer training of another specific cognitive domain. While the exercises completed by the EC are continuously adjusted to match the current level of the participant, nothing is stated regarding continuous adjustment for the ACC. This study also does not state anything about variation in training material, expectations of the interventions or interest value of the interventions. Therefore, these constitute possible confounding variables which weaken the interpretations of the study-results.

Palmer, Cooper, Enderby, Brady, Julious, Bowen & Latimer [42]

Methods: This paper is a study protocol of a randomized, single-blinded clinical trial which aims to explore the effects of CBCR on aphasia in 285 patients (estimated) with stroke. The study employs a parallel design consisting of three groups: An EC, ACC and PCC, the latter of which being of no relevance to this paper and will thus not be discussed further. The EC will perform computerized practice of communicating 100 personally relevant words, and the ACC will complete puzzle-books (not computerized) including word searches, sudoku, spotting differences between pictures and so forth. The intervention period for both the EC and ACC are scheduled to last 26 weeks. The computer intervention is predominantly self-managed by patients in their home setting (with regular visits and technical assistance from volunteers and speech and language therapists). The active control group completes

puzzle books on their own and are contacted once a month by phone or email.

As a rationale for the design of the ACC, the authors state that they intended to control for the potential impact of elements of the intervention which by themselves do not provide or require speech or language intervention.

Results: As this paper is a protocol, study results are not yet available.

Strengths and limitations of study design: The study will compare a domain-specific intervention for the targeted cognitive impairment (aphasia), with a general stimulation intervention. This allows for comparison of the differences between specific versus general cognitive stimulation on symptoms of aphasia. However, the EC and ACC will not use the same intervention medium, which can possibly cause different experimental effects and side-effects between the two groups. Furthermore, the protocol reports no plans of measuring patient expectations or interest value. It is not stated how many different exercises the ACC has access to, and it is therefore not possible to comment on variations in training material. Thus, several possible confounding variables can reduce the certainty of the interpretation of study-results.

Robertson, Gray, Pentland & Waite [43]

Methods: This semi-randomized, blinded, parallel clinical trial explored the effect of CBCR on visuospatial symptoms (neglect) in 36 patients with stroke, traumatic brain injuries or brain tumors. The study consisted of an EC and ACC, both with intervention periods of seven weeks. The EC completed five computerized visual scanning and visual attention exercises with unspecified software, whereas the ACC completed computerized recreational games like word games, anagram tasks, quizzes and reds and greens. The authors have not explicitly stated the setting in which the trial took place.

Results: There were no significant differences between the EC and ACC on any of the primary outcome measures of visuospatial functions. As rationale for the choice of ACC, the authors state that patients in this group are exposed to computerized activities without any known mechanisms that should improve cognition, and that sham-games were excluded if they included any speed component or tasks with a high load on visuospatial functions.

Strengths and limitation of study design: This study compares the effects of specific cognitive training for visuospatial impairments with continuous adjustment of task difficulty with non-adjustable general cognitive stimulation. The EC gets a high load on the targeted cognitive function, and the ACC gets general cognitive stimulation with presumed low load on the targeted cognitive function. The EC and ACC use the same medium for their interventions and are matched on most demographic variables. However, the ACC on average completed 11.4 hours of sham-training, while the EC on average completed 15.5 hours of CBCR. This is a significant difference in intervention intensity with possible confounding effects on the interpretations of overall results of the study. Furthermore, expectations and interest value of the interventions were not measured, and the authors do not

mention anything regarding variability in training material for the ACC group, which makes it impossible to interpret the possible impact of these variables on the overall study outcome.

Van de Ven et al. [36-38]

Three papers were identified for this study: One study protocol from 2015, and two papers with results from 2017. All three papers are jointly presented here.

Methods: This study was a double-blind, randomized, parallel clinical trial with three groups (EC, ACC and PCC). The PCC will not be discussed further. The study enrolled a total of 120 stroke patients with impairments in reasoning, working memory and attention for 12 weeks of sham-training or CBCR. The EC completed nine computerized exercises of attention, reasoning and working memory using the BrainGymmer software, whereas the ACC completed four computerized exercises of visuospatial functions and visual attention with the same software. All participants in the training groups trained in their home setting for half an hour, five times a week.

Results: The study found no significant differences between the EC and the ACC on any of the primary outcome measures of attention, working memory or reasoning after the intervention period. According to the authors, the ACC was designed to be a non-adaptive computerized intervention with a low chance of increasing executive functioning.

Strengths and limitation of study design: This study compared a specific CBCR-intervention for executive symptoms which were continuously adjusted to the patients' current level with a less adjustable specific CBCR intervention for visuospatial symptoms. This design enabled exploration of whether near-transfer specific training of executive functions is more beneficial for executive functions than far-transfer training of another specific cognitive domain. Whereas the EC received high load on targeted functions (attention, reasoning and working memory), the ACC received a high load on visuospatial functions and visual attention – with presumed low load on the targeted functions. Furthermore, both groups used computer-software as the intervention medium, and as such the interventions can be expected to cause similar side-effects. However, the EC had access to nine exercises and the ACC had access to four, which is a possible confounder of the interpretations of the study results. The study also did not include a measure of the expectations of the interventions, and even though the protocol states that the interventions are thought to have an equal interest value, this is not measured.

Wentink et al. [44]

Methods: This paper did not specifically state whether the included control group was deemed active or passive, but because the control group was not entirely passive between pre- and post-intervention assessment, the paper is included here. This study was a randomized, single-blinded, parallel trial of the effects of CBCR on executive functions (attention, speed, memory, flexibility and problem solving) in 110 stroke patients. The EC completed 16 computerized exercises of attention, speed, memory, flexibility and problem solving with the Lumosity software, whereas the ACC was instructed to

visit a homepage in which participants received information about the brain once a week. The intervention period was eight weeks, in which the EC was exposed to CBCR for an average of 10 hours, and the ACC was exposed to computerized psychoeducation for approximately one hour. Although not explicitly stated, the authors write that participants received the contact details of a research assistant “in case of difficulties using the website or software”, thus implying that participants completed training from home.

Results: The study reported significant differences between the EC and ACC on two out of seven primary outcome measures. No reflections regarding choice of ACC are reported in the paper.

Strengths and limitations of study design: This study compared the effects of a specific CBCR-training targeting attention, speed, memory, flexibility and problem solving with a sham-intervention consisting of computerized psychoeducation with presumed low load on targeted functions. The ACC in this study used the same intervention medium as the EC and patients were matched on demographic variables. However, several variables are not accounted for, including variation in training material, intensity of the intervention, expectations of the interventions and disparities in interest value between the two interventions. There are thus several confounding variables between the EC and ACC which reduce the validity of the interpretation of study results.

Zucchella et al. [45]

Methods: This study was a randomized, single-blinded, parallel clinical trial of 87 stroke patients split into two groups: EC and ACC. The study explored the effects of four weeks of CBCR targeting several cognitive domains (time and spatial orientation, visual attention, logical reasoning, memory and executive functions) using the software ‘Una palestra per la mente’ and ‘Training di riabilitazione cognitiva’. This is contrasted with a four-week sham-intervention consisting of spending time with a psychologist discussing general topics, news and recent activities. The authors have not explicitly stated the setting in which the trial took place.

Results: The study reported significant cognitive improvement in the EC compared to the ACC after the intervention on four out of twelve primary outcome measures. No reflections are stated regarding the choice of ACC.

Strengths and limitations of study design: This study compares the effects of general CBCR training with regular conversations with a psychologist to explore if CBCR is more beneficial to global cognition than being attended to by a health professional on a regular basis. The EC and ACC are matched on demographic variables and their interventions are of similar intensity in terms of hours spent. However, several variables are not matched between the groups, which confounds the interpretations of the study results. Firstly, the intervention-mediums are so different that is difficult to isolate which potentially relevant variables differ between them and what makes them efficacious or not. Secondly, expectations for the interventions are not measured, rendering it impossible to determine whether differences in outcome measures are due to differences in training. However, this is the only study which

measures the interest value of the interventions by asking patients to score it on a scale from 1-4. The EC group were significantly more satisfied with their intervention than the ACC group was.

Discussion

Summary of evidence

The identified literature reveals a limited consensus among researchers on how properly to design active control groups in studies of CBCR for patients with ABI. Here current practice is briefly summarized, and the most crucial limitations in terms of reporting and constructing active control group designs in trials of CBCR after ABI are discussed. Based on this, suggestions for future research is provided to overcome these limitations and improve the overall quality of cognitive rehabilitation studies making use of active control groups.

Of the 10 variables identified as important to consider in the construction of an active control condition (ACC), only four were adequately reported in all studies. These were the variables of demographic matching and individual-related variables, the type of medium used, intervention intensity and load on the cognitive function(s) of interest. As for the variable of continuous adjustment of task difficulty, several studies failed to report whether this was included in either conditions or only the experimental condition (EC). Similarly, several studies neglected to precisely report the setting as well as the amount of variation in training material for both groups. None of the identified studies controlled for potential differences in expectations or stated any reflections on matching for possible side effects of the interventions, and only one study measured the patients’ perceived interest value of the interventions [45]. Below is an in-depth summary and discussion of the current state of active control group designs in trials of CBCR after ABI. The methodological limitations of each study are also summarized in table 2.

Demographics and individual related-variables

All 11 reviewed studies included reports of whether participants in the EC and ACC had been matched on demographic and individual-related variables, the only exception being a research protocol describing a study not yet published [42].

Intervention intensity

All completed studies reported intervention intensity measured as the amount of time spent completing tasks in both the EC and the ACC. Six of the studies reported no significant difference in average time spent in each condition [35-41, 45], whereas two studies did report significant differences between groups [43, 44]. Interestingly, of the two studies which did report a significant difference, neither mentioned this fact as a potential limitation of the study. However, Robertson et al. [43] argued that the EC spending significantly more time training than the ACC only strengthened their conclusion that training had no effect on rate of recovery. Differences in intervention intensity generally lowers validity of results.

Expectations, motivation and interest value of the intervention

None of the reviewed studies included a measure of

Table 2: Summary of methodological limitations of studies.

	Gray et al. (1992)	Katz et al. (1997)	Kerner et al. (1985)	Niemann et al. (1980)	Palmer et al. (2015)	Robertson et al. (1990)	Van de Ven et al. (2015; 2017A; 2017B)	Wentink et al. (2016)	Zuchella et al. (2014)
Demographics and individual-related variables	VAF	VAF	VAF	VAF	VAF	VAF	VAF	VAF	VAF
Intensity of the intervention	VAF	VAF	VAF	VAF	VAF	VAF	VAF	VAF	VAF
Expectations of intervention effects	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF
Interest value of the intervention and patient motivation	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VAF
Intervention-setting	VNAF	VNAF	VAF	VNAF	VNAF	VNAF	VAF	VNAF	VNAF
Continuous adjustment of task difficulty	VOI	VNAF	VNAF	VNAF	VNAF	VOI	VOI	VNAF	VNAF
Side-effects of intervention	VAF	VAF	VAF	VAF	VNAF	VAF	VAF	VNAF	VNAF
Variation in training-material	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF	VNAF
Type of medium used for the intervention	VAF	VAF	VAF	VAF	VNAF	VAF	VAF	VAF	VNAF
Cognitive load on targeted function	VOI	VOI	VOI	VOI	VOI	VOI	VOI	VOI	VOI

VAF= Variable accounted for: The study accounted for this experimental variable, as it is equal between groups or significant differences are reported and considered
VNAF= Variable not accounted for: The study did not account for his experimental variable, as it is not equal between groups, or the study stated nothing about this variable
VOI = Variable of Interest: This variable is intentionally different between groups, as it is the variable of scientific interest

participant’s expectation for improvement or motivation to complete the intervention. Only one study [45] included a measure of the perceived interest value of the interventions. This highlights an important issue in psychological research: The need to consider all the variables that make an active control condition effective for comparison and how to design it accordingly. Unfortunately, the predominant approach seems to be that since non-pharmacological research can rarely blind participants to the intervention or isolate the active component of a given treatment to the same degree as a pharmacological intervention, simply including any kind of active control condition provides a basis for comparison. However, although it is undoubtedly true that designing active control conditions for psychological research poses a greater challenge than is often the case in pharmacological interventions, it is nonetheless possible to improve current practice. One step will be for researchers to adopt the norm of always including assessments of patients’ expectations of intervention-effects, motivation and perceived interest value of the interventions between groups in studies employing an active control group.

Setting

Five trials included information regarding the setting in which the intervention took place [35-38, 40, 42, 44]. Of the five, three made use of home training [36-38, 42, 44], and two

had participants complete training at an institution [35, 40]. All five studies had matched the EC and ACC in terms of setting. The fact that the remaining four trials did not include any information related to the training environment for the two groups, highlights the need for future research to include clear and explicit descriptions of the settings in which training takes place. The lack of such descriptions casts doubt on whether the comparison was fully justified, and additionally prevents other researchers from recreating the study design and replicating results.

Continuous adjustment of task difficulty

Of the nine trials, five reported whether the interventions made use of continuous adjustment of task difficulty in one or both groups [36-39, 43, 44, 45]. Two of these reported that the EC used an adjustable CBCR-intervention, while the ACC used an intervention which in no way resembled that of the EC (psychoeducation and conversations with a therapist; [44, 45]). Therefore, for these two studies this variable is listed as ‘not accounted for’ in table 2. In three studies continuous adjustment of task difficulty was one of the variables of scientific interest [36-39, 43]. Accordingly, the EC used an adjustable intervention while the active control condition used an intervention which was either not adjustable at all or adjustable to a lesser degree. The remaining four studies did not clearly state whether the intervention of the ACC was

adjustable or not. This limits the possible interpretations of study results since it leaves doubt as to whether between-group differences in outcome measures are due to differences in continuous adjustment. Future trials should aim to report this variable for both conditions.

Matching side effects or byproducts of the intervention

None of the reviewed trials included reflections on whether tasks in the ACC were designed to mimic potential side effects of the intervention. This is potentially problematic given that any difference in the two conditions not associated with the active variable under investigation could act as a confounder. Although not explicitly reported in any of the trials, most studies implemented an ACC which would be expected to mimic side-effects similar to the EC, as it employed the same intervention medium with equal intensity. However, for three of the included trials the ACC cannot be expected to cause side-effects comparable to the EC - either because the ACC intervention was not computerized [42] and/or because the ACC intervention was not a form of cognitive rehabilitation [44, 45]. A failure to match side-effects of the interventions to a realistically possible degree confounds interpretations of study-results and should be avoided.

Variability in training material

None of the studies included for review had matched the EC and ACC in terms of variability of the tasks. Five studies failed to report how many tasks were completed in both conditions [39-43], some neglecting to report the precise amount of tasks completed in the ACC, instead describing only a few task examples [39, 40, 43]. The lack of variation in training material is problematic given that variation in training material is known to be one of the key ways to promote both near- and far-transfer training effects [23, 30]. It follows that a failure to match groups in terms of training variation may seriously skew results in the direction of improvement in the group receiving more variation - which, based on the papers reviewed here, is usually the EC.

Future research should aim to report variation in training material for both the EC and ACC, preferably attempting to match groups on this variable.

Cognitive load on targeted function

This was the variable of scientific interest in all nine studies (along with continuous adjustment of task difficulty in three studies, see table 2). Three overall active control group design strategies were identified regarding the load on the targeted cognitive functions. These are described below:

- Specific cognitive training versus general cognitive stimulation: Four studies compared a cognition-specific, adjustable CBCR intervention with high load on the targeted cognitive functions with non-adjustable general cognitive stimulation [39, 40, 42, 43].

- Near-transfer cognitive training versus far-transfer cognitive training: Three studies compared an adjustable near-transfer CBCR intervention which presumably had a high load on the targeted cognitive functions with a less adjustable far-transfer CBCR intervention with presumable low load on the targeted cognitive functions, but with high load on another

cognitive domain [35-38, 41].

- Specific cognitive training versus unrelated intervention: Two studies compared a specific CBCR intervention with an unrelated active control intervention, such as psychoeducation or conversations with a psychologist [44, 45].

The third design-strategy is generally inadvisable, because this design introduces many possibly confounding variables. Whether design number one or two is preferable depends on the nature of the specific research question: Whether the trial aims to compare the difference between specific versus general stimulation (design 1) or aims to compare the difference between near and far-transfer training (design 2).

Intervention medium

The type of intervention medium employed was reported in all included studies. In seven of the nine studies both the EC and ACC used computer software. As for the two studies which did not employ the same type of intervention-medium in both groups, participants in the ACC were instead made to complete puzzle-books [42] or engage in conversation with a therapist [45]. As outlined in the first section of this article, converting the same training paradigm from one medium to another can produce remarkable differences in effects of training. When researchers then add to this confounding variable by designing control conditions which do not resemble the experimental intervention, they risk to seriously obfuscate results. Thus, unless the impact of the intervention medium is the topic of research, the EC and ACC should use the same intervention-medium.

Limitations of this Review

Being qualitative in nature, this review is limited in terms of the predefined variables on the basis of which the literature was examined. Although these were informed by previously published research, there may well be other important experimental variables than those identified here. Furthermore, despite our belief that the discussions outlined in this review will generalize to the broader area of cognitive rehabilitation research, this review has focused only on a limited subdomain within this field, and other subdomains warrant other considerations.

Conclusion

When designing trials of CBCR after ABI with active control conditions, it is important to consider and control for several relevant experimental variables. These include: Demographics and individual-related variables, intensity of the intervention, intervention expectations, motivation and interest value of the intervention, intervention-setting, continuous adjustment of task difficulty, side-effects of the intervention, variability in training material, cognitive load on the targeted cognitive function and the type of intervention medium. All experimental variables except the variable(s) of scientific interest should be held equal between groups to a realistically possible degree.

A total of 11 papers based on nine studies were included in

this review. No studies accounted for all identified experimental variables. As such, there are currently several methodological shortcomings in the design of trials using active control conditions within in the field of CBCR after ABI. Although this methodological review only explored a subfield within cognitive rehabilitation research, the conclusions drawn here are believed to generalize to the overall research field of cognitive rehabilitation. Finally, it is the hope of the authors that the relevant experimental variables outlined here may serve as a tool in the design-phase of future trials including active control conditions within cognitive rehabilitation research.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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