Rehabilitation for post-stroke cognitive impairment

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Abstract:

Background: Although cognitive impairments are common following stroke, there is considerable uncertainty about the types of interventions that can reduce activity restrictions and improve quality of life. Indeed, a recent project to identify priorities for research into life after stroke determined that the top priority for patients, carers and health professionals was how to improve cognitive impairments.

Objective: To provide an overview of the evidence for the effectiveness of cognitive rehabilitation for patients with stroke and to determine the main gaps in the current evidence base.

Methods: Evidence was synthesised for the six Cochrane reviews relating to rehabilitation for post-stroke cognitive impairment and any subsequently published randomised controlled trials to February 2012.

Results: Data arising from 44 trials involving over 1500 patients was identified. Though there was support for the effectiveness of cognitive rehabilitation for some cognitive impairments, significant gaps were found in the current evidence base. All of the Cochrane reviews identified major limitations within the evidence they identified.

Conclusions: There is currently insufficient research evidence, or evidence of insufficient quality, to support clear recommendations for clinical practice. Recommendations are made as to the research required to strengthen the evidence base, and so facilitate the delivery of effective interventions to individuals with cognitive impairment after stroke.

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Introduction

After stroke most patients experience some disturbance of cognitive functioning, [1, 2] and many have enduring difficulties in specific cognitive domains such as attention and concentration; [3] memory; [4] spatial awareness; [5] perception; [6] praxis; [7] and executive functioning. [8] Although it is possible to have a deficit in one cognitive domain only, usually stroke survivors experience deficits across several domains. [9, 10] Cognitive impairment has a significant impact on activities of daily living (ADL) [11] and self-rated quality of life [12] and it is among the most difficult losses to manage, with high levels of unmet need. [13]

Treatments aim either to restore lost skills or to teach compensatory techniques. However, the evidence base is weak. [14-16] Recently, establishing the best treatment approach for patients with cognitive losses after stroke was identified as a research priority area. [17] In this project: (1) 548 treatment uncertainties were collected; (2) after checking research evidence these were reduced to 226 unique unanswered research questions; (3) 97 people participated in the interim prioritisation process, leading to the identification of 24 shared top priorities; (4) at a final consensus meeting, a representative group of stroke survivors, carers and health professionals decided their research priorities. During the final consensus meeting it was agreed to place the question relating to cognition first in the priority list. [17]

This paper should be of interest to clinicians responsible for stroke patients with any cognitive deficit, and will also guide stroke researchers planning future rehabilitation studies for patients with cognitive deficits. The need for such guidance is clear: much previous research has been either small scale or of poor methodological quality and

the same types of methodological limitation have recurred over the years. In order to improve the robustness of cognitive rehabilitation research for stroke, the remaining sections of the current paper (a) outline what is already known about the effectiveness of cognitive rehabilitation treatment approaches from the findings of published systematic review evidence; and (b) make recommendations as to the types of research studies that are required to strengthen the available evidence.

Method

This review is based on Cochrane systematic reviews and randomised controlled trials (RCTs) published since their last search. There are currently Cochrane reviews which synthesise evidence relating to treatments for stroke patients with: (a) attention deficits; (b) memory deficits; (c) spatial neglect; (d) perceptual disorders; (e) motor apraxia; and (f) executive dysfunction. The reviews relating to perceptual disorders and executive dysfunction included studies of mixed aetiology groups (usually stroke and other acquired brain injury), whilst the other reviews only included studies including participants with stroke. For this synthesis, we removed studies that recruited participants with brain damage other than stroke, unless a subgroup of those with stroke could be identified for which results were reported separately, or 75% or more participants in the sample were individuals with stroke.

As the six Cochrane reviews had different publication dates, if a review had been published more than 12 months previously, more recently published RCTs for that cognitive domain were identified from the results of comprehensive literature searches made available to us by the Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians (RCP) London. These systematic searches (of the

computerised databases Medline, AMED, CINAHL, PsycINFO and Embase using keywords for stroke (e.g. cerebrovascular accident) and a full list of terms for the cognitive domains (a) to (f) above) were undertaken for the 2012 edition of the UK *National Clinical Guideline for Stroke*. [16]

We systematically synthesised the characteristics of studies included in the reviews, and summarised the results of meta-analyses, presenting an overview of current knowledge and understanding, and enhancing access to the detailed evidence which is provided within these published reviews. For each review, and supplemented by the additional RCTs, we explored the recommendations for research considering: (i) evidence relating to the effectiveness of cognitive rehabilitation, and (ii) the key methodological components recommended for future studies in order to address the gaps and uncertainties.

Results

Attention deficits

The review on this topic [18] identified six RCTs, [19-24] which had recruited a total of 223 participants. The RCTs had small sample sizes (range 18 to 78), with a mean age of under 65 in all but one trial. Inclusion criteria were variable. Treatment duration ranged from 3 to 11 weeks, and was almost all computer-based with the aim of restoring underlying attentional functioning. The control groups in all trials received treatment as usual, with unblinded outcomes on psychometric measures. Few studies assessed functional ability or long-term outcomes (see Table 1 – web only).

Meta-analysis found improvement in divided attention immediately following treatment (Standard Mean Difference (SMD) 0.67, 95% CI 0.35 to 0.98, p <0.0001), but no impact on other attentional domains (e.g. alertness, selective attention, sustained attention; all p> 0.05). There was no impact on psychometric test scores in any attentional domain at long-term follow-up (defined as three months post intervention). Nor was there was evidence that interventions for attention deficits improved functional abilities, mood or quality of life either immediately, or late after treatment. No additional literature searches were undertaken because the Cochrane review was recent.

Memory deficits

The Cochrane review [25] identified two trials [26, 27] both of which provided group interventions to a combined total of 18 participants (see Table 1). Treatment was provided over 4 weeks [26] and 10 weeks, [27] and pragmatic control arms were employed in both investigations. Outcome assessments were unblinded. Although neither study included a functional or quality of life measure, both employed subjective memory questionnaires alongside objective memory test data, and one study reported both short- and longer-term (3 months post-treatment) outcomes [27] (see Table 1).

Neither investigation reported improvement on memory tests, or on subjective and objective-rated measures of memory. The RCP searches [16] identified one additional study [28] that found memory improvement on a range of person-centred goals for individuals using an electronic paging reminder system, and replication of this study is required.

Spatial neglect

The review of the rehabilitation of neglect [29] identified 23 trials comprising a total of 628 participants. Sample sizes were mostly small. Twelve were compensatory studies; [30-41] 10 restorative [38, 42-50] and 2 studies combined both approaches [51, 52] (see Table 1). Although the interventions were usually well described, and the majority included ADL outcomes, methodological quality of the studies was generally poor. Only 6 studies [34, 39, 44, 46, 49, 50] included a follow-up assessment of ADL to determine the long-term impact of intervention, and other meaningful outcomes (e.g. discharge destination, falls, quality of life) were rarely reported.

Meta-analyses demonstrated no *persisting* impact of cognitive rehabilitation on functional disability (SMD 0.31, 95% CI -0.10 to 0.72, $p>0.05$), standardised neglect assessments (SMD 0.28, 95% CI -0.03 to 0.59, $p>0.05$), or for immediate effects on ADL (SMD 0.23, 95% CI -0.02 to 0.48, $p>0.05$). Although treatment resulted in an *immediate* impact on standardised neglect assessments (SMD 0.35, 95% CI 0.09 to 0.62, $p<0.05$), was not the case when only studies with the lowest risk of bias were examined (all $p>0.05$). Also, the impact of intervention when rehabilitation was compared with 'no treatment' versus 'attention control' was found to be significantly different, suggesting that time spent with a therapist may be the active ingredient rather than therapy content per se. No additional searches were undertaken.

Perceptual disorders

The Cochrane review [53] identified 6 RCTs [35, 54-58] with 338 participants in total. Two studies were excluded from the current paper, because > 90% of the sample had suffered a TBI, [58] and because separate stroke data were unavailable. [56] This left 275 participants from 4 trials, on which this evidence is based. Samples ranged from 20-97 participants, and covered a good age range (26 to 86 years). All studies provided sensory stimulation (e.g. shape recognition tasks), and this was combined with strategy training in one study [54] and functional training in another. [35] Unfortunately, the interventions were described in too little detail to allow replication or implementation into practice. Only one study [54] employed adequate allocation concealment methods, and no study assessed long-term outcome.

No evidence was found for the benefits of treatment on any outcome measure ($p>0.05$ for perceptual intervention versus control; and $p>0.05$ for functional training versus sensory stimulation). No additional studies were identified in a more recent literature search. [16]

Motor apraxia

The Cochrane review [59] identified 3 trials incorporating 132 participants. [35, 60, 61] The trials comprised strategy training; [61] transfer of training; [35] and gesture training [60] (see Table 1). Treatment was delivered over 6 to 19 weeks. Two studies [35, 61] measured outcome at the level of function (both with blinded outcome assessment), but none reported on quality of life, patients' or carers' perception of outcome, or mood. Only the largest study [61] assessed the persistence of treatment with five month follow-up.

The review found ADL improvement immediately after treatment (Mean Difference (MD) 1.28, 95% CI 0.19 to 2.38, p= 0.02) but not six months post-treatment (MD 0.17, 95% CI -1.41 to 1.75, p= 0.83). No additional studies were identified in a more recent literature search. [16]

Executive dysfunction

From the Cochrane review, [62] only five studies provided data on individuals with stroke (211 participants). Four were interventions designed to restore components of executive functioning, [22, 63-65] and one trial provided a video feedback compensatory treatment [66] (see Table 1). The overall reporting of methods was poor: only one study reported both allocation concealment and blinding of outcome assessment, [66] and a large number of executive outcomes were used across the studies (e.g. working memory, concept formation, inhibition, mental flexibility). Only two trials measured ADL [63, 66] and none considered patient quality of life. No study measured longer-term outcomes.

Meta-analysis found no statistically significant effect of cognitive rehabilitation on primary or secondary outcomes. No additional searches were undertaken because the Cochrane review was recent.

Discussion

Despite research involving over 1500 patients in 44 randomised studies, there is very little strong evidence for the effectiveness of rehabilitation for cognitive deficits found after stroke, and very few direct clinical recommendations can be made. There are, as we will outline, recommendations that can be made for future research.

Current Cochrane review evidence suggests that cognitive rehabilitation for attention deficits, spatial neglect and motor apraxia all improve standardised assessments of impairment immediately following treatment, but that improvements may not persist and (with the possible exception of motor apraxia) do not improve everyday function. There is currently no evidence that memory deficits, perceptual disorders or executive dysfunction respond to the cognitive rehabilitation interventions included in these reviews. Can it therefore be concluded that cognitive rehabilitation following stroke is of only limited effectiveness? We do not believe so, because absence of evidence is not the same as evidence of absence. All of the reviews [18, 25, 29, 53, 59, 62] identified major limitations within the evidence they identified, justifying the decision to place cognitive rehabilitation as the top current research priority. [17] Overall, there is a clear need for methodological improvements in three categories: (i) sample considerations; (ii) descriptions of interventions; and (iii) measurement of outcome.

As far as sampling is concerned, trials need to recruit larger numbers of participants to ensure sufficient power to detect any impact of treatment. It is important that sample size calculations are carried out for future RCTs, so that studies are adequately powered. There is also a need for research to include samples of stroke survivors that are representative of the population of people with stroke. One important consideration is participant age. To take an example, the Cochrane memory review comprised a study that included only patients aged under 60 years of age [27] and another that recruited from a centre with patients "who are relatively young" (p. 394). [26] The samples in these two studies were in their 40s and 50s, i.e. younger than the typical stroke survivor. An important question is which patients benefit most from

cognitive rehabilitation. Do older patients have the same potential for improvement as younger patients? This and related questions can only be answered if researchers recruit stroke samples that are not overly restricted on dimensions of interest, and if appropriate measurements of demographic variables are recorded and reported consistently between trials.

Likewise, more consideration should be given to the therapies that are offered, as well as to their delivery. Treatments should have a clearly stated rationale and should be described in sufficient detail to permit replication. Researchers can consult a recent checklist for the description of rehabilitation interventions to help them do this. [67] Cognitive rehabilitation is a therapy-intensive endeavour, particularly if the time to assess cognitive strengths and weaknesses prior to intervention is taken into account. Most previous studies have involved relatively short periods of therapy. Although the impact of treatment intensity for cognitive rehabilitation after stroke is largely unknown, it has been suggested that much rehabilitation is delivered with inadequate 'dose'. [68] The optimum intervention intensity has yet to be established for post-stroke cognitive impairments and is an important area of future research, particularly for service commissioners. Likewise, little is known about the active ingredients of cognitive rehabilitation. Researchers should consider the use of attention control arms to investigate this issue, so that the direct effect of interventions can be determined, separate from the effects that may result from clinicians showing interest in, and spending time with, patients as suggested by the neglect review. [29]

The fundamental aim of rehabilitation is to improve everyday functioning and yet, many existing studies have been limited to assessing outcome at an impairment level,

e.g. on paper-and-pencil tests. We propose that researchers always keep the functional, 'real life' significance of cognitive rehabilitation in mind. It is important to determine the impact of treatment on ADL, mood, quality of life, and discharge destination, and also to obtain patient and caregiver views of treatment. The establishment of a core set of outcome measures would be particularly helpful, because this would enable participant data from different studies to be combined using meta-analysis. Also, outcome measurement should not be limited to the short-term (i.e. immediate post-treatment), but should establish whether individuals maintain any improvements over time. Only long-term follow-up can enable both the providers and recipients of cognitive rehabilitation to understand the true costs and benefits of treatment.

As far as trial design is concerned, we believe that future cognitive rehabilitation research should include both explanatory and pragmatic aspects. [69] Most previous research in this area has been explanatory, designed to determine efficacy under optimal conditions; pragmatic trials evaluate the impact of an intervention in routine practice. Both designs are needed to answer the complicated questions posed by rehabilitation research. The former can help us decide if (and how) an intervention works; the latter can reassure us that an intervention is effective in real life settings, an important consideration in resource-limited clinical services. Researchers are encouraged to consult the pragmatic-explanatory continuum indicator summary (PRECIS) tool, [69] and the Medical Research Council (MRC) guidance for complex interventions [70] to help them inform trial design along the pragmatic-explanatory continuum. In doing so, they might wish to consider the following important issues.

The first is the complex clinical presentations typical of stroke, for cognitive impairments rarely occur in isolation. As an example, stroke survivors with memory impairment [71] and executive dysfunction [72] are at increased risk of depressed mood, which may influence their engagement with rehabilitation, and so negatively impact on outcomes. Future research should aim to study the impact of mood on cognitive rehabilitation outcomes. Of interest to researchers is the finding that improved mood often has a positive impact on cognition. [73, 74] Research could compare treatments that aim to improve cognition with those that aim to enhance mood, and determine whether combined cognition-mood interventions might be optimally effective. Combined interventions would be in keeping with comprehensive-holistic rehabilitation programmes as recommended in the recent RCP Stroke Guideline. [16]

A second issue is that of patient preference. Stroke survivors may have significant preferences for treatments, [75] and these preferences are likely to influence engagement. The importance of patient preference in rehabilitation research has been highlighted before; [76] if patients are allocated randomly to treatments that they may not desire, it will be difficult to distinguish between an inherently ineffective treatment and one that failed because it was targeted to patients who were insufficiently motivated to engage with it. These are important concerns because many stroke survivors experience poor awareness of their deficits, and also motivational difficulties. [77] One approach is to conduct a 'patient preference' trial, in which treatment allocation is influenced, at least partly, by what patients would like to receive.

The third issue for researchers to consider is that of cost-effectiveness. This has rarely been reported in trials of cognitive rehabilitation after stroke, but is crucial to health policy and the commissioning of services. The variability in cost data in rehabilitation studies is often much greater than for the clinical outcomes, [78] and so the required sample size is also much greater. Multi-centre recruitment would be one way in which researchers could ensure that their studies had adequate numbers of participants.

Finally, it is notable that this review of published research has been limited to trials of interventions. As well as the complexities and variation of cognitive rehabilitation interventions, factors relating to service delivery also contribute methodological challenges. [79] The current paper has not included evaluation of aspects that are crucial to the delivery of care, such as the best tools for screening or diagnosing cognitive impairments, or the required skill mix in rehabilitation teams. These important aspects of care provision should also be the focus of primary and systematic secondary research.

Conflict of interest

DG, AB, CC, PK and AP are contributing authors of four of the six Cochrane reviews included in the current paper, and AP is a member of the Cochrane Stroke Group Editorial Group. AB and PK were members of the Intercollegiate Stroke Working Party (ICSWP) of the Royal College of Physicians London, and together with DG and JC were members of a psychology subgroup that reviewed evidence for the ICSWP.

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Clinical Messages

- There is currently insufficient evidence to make more than a few recommendations concerning cognitive rehabilitation after stroke.
- A review of existing research enables specific recommendations to be made for future research design and execution.

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Abstract

Background: Although cognitive impairments are common following stroke, there is considerable uncertainty about the types of interventions that can reduce activity restrictions and improve quality of life. Indeed, a recent project to identify priorities for research into life after stroke determined that the top priority for patients, carers and health professionals was how to improve cognitive impairments.

Objective: To provide an overview of the evidence for the effectiveness of cognitive rehabilitation for patients with stroke and to determine the main gaps in the current evidence base.

Methods: Evidence was synthesised for the six Cochrane reviews relating to rehabilitation for post-stroke cognitive impairment and any subsequently published randomised controlled trials to February 2012.

Results: Data arising from 44 trials involving over 1500 patients was identified. Though there was support for the effectiveness of cognitive rehabilitation for some cognitive impairments, significant gaps were found in the current evidence base. All of the Cochrane reviews identified major limitations within the evidence they identified.

Conclusions: There is currently insufficient research evidence, or evidence of insufficient quality, to support clear recommendations for clinical practice. Recommendations are made as to the research required to strengthen the evidence base, and so facilitate the delivery of effective interventions to individuals with cognitive impairment after stroke.

Table 1. Summary of stroke studies arising from Cochrane reviews and subsequent searches

	Patient characteristics				Treatment characteristics		
Domain	***n***	**Details of stroke**	**Method of deficit identification**	**Major exclusions**	**Experimental treatment**	**Intensity of treatment**	**Primary outcomes (f-up interval)**
Attention							
Sturm 1991	E 13 C 14	E 15w p-s; all LHS C 16.4w p-s; all LHS	All patients had attentional deficits according to authors	None stated	Computerised training using reaction times and pattern recognition	14 sessions over 3w	Scores on psychometric measures of attention (6w post-tmt)
Schottke 1997	E 16 C 13	E 52d p-s; 11RHS/5LHS C 38d p-s; 11RHS/2LHS	Standard score <80 on any of the attentional tests	Aphasia	Computerised reaction training; paper/pencil tasks; scanning training	13 sessions over 3w	Several standardised measures of attention (no f-up)
Rohring 2004	E 24 C 24	25.5mo p-s for E and C pts combined	All patients had attentional deficits according to authors	>70y; other neurological/ psychiatric disorders	Computerised training using Cogpack software	30-45min training 5d per w for 11w	Several standardised measures of attention (no f-up)
Westerberg 2007	E 9 C 9	E 19.3mo p-s; 4RHS/4LHS/1? C 20.8mo p-s; 4RHS/3LHS/2?	Self-reported deficits in attention	IQ<70; motor or perceptual impairment preventing computer use; depression	Computerised training emphasising visuo-spatial and auditory working memory	40min training 5d per w for 5w	Several standardised measures of attention (no f-up)
Barker-Collo 2009	E 38 C 40	E 18d p-s; 15RHS/14LHS/3 other C 19d p-s; 17RHS/25LHS/1 other	Score >1SD below norm on any attentional test	MMSE<20; medically unstable; non-English speaking; dementia	Attention Process Training	60min training 5d per w for 4w	Scores on psychometric measures of attention (6mo post-tmt)
Winkens 2009	E 20 C 17	E 19.3mo p-s C 6.9mo p-s	Referred for cognitive rehabilitation for mental slowness	<18y; severe cognitive, communication, physical or psychological problems	Time Pressure Management	10hrs training (1-2 hrs per w)	Scores on psychometric measures of attention and self-report questionnaire (3mo post-tmt)
Memory							
Doornhein 1998	E 6 C 6	All pts 3-5 mo p-s	Patients had complained of memory problems	Severe aphasia, apraxia or agnosia	Memory strategy training focusing on people's names and routes	2 sessions per w for 4w	Scores on psychometric measures of memory and self-report questionnaire (no f-up)
Kaschel 2002	E 3 C 4	All pts >6mo p-s	Score <= 15 on immediate/delayed story recall test from RBMT	Severe memory problems (standardised profile score <= 12 on RBMT); aphasia; visual problems; apraxia; neurological/ psychiatric disorders	Imagery training	3 sessions per w for 10w	Scores on psychometric measures of memory and self- and carer-report questionnaire (3mo post-tmt)

Fish 2008*	36	3.3y p-s	Functional impairment of memory/planning and previous unsuccessful compensatory treatment	None stated	Paging system	Pagers used for 7w	Proportion of everyday tasks achieved, i.e. prospective memory (7w post-tmt)
Spatial neglect							
Weinberg 1977	E 25 C 32	E 9.9w p-s (though 2 pts had "aberrantly long times since onset") C 10.5w p-s	Performance on cancellation tasks	<4w p-s; previous stroke; bilateral damage; "severe organic mental syndrome"	Visual training (reading, writing and calculation)	20hrs (1h per day for 4w)	A series of paper and pencil tasks (e.g. cancellation, copying, matching faces) (no f-up)
Cottam 1987	E 6 C 6	E 6w p-s C 6.3w p-s All pts had right middle cerebral artery lesions and left hemispatial neglect	Evidence of left hemispatial neglect on at least 3 different psychometric tests	Left-handed; visual acuity <20/100; disorientated in time, place, person; unable to self-propel wheelchair	Visual scanning training	5 half hr sessions per day	Psychometric measures of neglect and a task requiring avoidance of obstacles on a wheelchair course (6w post hospital discharge)
Robertson 1990	E 17 C 13	E 19.2w p-s C 10.8w p-s	Left visual neglect on the BIT	BIT score >70	Computerised scanning and attention training	15.5 hrs (14 sessions of 75min, 2d per w for 7w)	Behavioural subtests from the BIT (6mo post-tmt)
Rossi 1990	E 18 C 21	E 4.4w p-s; 16RHS/2LHS C 4.7w p-s; 13RHS/8LHS	Inability to detect bilateral tachistoscopically presented targets	Visual acuity <20/200; inability to cooperate with assessments	15-diopter plastic press-on prisms worn for all daytime activities	No intensity/dose information beyond for all daytime activities	Psychometric measures of neglect and an ADL measure (4w post baseline with prisms still being used)
Fanthome 1995	E 9 C 9	E 1mo p-s C 0.6mo p-s	Score <130 on the BIT	>= 80 years; history of dementia or psychiatric problems; left-handed; score <= 6 on Abbreviated Mental Test; LHS; >= 130 on BIT	Feedback of eye movements (wearing specially adapted glasses with auditory signal)	4w (2hrs 40min per w)	Eye movement data and scores on the BIT (4w post-tmt)
Kalra 1997	E 24 C 23	6d p-s for E and C pts combined E 16 RHS and C 17 RHS	Visual and sensory confrontation tests; line bisection; observation during activities using structured observations; scores on RPAB	TIA; reversible neurological deficits; hemianopsia or severe dysphasia	Spatio-motor cueing during limb activation	Not given Physio (h): C 22.6 +-8 E 17.1 +-4.9 OT (h): C 16.7 +-2.9 E 17.0+-2.9	ADL measure and RPAB (12w post-tmt)

Wiart 1997	E 11 C 11	E 35d p-s C 30d p-s	Participants were positive for neglect on 3 tests (line bisection, line cancellation, bell cancellation)	Previous stroke; cognitive difficulties incompatible with rehabilitation	Wearing of thoracolumbar vests with attached metal pointer; individuals point to specific audible and luminous biofeedback	1hr per day for 20d followed by traditional rehabilitation	Psychometric measures of neglect and level of autonomy (60d post-tmt)
Edmans 2000	E 24 C 18	E 40d p-s C 33d p-s	Letter cancellation test of the RBAB	Unable to assess on RPAB; insufficient functional use of 1 hand (unable to carry out treatment activities)	Transfer of Training approach (i.e. practice of paper-and-pencil perceptual tasks)	2.5hrs per w for 6w in addition to standard Occupational Therapy	ADL measures and RPAB (no f-up)
Cherney 2002	E 2 C 2	E 16mo p-s; both RHS C 7.5mo p-s; both RHS	Unclear	Left handed; LHS; English not primary language; corrected visual acuity insufficient to read newsprint	Visual scanning training; experimental and control tasks included visual and tactile cues to attend to the left	20 sessions (frequency not reported)	Scores on the BIT and a functional reading task (no f-up)
Robertson 2002	E 19 C 21	E 153d p-s C 152d p-s	Performance on tests of cancellation or line bisection	LHS; major psychiatric problems or organic disorder likely to affect cerebral function; >=52 on star cancellation of BIT; aged >80y; left handed; <7 on Hodkinson Mental Test	Limb activation device worn during perceptual training (perceptual puzzles and reading tasks)	45min per w for 12w	Measures of ADL (6mo f-up)
Rusconi 2002	E 12 C 8	E 6.9w p-s C 8.4w p-s	Unclear	Dementia	Scanning training (involving: reading, line drawing, assembling 3D cubes, matching cards)	5x 1hr sessions per w for 2mo (i.e. 40 sessions)	Psychometric measures of neglect and a measure of ADL (no f-up)
Zeloni 2002	E 4 C 4	E 11.2mo p-s C 4.5mo p-s	A battery of paper-and-pencil tests including cancellation, line bisection and copying of drawings	Wearer of glasses	Wearing plastic goggles (the right side of each lens was blinded)	1w (only removing them to go to sleep)	Psychometric measures of neglect (1w post-tmt)
Fong 2007	E1 20 E2 20 C 20	E1 12d p-s; all RHS E2 12d p-s; all RHS C 12d p-s; all RHS	Scores < 51 on star cancellation subtest of the BIT	Severe aphasia; significantly impaired visual acuity; hemianopia; visual sensory deficit	E1 voluntary trunk rotation E2 voluntary trunk rotation and half field eye-patching	1hr per day, 5d per w for 30d (i.e. 30hrs)	Full BIT and clock drawing test (30d post-tmt)
Nys 2008	E 10 C 6	E 9d p-s; all RHS C 11d p-s; all RHS	Scores below cut-off on >=2 subtests from the BIT	Ocular problems; disturbed consciousness; limited attention span	Prism adaptation (prisms with 10° rightward optical shift)	30min for 4d	Psychometric measures of neglect and a measure of ADL (1mo post-tmt)
Luukkainen-Markkula 2009	E1 6 E2 6	E1 81d p-s; all RHS; one pt with complete	Scores below cut-off on >=2 subtests from	Co-existing diseases causing cognitive decline	E1 Visual scanning training E2 Arm activation training	E1 1hr, 5 x w over 3 w	A wide range of outcomes comprising

		hemianopia E2 96d p-s; all RHS; 3 pts with complete hemianopia	the BIT			E2 20-30hrs over 3w (amount determined by subjective needs of pt)	paper-and-pencil tasks, functional tasks and a measure of ADL (time point of f-up unclear)
Polanowska 2009	E 20 C20	E 44.4d p-s; all RHS C 46.6d p-s; all RHS	Psychometric tests of neglect and behavioural assessment	Previous stroke; if electrical stimulation contraindicated; dementia; neurological or psychiatric disorder; unable to co-operate; > 75y	Electrical somatosensory stimulation of the left hand combined with conventional visual scanning training	20 x 45min sessions x 5d per w for 1mo	Psychometric tests of neglect and a measure of ADL (no f-up)
Schroder 2008	E (OKS) 10 E TENS 10 C 10	E OKS 43.8d p-s; all RHS E TENS 24.6d p-s; all RHS C 36.2d p-s; all RHS	Performance on a range of paper-and-pencil tests (no cut-off details provided)	Left handed; > 90d p-s; mild neglect	E OKS, visual exploration and TENS (TENS: 100 Hz, over left trapezius, applied throughout exploration training) E TENS, visual exploration and OKS (OKS: small randomly spaced squares moving slowly leftward across screen)	20 sessions of 25-40min over 4w	Psychometric tests of neglect (1w post-tmt)
Tsang 2009	E 17 C 17	E 22d p-s C 22 d p-s	Scores <129 on conventional subtests from the BIT	Severe dysphasia; TIA; significant impairment in visual acuity; history of other neurological disease; psychiatric disorder	Right half-field eye patching glasses	5 x1hr per w for 4w	Conventional subtests from the BIT and a measure of ADL (no f-up)
Turton 2010	E 17 C 19	E 45d p-s C 47d p-s	Performance on cancellation and line bisection subtests from the BIT	Neglect prior to current stroke	Prism adaptation	Once per day for 2w	Conventional subtests from the BIT and measures of ADL (8w post-tmt)
Ferreira 2011	E1 5 E2 5	All pts RHS; ischemic strokes (>3mo p-s)	Scores <129 on conventional subtests from the BIT	Locomotion problems or ataxia effecting task completion; dysphasia; PD, dementia or neurodegenerative condition	E1 Visual scanning training E2 Mental practice	E1 E2 10x 1h over 5w	Conventional subtests from the BIT and a measure of ADL (3mo post-tmt)
Mizuno 2011	E 20 C 18	E 67d p-s C 64d p-s	At least one value below cut-off on a subtest from the BIT	Unable to sit in wheelchair; aphasia or cognitive impairment; impaired vision/hearing; significant weakness in right arm; previous brain injury	Prism adaptation (shifting visual field 12° to right)	2 training sessions of 20min per day, 5d per w for 2w (i.e. total of 20 sessions)	Scores on the BIT and a measure of ADL (f-up was to point of hospital discharge)

Welfringer 2011	E 15 C 15	E 3.2mo p-s C 3.4mo p-s	Scores below cut-off on a letter cancellation test (unclear which)	Diagnosis of hemianopia; <20y or >75y; left handed	Visuomotor-imagery therapy	2 sessions of 30min per day over 3w	Psychometric measures of neglect (no f-up)
Kerkhoff 2012 (study 2)	E1 3 E2 3	All RHS	Visual neglect on cancellation task and line bisection task *and* auditory neglect task using headphones	LHS; no pathological rightward shift in ASMP	E1 OKS E2 Visual scanning	20 sessions of 50min, 5 sessions per w	Visual neglect on cancellation, line bisection and reading tasks; auditory neglect on headphone task (2mo post –tmt)
Perception							
Taylor 1971	78 65 entered 47 analysed	55d p-s; all RHS	Scores on a non-standardised measure of perception (PCMF test battery)	70y; previous stroke; other medical, psychiatric or neurological disorder	Sensory stimulation	20d of treatment	Psychometric measures of perception (no f-up)
Hajek 1993	20	1-5mo p-s	Participants not selected on the basis of perceptual impairment	Previous stroke; pre-existing visual impairment; psychological distress	Computerised visuospatial training package	3 sessions of 30min per w for 4 w	Psychometric measures of perception and measure of ADL (note, >40 outcomes in psychometric battery and no explicitly stated primary outcome (no f-up)
Edmans 2000	E 40 C 40	E 38d p-s, 40% RHS C 31d p-s, 48% RHS	Impaired scores on the RPAB	Unable to assess on RPAB; unable to transfer with ≤2 nurses	E ('Transfer of Training', i.e. practise paper-and-pencil perceptual tasks) C ('Functional Approach'; practise ADL tasks)	5 sessions of 30min per w for 6w	Psychometric measures of perception and ADL ratings by both nurses and therapists (no f-up)
Mazer 2003	E 47 C 50	E 91d p-s C 67d p-s	All participants referred for driving evaluation after stroke: not selected on basis of perceptual impairment	Contra-indications to driving; bilateral lesion; severe cognitive, perceptual or motor deficit	Computerised strategy training programme	30-60min sessions, 2-4x per w for 20 sessions	Pass/fail of an on-road driving evaluation (no f-up)
Apraxia							
Edmans 2000	E 3 C 6	Overall 22-76d p-s; all LHS	Psychologist identified apraxia using a standardised	Unable to complete RPAB	E ('Transfer of Training', i.e. practise paper-and-pencil perceptual tasks)	5 sessions of 30min per w for 6w	A measure of ADL and the Kertesz apraxia test (no f-up)

			measure (the Kertesz test)		C ('Functional Approach'; practise ADL tasks)		
Smania 2000	E 6 C 4	E 14.7mo p-s; all LHS C 18mo p-s; all LHS	Apraxia identified using the van Heugten test	History of stroke; history of psychiatric disturbance	Gesture training	35 sessions of 50min	Tests of apraxia, but no ADL assessment (no f-up)
Donkervoort 2001	E 56 C 57	E 60 d p-s C 103 d p-s all LHS	Apraxia identified by a trained researcher using the de Renzi test	Previous history of apraxia, TBI, tumour or psychiatric disturbance	Strategy training	25 sessions over 8w (15 hrs OT)	ADL measures completed by patient and occupational therapist (5mo post-tmt)
Executive functioning							
Carter 1980	E 10 C 8	None stated	Determined by scores on a working memory task	None stated	Cognitive remediation	30-40min sessions, 3x per w for 4w	Digit span test for working memory (no f-up)
Hu 2003	E 44 C 42	Limited details as this study was part translated from Chinese into English	Unclear	Not available from the translation	Cognitive rehabilitation including attention, visual-spatial, memory, orientation and executive function training using card activities, practical objects, self-programmed computer software and transition to ADL training	One session of 45min, 5x per w (total number of sessions unknown)	Executive functioning subcomponent from the NCSE (f-up details unclear from the translation)
Chung 2007	E 4 C 3	E 7d p-s; 3 RHS, 1 LHS C 27d p-s; 2 RHS, 1 LHS	Executive dysfunction determined by scores on BADS and Hayling and Brixton Tests	Previous stroke; receptive aphasia; unable to give informed consent	Video feedback of dressing performance	30min sessions 3x per w for 2w	Scores on psychometric measures of executive functioning and a dressing assessment (no f-up)
Westerberg 2007	E 9 C 9	E 19.3mo p-s C 20.8mo p-s	Self-reported deficits in attention	IQ<70; inability to use computer programme; medication alterations during the programme; depression or substance misuse	Computer working memory training	Daily 40min sessions, 5x per w for 5w	Several standardised measures of attention (no f-up)
Jorge 2010	E 41 C 45	E 32d p-s C 25d p-s	Participants not selected on the basis of executive functioning impairment	Depression; severe comprehension deficits; impaired decision making capacity; strokes resulting from aneurysm, AVM, surgery or MI	Problem-solving training	Not reported	Scores on psychometric measures of executive functioning (no f-up)

Key. F-up= follow up; E= experimental; C= control; LHS= left hemisphere stroke; RHS= right hemisphere stroke; MMSE= Mini Mental State Examination; RBMT= Rivermead Behavioural Memory Test; BIT= Behavioural Inattention Test; TIA= transient ischaemic attack; PCMF= Percept-Concept-Motor Function test; RPAB= Rivermead Perceptual Assessment Battery; OKS= optokinetic stimulation; TENS= transcutaneous electrical nerve

stimulation; PD= Parkinson's Disease; ASMP= auditory subjective median plane; ADL= activities of daily living; TBI= traumatic brain injury; OT= occupational therapy; NCSE= Neurobehavioral Cognitive Status Examination; BADS= Behavioural Assessment of the Dysexecutive Syndrome; AVM= arteriovenous malformation; MI= myocardial infarction ; * study identified by searching after Cochrane review