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HEART & STROKE FOUNDATION
**Canadian Partnership
for Stroke Recovery**

Chapter 12: Cognitive Rehabilitation

Abstract

Vascular cognitive impairment is the current term that reflects the range of cognitive deficits due to the impact of cerebrovascular disease, including stroke. According to the Canadian Study of Health and Aging (2000), it is estimated that 5% of all people over the age of 65 years have evidence of vascular cognitive impairment. The risk for cognitive impairment or decline is augmented by a history of stroke. As many as two-thirds of patients experience cognitive impairment or decline following stroke and approximately one third develop dementia. Risk for developing dementia may be up to 10 times greater among individuals with stroke than for those without. In this review, we examine issues regarding the definition, prevalence, and natural history of post-stroke cognitive impairment as well as its clinical consequences. Treatment interventions are identified, including cognitive rehabilitation strategies for remediation of deficits in attention, memory, executive function, and problem solving; nerve and brain stimulation; exercise programs; music listening; and pharmacotherapy.

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Chapter 12: Cognitive Rehabilitation Interventions Table of contents

Key points

Attentional training may not be helpful for improving cognitive rehabilitation.

The literature is mixed regarding memory training for cognitive rehabilitation.

Mental imagery may be beneficial for improving attention, and activities of daily living.

Mental imagery may not be beneficial for improving learning and memory.

The literature is mixed regarding cognitive-motor interference for cognitive rehabilitation.

Exercise may be beneficial for improving learning and memory, and overall cognitive abilities.

Exercise may not be beneficial for improving attention or executive function.

Higher intensity exercises may not be more beneficial than lower intensity exercises for improving cognition.

The literature is mixed regarding multimodal interventions for improving cognitive rehabilitation.

Music therapy may not be helpful for improving cognitive rehabilitation.

Board games and puzzles may not be helpful for improving global cognition.

Pager prompting systems may be beneficial for improving activities of daily living.

Occupational workplace intervention may be beneficial for improving activities of daily living, but not global cognition.

Trial and error training may not have greater efficacy than errorless training for improving cognitive rehabilitation.

Problem solving therapy may not be beneficial for improving activities of daily living.

The literature is mixed regarding computer-based training for improving attention.

Computer -based training may not be helpful for improving executive function or global cognition.

Virtual reality may not be beneficial for improving cognition.

rTMS may not be beneficial for improving cognitive rehabilitation.

tDCS may not be beneficial for improving cognitive rehabilitation.

Intense lipid lowering may be beneficial for improving attention and executive function.

Antihypertensive medication may not be beneficial for improving cognitive rehabilitation.

Actovegin may be beneficial for improving global cognition.

GABA agonists may not be beneficial for improving cognitive rehabilitation.

Nimodipine may be beneficial for improving learning and memory, and global cognition.

Nimodipine may not be beneficial for improving activities of daily living.

Citicoline may be beneficial for improving executive function, but not learning and memory or global cognition.

Antidepressants may be beneficial for improving learning and memory but may not be beneficial for improving other cognitive outcomes.

Selegiline may be beneficial for improving attention, but not other cognitive outcomes.

Vinpocetine may beneficial for improving global cognition, and activities of daily living.

Rivastigmine may not be beneficial for improving cognitive rehabilitation.

Xueshuan xinmai may be beneficial for improving learning and memory, but not other cognitive outcomes.

Acupuncture may be beneficial for improving global cognition and activities of daily living.

Electroacupuncture may be beneficial for improving attention, and visuospatial perception and orientation, but not other cognitive outcomes.

Modified Sackett Scale

Level of evidence	Study design	Description
Level 1a	Randomized controlled trial (RCT)	More than 1 higher quality RCT (PEDro score ≥6).
Level 1b	RCT	1 higher quality RCT (PEDro score ≥6).
Level 2	RCT	Lower quality RCT (PEDro score <6).
	Prospective controlled trial (PCT)	PCT (not randomized).
	Cohort	Prospective longitudinal study using at least 2 similar groups with one exposed to a particular condition.
Level 3	Case Control	A retrospective study comparing conditions, including historical cohorts.
Level 4	Pre-Post	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects.
	Post-test	A prospective post-test with two or more groups (intervention followed by post-test and no re-test or baseline measurement) using a single group of subjects
	Case Series	A retrospective study usually collecting variables from a chart review.
Level 5	Observational	Study using cross-sectional analysis to interpret relations. Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or "first principles".
	Case Report	Pre-post or case series involving one subject.

New to the 19ᵗʰ edition of the Evidence-based Review of Stroke Rehabilitation

1) PICO conclusion statements

This edition of Chapter 12: Cognitive rehabilitation interventions synthesizes study results from only randomized controlled trials (RCTs), all levels of evidence (LoE) and conclusion statements are now presented in the Population Intervention Comparator Outcome (PICO) format.

For example:

New to these statements is also the use of colours where the levels of evidence are written.

Red statements like above, indicate that the majority of study results when grouped together show no significant differences between intervention and comparator groups.

Green statements indicate that the majority of study results when grouped together show a significant between group difference in favour of the intervention group.

For example:

Yellow statements indicate that the study results when grouped together are mixed or conflicting, some studies show benefit in favour of the intervention group, while others show no difference between groups.

For example:

Population: Stroke survivors

2) Cognitive rehabilitation outcome measures

Outcome measures were classified into the following broad categories:

Attention: These outcome measures assessed an individual's ability to attend as well as identify target stimuli and remain focused on a particular goal.

Executive function: These outcome measures assessed an individual's ability to plan, follow rules and self-monitor.

Learning and Memory: These outcomes measures assessed an individual's ability to explicitly and implicitly learn and recall information.

Global Cognition: These outcome measures assessed an individual's overall cognitive processing capability factoring in multiple domains.

Visuospatial perception and orientation: These outcome measures assessed an individual's ability to correctly process and mentally manipulate visuospatial information.

Amusia: These outcome measures assessed an individual's ability to perceive pitch and recognize music.

Activities of Daily Living: These outcome measures assessed an individual's proficiency at performing everyday activities.

Outcome measures that fit these categories are described in the next few pages.

Outcome measures definitions

Attention

Attentive Matrices Test: Is a measure of selective and sustained attention. The participant attempts to find a target number by scanning a series of patterns of numbers. It has been found to be a valid measure of attention. Many variations of the test exist (Daliento et al. 2005).

Charron Test: Is a measure of visual and attentional processing ability. Subjects are provided with 19 pairs of objects/symbols and 37 pairs of numbers and asked to place a checkmark next to any pairs that are not identical. Their total number of errors are recorded. The test is not standardized and there is a lack of data regarding the test's validity or reliability (Korner-Bitensky et al. 1994).

Colour Trails Test: Is a measure of visual scanning and mental processing speed, designed as a culturally neutral alternative to the trail-making test. It has been shown to have high criterion validity in a population of stroke patients and can reliably distinguish between stroke and Parkinson's disease patients (Messinis et al. 2011).

Continuous Performance Task (CPT): Is a measure of both vigilance and response inhibition requiring subjects to respond to target stimuli (typically by pressing a button) and discriminate the target from distractor stimuli. The test can be conducted with either auditory or visual stimuli. Stimuli are presented at regular intervals (on the order of seconds) and the test lasts 10-15 minutes. Studies have shown the task is a valid measure of symptomatology and has high test-retest reliability in ADHD. (Weafer, Baggott & de Wit, 2013; Edwards et al. 2007).

EEG Signal Detection: is the assessment of the negative or positive potentials that occur during attentional tasks. One such signal is the N140, a somatosensory processing potential activated when a expected stimuli is received. It is believed to be indicative of attentional processing, and its presence and magnitude can predict performance on attentional tasks (Giaquinto & Fraiolo, 2003). Another signal is the P300, which occurs whenever an individual is involved in a decision-making task, particularly discrimination of two stimuli (Picton, 1992). Event related potentials have been able to predict rehabilitation outcomes and future success in stroke populations (Ehlers et al., 2015) and can therefore provide a non-invasive method to quantity neural correlates of cognitive functioning.

Ruff 2 & 7 Selective Attention Test: Is a measure of visual attentional capacity. The test consists of 10 automatic detection trials and 10 controlled search trials for a total of 20 trials. Each trial lasts 15 seconds. In automatic detection trials, target numbers are presented among distractor letters. In controlled search trials, target numbers are presented among distractor numbers. The automatic task is said to involve parallel search processing and selective attention while the controlled task involves serial search processing and sustained attention. Scores are based on errors of omission, commission, total speed and total accuracy. Test-retest reliability is reported as adequate-high and the test exhibits discriminant validity in older, healthy adults (Knight et al., 2010).

Schulte's Tests: Is a measure of attention deficit used for estimating concentration and switching of attention. The test consists of a table with 25 cells arranged in a five-by-five square, where each cell contains a number from 1 to 25 in a random order. A patient is offered to find and show, as quickly as possible, all the numbers in an increasing order. Standard values of full

completion correspond to 40–45 seconds, while persons with attention deficit demonstrate extended time of test performance. The measure has been validated for use in post-stroke populations with cognitive impairments (Prokopenko et al. 2012).

Symbol Digit Substitution Test (Symbol Digit Modalities Test): Is a test that relies on good visuo-motor speed, visual scanning, graphomotor skills and mental processing and shifting. It is a component of the Wechsler Adult Intelligence Scale. Subjects are presented with 9 symbol-digit pairs as a key at the top of the page then given rows consisting of numbers only. Subjects must write the corresponding symbol as quickly as possible within a set time period. Scoring is based on the number of correct symbols paired. The test has been validated extensively as a sensitive measure of cognitive impairment, although the exact cognitive processes used in the test are not clear. The test also has good test-retest reliability (Jaeger, 2019; Applegate et al. 1994).

Talking-While-Walking Test: Is a measure of divided attention and cognitive impairment used to predict falls. Subjects walk 20 feet, turn and walk another 20 feet back at a normal walking pace while reciting the letters of the alphabet (simple task) or alternating letters of the alphabet (complex task). The walking time is measured. The test has high specificity but low/modest sensitivity and is reliable and valid for identifying elderly individuals at risk for falls (Verghese et al. 2002).

Test of Everyday Attention (TEA): Is a measure of attention. The test attempts to asses attention in an ecologically valid manner. It consists of 8 subtests including tests of: sustained attention (elevator counting and lottery), selective attention (map search and telephone search) switching attention (visual elevator), working memory (elevator counting with distraction and auditory elevator with reversal), and divided attention (telephone search while counting). The test has been shown to have good/excellent test-retest reliability in a chronic stroke population (Chen et al. 2013; Robertson et al. 1994).

Trail-making Test A: Is a neuropsychological instrument often used in patients with suspected cognitive impairment to measure the cognitive domains of processing speed, sequencing, mental flexibility, and visual-motor skills. The most widely used version comprises of 2 parts: A and B. In part A, the patient uses a pencil to connect a series of 25 encircled numbers in numerical order. In part B, the patient connects 25 encircled numbers and letters in numerical and alphabetical order, alternating between the numbers and letters. The primary variable of interest is the total time to completion for parts A and B, which is used to obtain a ratio of total time to complete part B/A for all trials. A lower value (closer to 1.0) is indicative of better performance. Part A of the measure is thought to be a test of visual search and motor speed skills, whereas part B is considered also to be a test of higher-level cognitive skills such as mental flexibility. The measure has excellent construct validity and interrater reliability, however may be susceptible to practice effects at shorter intervals (Bowie & Harvey 2006; Piper et al. 2015).

Useful Field of View: Is a measure of functional visual field. It can map an individual's visual field (area that information can be acquired and processed without eye or head movement). The tool consists of a large computer screen and can evaluate visual processing speed, divided attention and selective attention through the completion of 3 computerized tasks. A percentage score is given based on the percentage reduction in useful field of view. The test has been shown to have moderate/high test-retest reliability and good criterion validity in a post-stroke population assessed for driving ability (George & Crotty, 2010; Mazer et al. 2003).

Executive function

Controlled Oral Word Association Test (COWAT): see "Verbal Fluency Test." The COWAT is a form of verbal fluency test in which the subject must rapidly produce a list of word beginning with specified letters. It is a component of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Jorge et al. 2013).

Categorical Word Fluency (Verbal Fluency Test): Is a measure of language ability and executive function. Categorical word fluency is one type of verbal fluency test, in which subjects are asked to list as many words as they can from a given category (e.g. "animals"). Reliability estimates for verbal fluency tests vary widely, and educational experience and age are common confounds for test performance (Brucki & Rocha, 2004; Tombaugh, Kozak & Rees, 1999).

Corsi Block Tapping (Block Span) Test (Backwards): Is a measure of short-term visuospatial and working memory. The examiner taps a series of blocks in succession, one at a time, then the participant is asked to tap the blocks either in the same sequence (forward test) or in reverse (backward test). Backwards tests are thought to involve executive function to a greater degree. The test can also be computerized. Span tests have shown to be valid assessments of working memory and are specific, however their sensitivity and symptom validity are variable (Wentink et al. 2016; Birch, Krikorian & Huha, 1998).

Digit Span Test (Backward): Is a measure of working memory. The participant is presented with a series of digits, one at a time, then is asked to report the digits back to the examiner in the same order (forward test) or backwards (backward test). Backwards tests are thought to involve executive function to a greater degree. The test can involve either visual (visual digit span test) or auditory (auditory digit span test) stimuli presented to the participant. The test can also be computerized. Span tests have shown to be valid assessments of working memory and are specific, however their sensitivity and symptom validity are variable (Wentink et al. 2016; Schroeder et al. 2012).

Flanker Task: Is a measure of inhibitory control and attention. Subjects are asked to determine the direction of a target arrow that is flanked by other arrows that are either congruent (same direction as target) or incongruent (varying directions). The number of completed trials, accuracy and reaction times can be scored. The test has good test-retest reliability but questionable validity since it has fair/poor correlations with other neuropsychological tests evaluating attention and cognitive impairment (eg. Stroop) (Rouder and Haaf, 2019, Sanders et al. 2018).

Frontal Assessment Battery (FAB): Is a measure of frontal lobe function including executive function. It is frequently used to evaluate various forms of dementia as well as other neurodegenerative diseases such as Parkinson's Disease. The battery consists of 6 subtests evaluating: 1) conceptualization; 2) mental flexibility; 3) motor programming; 4) sensitivity to interference; 5) inhibitory control; and 6) environmental autonomy. The test demonstrates good interrater reliability, internal consistency and discriminant validity. Evidence also validates the FAB as a measure of executive dysfunction after stroke affecting the frontal lobe (Kopp et al. 2013; Dubois et al. 2000).

Go/No-Go Task: is a task meant to assess inhibitory control. Each trial will consist of a 'go' cue or 'no-go' cue. In general, 'no-go' cues are relatively infrequent, making it more beneficial to select go from a probabilistic standpoint. Because of this, the individual will be primed for 'go' cues and must actively inhibit a response when a 'no-go' cue is presented (Wessel, 2018).

Stroop Interference Test: Is a measure of selective attention, response inhibition and automatic processing. In the classic test, incongruent stimuli are presented in the form of coloured words (e.g. the word "green" with red-coloured font). Subjects are asked to name the colour of the word, rather than the word itself. The more automatic reading response must be inhibited to produce the correct response. Subjects are also presented with congruent stimuli where the colour of the word matches the name. The mistakes made and reaction times can be measured and compared between incongruent and congruent stimuli. In recent years, many variations of the test have been developed (e.g. numerical, spatial, emotional). The Stroop Test has demonstrated moderate-good test-retest reliability and internal consistency as well as concurrent validity. It has shown good discriminant validity in detecting mild cognitive impairment (Bezdicek et al. 2015; Sullivan, 2009; Gualtieri & Johnson, 2006).

Tower of London Test: is used for the assessment of executive functioning, specifically the ability to plan. It is based on the puzzle game towers of Hanoi, where individuals are asked to get a series of different sized ring moved from one end of the peg board to another. The game has rules however, that create a situation in which planning multiple moves ahead is necessary for timely completion. This measure has shown good reliability and validity in stroke populations(Köstering et al., 2015; Morris et al. 1993).

Trail-making Test B: Is a neuropsychological instrument often used in patients with suspected cognitive impairment to measure the cognitive domains of processing speed, sequencing, mental flexibility, and visual-motor skills. The most widely used version comprises of 2 parts: A and B. In part B, the patient connects 25 encircled numbers and letters in numerical and alphabetical order, alternating between the numbers and letters. The primary variable of interest is the total time to completion for parts A and B, which is used to obtain a ratio of total time to complete part B/A for all trials. A lower value (closer to 1.0) is indicative of better performance. Part A of the measure is thought to be a test of visual search and motor speed skills, whereas part B is considered also to be a test of higher-level cognitive skills such as mental flexibility. The measure has excellent construct validity and interrater reliability, however may be susceptible to practice effects at shorter intervals (Bowie & Harvey 2006; Piper et al. 2015).

Verbal Fluency Test: Is a measure of impairment of verbal production, semantic memory, language, and general cognitive decline in the elderly. Subjects are asked to name as many words as possible belonging to a category (ex: name as many animals as possible in 1 minute). This is *semantic* fluency. Subjects can also be asked to name as many words as possible beginning with certain letters or sounds. This is *phonological fluency*. Verbal fluency is sensitive to early decline in the context of dementia, and as particularly sensitive to damage in the left lateral frontal lobe as it may be affected in stroke. The test has high test-retest and interrater reliability and is generally accepted as a valid measure of cognitive decline in dementia (Fillenbaum et al. 2008; Fogari et al. 2004; Harrison et al. 2000).

Wisconsin card sorting task: Is a measure of prefrontal function, specifically measuring rule learning and resistance to perseveration. The test requires participants to sort 64 cards based on color, shape, or number of items, without having knowledge of the "sorting rules".

Once they make several correct responses and figure out the rule, the rule changes and they must learn a new sorting rule. The test is not timed and sorting continues until all cards are sorted or a maximum of six correct sorting criteria have been reached (Nyhus & Barcelo 2009; Quaney et al. 2009).

Learning and Memory

10-word recall test (RBANS): is a subtest test on the repeatable battery assessment of neuropsychological status (RBANS). 10 common, semantically unrelated words are given to the participant to recall either immediately and/or after a delay period. This can provide information on both working memory, and delayed memory recall (Garcia et al. 2008).

California Verbal Learning Test (CVLT): Is a measure of episodic verbal learning and memory used to assess of a wide variety of conditions. It assesses encoding, recall and recognition as well as immediate, short-term and long-term memory. The CVLT has high construct validity and test-retest reliability (Woods et al. 2006).

Claeson-Dahl Test: Is a measure of learning and declarative memory. A fixed sequence of 10 words is presented to the subject repeatedly until they have learned the sequence or until 10 presentations, whichever comes first. 30-minutes later, the subject is asked to recall as many words as possible. The test has moderate construct and criterion validity and has moderate-high test-retest reliability (Westerberg et al. 2007).

Corsi Block Tapping (Block Span) Test (Forward): Is a measure of short-term visuospatial and working memory. The examiner taps a series of blocks in succession, one at a time, then the participant is asked to tap the blocks either in the same sequence (forward test) or in reverse (backward test). Backwards tests are thought to involve executive function to a greater degree. The test can also be computerized. Span tests have shown to be valid assessments of working memory and are specific, however their sensitivity and symptom validity are variable (Wentink et al. 2016; Birch, Krikorian & Huha, 1998).

Delayed Recognition Span Test (DRST): Is a measure of delayed recognition memory, memory span, and learning, and can be administered in either a verbal or spatial format. Subjects are presented with a series of stimuli of increasing number and are asked to identify the novel stimuli after a 15-second or 2-minute delay. A maximum of 14 stimuli are used. Scoring may include the total number correct before the first error, total number correct, total correct on assessment of incidental memory at 15 seconds and 2 minutes, and total number correct after a 2-minute delay. Although the DRST is a widely used test, there is a lack of data detailing its validity and reliability (Krengel et al. 1996; Applegate et al. 1994).

Digit Span Test (Forward): Is a measure of working memory. The participant is presented with a series of digits, one at a time, then is asked to report the digits back to the examiner. The participant is then asked to report the digits back either in the same order (forward test) or backwards (backward test). Backwards tests are thought to involve executive function to a greater degree. The test can involve either visual (visual digit span test) or auditory (auditory digit span test) stimuli presented to the participant. The test can also be computerized. Span tests have shown to be valid assessments of working memory and are specific, however their sensitivity and symptom validity are variable (Wentink et al. 2016; Schroeder et al. 2012).

Fuld Object-Memory Evaluation (FOME): Is a measure of memory impairment, typically employed in the geriatric population. The test uses multiple sensory modalities for encoding of information. It may be useful in the early detection of dementia and can also distinguish dementia from mild cognitive impairment. The test has good test-retest reliability, and

convergent and discriminant validity (Ho et al. 2019; Wall et al. 1998).

Memory Interference Tasks: are tasks that asses an individual's working memory, specifically a difficult delayed recall. In an interference task, and individual is generally asked to memorize something, and then an unrelated task is given to the participant before they are asked to recall what they were originally supposed to remember. This secondary task can interfere with the encoding processes for the original stimuli (Brown, 1997).

Oxford Recurring Faces Test: Is a measure of memory for faces. Photos of 6 target faces are presented to the subject, then they are asked to identify the target faces among a set of 60 other photographed faces (Doornhein & De Haan, 1998).

Paced auditory serial addition test (PASAT): Is a measure of processing speed and working memory. Subjects are verbally given 61 consecutive single-digit numbers (from 1 to 9) and are asked to sum the most recent 2 numbers they heard. The test has shown to exhibit face, convergent and divergent validity as well as strong test-retest reliability (Nikravesh et al. 2017).

Paired Associates Test: Is a measure of memory. The test can be conducted in a visual or verbal format. In either case, pairs of unrelated stimuli (most often stimuli are words) are presented to the subject repeatedly. After a delay, the subject is asked to identify the pairs either as cued recall (one half of the pair is given and subject must recall the other half), or as recognition (both stimuli are given and subject indicates whether pairs are correct or incorrect). The test's reliability has been reported as poor to acceptable (Lowndes et al. 2008; Elwood, 1991).

Rey Auditory Verbal Learning Test: Is a measure of verbal memory that consists of learning a list of 15 unrelated words, and recalling them immediately, 20 minutes later, and recognizing them out of a list of 50 words. The test measures various aspects of learning and memory, including learning rate, immediate memory, intermediate memory, delayed recall, recognition, and proactive and retroactive interference. The assessment of multiple memory components enhances the test's sensitivity. Research regarding the reliability and validity of multiple versions of this test has been conducted and compiled into metanorms for use (Paran et al. 2009; Denhart 2018).

Rivermead Behavioural Memory Test: Is a test used to evaluate memory abilities when performing everyday tasks. The test consists of 11 subtests that assess verbal and visual recognition and recall, learning and recall of instructions, and recall of a spatial root. Subtests include remembering a name, belonging, appointment, pictures, story (immediate and delayed), faces, route (immediate and delayed), message, orientation, and date. All subtests use simple, everyday items. The test has been validated in a stroke population (Man et al. 2009).

Serial Reaction Time Task: Is a measure of implicit learning. Participants press keys mimicking a 12-element sequence of coloured circles as they appear on a screen. Sequences either of random stimuli or repeated stimuli are given. Faster response times to the repeated stimuli imply that the subject has learned the sequence, either consciously or unconsciously (Quaney et al. 2009).

Stroke Impact Scale (Memory Subsection): Is a patient-reported measure of multi-dimensional stroke outcomes. The measure consists of 59 functional tasks (e.g. dynamometer, reach and grab, walking, reading out loud, rating emotional regulation, word recall, number of tasks completed, and shoe tying). These tasks are then divided into 8 distinct subscales which include: strength, hand function, mobility, communication, emotion, memory, participation and activities of daily living (ADL). Each task is measured on a 5-point scale (1=an inability to complete the task, 5=not difficult at all). The measure has been shown to have good reliability and validity (Mulder et al. 2016; Richardson et al. 2016).

Stylus Maze Task: Is a measure of memory. Subjects must learn 3 paths of increasing complexity through a grid. After being exposed to the path, subjects can correct errors (feedback given by a bell or click) through trial-and-error learning (Doornhein & De Haan, 1998; Canavan, 1983).

Wechsler Memory Scale (WMS): Is a measure designed to provide a rapid, simple and practical memory examination. The original scale was developed in 1945 by Wechsler, however there have been many revisions since, including WMS-R, WMS-III, and WMS-IV. The current edition, WMS-IV, consists of 7 subtests: spatial addition, symbol span, design memory, general cognitive screener, logical memory (I & II), verbal paired associates (I & II), and visual reproduction (I & II). A subject's performance is reflected in 5 "Index" scores: auditory memory, visual memory, visual working memory, immediate memory, and delayed memory. The logical memory subtest of the WMS is the most frequently used subtest, and has an immediate (I) and delayed (II) condition. The test consists of two stories/paragraphs that are orally presented to the subject at a conversational pace. The subject is then asked to recall as much of the stories as possible, immediately (LM I), and again after 25-35 minutes (LM II). All relevant utterances and thematic units are then scored. The WMS has demonstrated high internal consistency and reliability overall, and within the logical memory subtest, with each newer version showing stronger psychometric properties (Morris et al. 2014; Gerhart 2005).

Word List Recall/Delayed Recall Test: Is a measure of memory impairment most frequently used in dementia. Subjects are presented with a list of 10 words and asked to recall the list 10 minutes later. The score given is the number of correctly recalled words (maximum score of 10). It is particularly sensitive to early decline in dementia. The test has high test-retest and interrater reliability and is generally accepted as a valid measure of memory impairment in dementia (Fillenbaum et al. 2008; Fogari et al. 2004).

Word List Memory Test: Is a measure of the ability to remember newly learned information. This test usually precedes the word list recall/delayed recall test allowing the subject to learn the words. The same 10 words used in the recall test are presented at a rate of 1 every 2 seconds. They are repeated 3 times, in a different order each time. After these 3 acquisition trials, the subject is asked to repeat as many of the 10 words as possible. The score given is the number of correctly recalled words (maximum score of 10). The test has high test-retest and interrater reliability and is generally accepted as a valid measure of memory impairment in dementia (Fillenbaum et al. 2008; Fogari et al. 2004).

Word List Recognition Test: Is a measure of delayed recognition memory. The test is usually given in addition to the word list memory test and word list recall test. After both tests have been completed, the subject is presented with the same 10 words they had previously been exposed to in addition to 10 distractor words. The score given is the number of correctly recognized words (maximum score of 10). The test has high test-retest and interrater reliability

and is generally accepted as a valid measure of memory impairment in dementia (Fillenbaum et al. 2008; Fogari et al. 2004).

Visuospatial Perception and Orientation

Benton's Temporal Orientation: Is a brief measure of a patient's orientation in time. The test is scored based on the degree of error (higher number=more errors). A maximum score is 113, with 10 points for each year, 5 points for a month, 1 for the date and day of the week , and 1 for each 30-minute deviation in time of day. It is frequently used as one component of the "7-minute screen." When used as a component of this tool, it has very high specificity and sensitivity for detecting cognitive decline (Meulen et al. 2004).

Benton Visual Retention Test: Is a measure of visual perception and memory. In the test, a series of 10 geometric designs are presented for 10 seconds then withdrawn. Subjects are then asked to recreate the design. The test is scored according to the number of designs correctly drawn as well as the total number of errors. Errors can be classified into 6 categories: 1) omissions; 2) distortions; 3) perseverations; 4) rotations; 5) misplacements; and 6) size errors. The test has good discriminate validity as it can accurately differentiate normal aging from Alzheimer's Disease, as well as stroke patients and healthy controls. In a Greek stroke population, test-retest reliability ranged from low to moderate (Messinis, 2009).

Money Road Map Test: Is a measure of right/left orientation with and without mental rotation in space. Subjects must trace a dotted line through a city map and indicate the left/right direction taken at each turn.(Vingerhoets, Lannoo & Bauwens, 1996).

Motor-Free Visual Perception Test (MVPT): Is a measure of visual- perceptual ability independent of motor ability. Spatial relationships, visual discrimination, figure-ground, visual closure and visual memory are assessed. A total raw score is obtained based on the number of correct responses and standard score, percentile rank and age-equivalent score are generated. In the current version (MVPT-4), the test contains 45 items. The MVPT exhibits acceptable construct, content and criterion validity as well as good test-retest reliability and internal consistency (Brown & Peres, 2018).

Rey-Osterrieth Complex Figure Test: Is a measure of visuo-spatial abilities and visual memory. The test requires the subject to copy a complex geometrical figure and, after an interval, reproduce the figure from memory without forewarning. The most used method of scoring the test is the Osterrieth method, a scoring system that provides a 36-point summary score based to the presence and accuracy of 18 units of the figure. The test has been shown to have excellent interrater reliability and good discriminant validity in differentiating healthy controls from patients with Parkinson's disease, OCD, ADHD, schizophrenia, alcohol abuse, and traumatic brain injury (Salvadori et al. 2018).

Toulouse-Pieron Test: Is a measure of visuospatial search and recognition. The test consists of a large amount of shapes on a page, with slightly differing orientations. Asmall reference group of shapes (2) is shown to the participant, and within the much larger group of similar shapes they must pick out where the reference group is located (Van der Merwe, 2009).

Global Cognition

Abbreviated Mental Test: Is a measure of cognitive impairment in the elderly. It is most frequently used to screen for dementia. The questionnaire consists of 10 questions with each correct answer given 1 point. A score ≤6 suggests probable dementia or delirium. Many modifications exist specific to different languages and cultures. The test and its modifications have been found to be reliable, and scores highly correlated with that of the Mini Mental State Exam (Piotrowicz et al. 2018).

Clock Drawing Test: Is a very brief screening tool used to detect cognitive impairment. It can also detect neglect and executive dysfunction. Participants are asked to draw a clock along with numbers and hands denoting a specified time. There are multiple different rating systems, with most classifying the number and type of errors made. The test is valid and reliable as a screening tool, with a high sensitivity and specificity (Duro et al, 2018; Sheehan, 2012).

Addenbrooke's Cognitive Examination (ACE): Is a measure of cognitive impairment originally developed to diagnose dementia. It has a total score of 100 and assesses five cognitive domains: attention scored from (0 to 18), memory (scored from 0 to 26), language (scored from 0 to 26), verbal fluency (scored from 0 to 14) and visuospatial abilities (scored from 0 to 16). The measure has been shown to have good internal consistency and convergent validity in a geriatric population (Matias-Guiu et al. 2017; Munoz-Neira et al. 2012).

Alzheimer's Disease Assessment Scale, Cogntitive (ADAS-COG): Is a measure originally designed to detect cognitive changes in Alzheimer's Disease. It is divided into cognitive (ASAD-Cog) and non-cognitive (ADAS-Noncog) sections. The scale and its sections have been shown to have high test-retest reliability and is valid, able to accurately discriminate varying severity of dementia. ADAS-Cog is often used to measure cognitive impairment in conditions other than Alzheimer's. However, it may be less sensitive in mild cognitive impairment. In patients with vascular lesions including vascular dementia and stroke, the derived Vascular Dementia Assessment Scale (VADAS**)** is often used due to its increased sensitivity in these contexts. Results of the VADAS are correlated with the severity of white matter lesions on seen on MRI (Skinner et al. 2012; Ylikoski et al. 2007; Weyer et al. 1997).

Category Test (from the Halstead-Reitan Neuropsychological Test Battery): Is reported to measure abstract reasoning, concept formation, spatial reasoning, general intelligence and other complex mental functions (cerebral dysfunction). Subjects are asked to identify the underlying concept of visual stimuli by giving a rating from 1 to 4. The examiner gives feedback (typically a bell or buzzer) about whether or not the subject is correct. The subject must form hypotheses about the underlying concept of the stimuli and test these hypotheses over repeated trials. Subjects are scored based on the number of errors made. The category test has relatively low test-retest reliability in non-impaired individuals but this is higher in the impaired. It had modest convergent validity and is highly sensitive but has low specificity (Man et al. 2006; Choca et al. 1997).

Cognitive Capacity Screening Examination (CCSE): Is a measure of delirium and other mental impairment. It is a 30-item test, with scores below 19 or 20 considered pathological. The

test appears to be valid, however there are mixed reports about its sensitivity and specificity (Schwamm et al. 1987; Beresford et al. 1985).

Cognitive Failures Questionnaire (CFQ): Is a measure of the self-perceived likelihood that one will commit an error in the completion of an every-day task that one would not normally commit an error completing. It consists of 25 questions, each scored from 0 (never) to 4 (very often) and providing a total score range from 0-100. Analysis showed the CFQ has high internal consistency and test-retest reliability (Wallace, Kass & Stanny, 2002).

Functional Independence Measure Cognitive Subscale (FIM-Cog): Is an 18-item outcome measure composed of both cognitive (5-items) and motor (13-items) subscales. Each item assesses the level of assistance required to complete an activity of daily living on a 7-point scale. The summation of all the item scores ranges from 18 to 126, with higher scores being indicative of greater functional independence. This measure has been shown to have excellent reliability and concurrent validity in its full form (Granger et al. 1998, Linacre et al. 1994; Granger et al. 1993).

Global Deterioration Scale: Is a measure of psychiatric symptoms and functional impairment in Alzheimer's Disease and other forms of primary degenerative dementia. It classifies impairment into 7 stages. Stage 1 represents no cognitive decline, while stage 7 represents very severe cognitive decline and loss of all verbal and psychomotor ability. At stage 5, patients can no longer survive without assistance. The Global Deterioration Scale is validated against behavioural, neuroanatomical and neurophysiological measures. It has also been validated against measures of instrumental activities of daily living in patients with vascular dementia (Paul et al. 2002; Reisberg et al. 1982).

Loewenstein Occupational Therapy Cognitive Assessment-Geriatric (LOTCA-G): The LOTCA is a measure of cognitive ability in brain-injured patients of any etiology including stroke. It was designed as a screening instrument for further investigation and to track progress in occupational therapy over time. The LOTCA consists of 20 subtests, divided into 4 domains: orientation, visual and spatial cognition, visuomotor organization, and thinking operations. The LOTCA-G is the geriatric version of the LOTCA specifically designed to assess cognition in the elderly. It consists of 23 subtests with perception, praxis and memory domains added in place of the visual and spatial cognition domain of the LOTCA. Both forms of the test have been found to exhibit construct validity, high interrater reliability and internal consistency in individuals with stroke and acquired brain injury (Katz, Elazar & Itzkovich, 1995; Katz et al. 1989).

Mini Mental Status Examination (MMSE): Is a brief screening tool and quantitative assessment of cognitive impairment. It is one of the most commonly used instruments for this purpose. The exam consists of 11 questions/tasks in 7 cognitive domains: 1) orientation to time; 2) orientation to place; 3) registration of 3 words; 4) attention and calculation; 5) recall of 3 words; 6) language; and 7) visual construction. The test is scored out of 30 possible points, with a score between18 to24 denoting mild impairment and a score between 0 to17 denoting severe impairment. The test has been found to be valid as a screening tool, and is sensitive for detecting moderate/severe impairment, but not mild impairment. It has good interrater reliability. The MMSE is appropriate for screening for post-stroke cognitive impairment (Bour et al. 2010; Tombaugh & McIntyre, 1992; Dick et al. 1984).

Montreal Cognitive Assessment (MoCA): Is one of the most commonly used tools designed to detect mild cognitive impairment. It is a brief, 30-item test that consists of various

subtests evaluating: short-term memory, visuospatial abilities, executive function, attention, concentration, working memory, language, and orientation to time and space. A cut-off score ≤26 represents cognitive impairment. The MoCA was found to be valid and exhibits excellent sensitivity in mild cognitive impairment. It was therefore found to be superior to the MMSE in screening for mild cognitive impairment. It exhibited good sensitivity in detecting moderate and severe impairment. Specificity was also high. It is sensitive and appropriate for use in detecting post-stroke cognitive impairment (Dong et al. 2010; Nasreddine et al. 2005).

Raven's Progressive Matrices: Is a measure of intelligence that consists of a series of multiple-choice items of abstract reasoning. Each item depicts an abstract pattern in a two by two or three by three matrix; all cells contain a figure except for one cell in the corner. Participants are asked to identify the missing segment that would best complete the pattern. The test is shown to be a reliable measure of linguistic, visuoperceptual, and memory cognitive functioning in persons with motor impairment and speech deficits (Brouwers et al. 2009; Pueyo et al. 2008).

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Is a measure of cognitive impairment designed to detect decline in older adults and act as a screening battery for younger patients. It assesses 5 cognitive domains: 1) Immediate memory; 2) Visuospatial/Constructional; 3) Language; 4) Attention; and 5) Delayed memory. Each domain is divided into 2-4 subtests. An advantage of the RBANS is its ability to detect more mild impairment compared to similar test such as the MMSE or Dementia Rating Scale. It is able to differentiate types of dementia by the score profile across its domains. It has been shown to be clinically valid and internally consistent in stroke populations. (Larson et al., 2005; Randolph et al. 1998).

Wechsler Adult Intelligence Scale (WAIS): Is a widely used IQ test designed to measure a person's intelligence and cognitive ability. The original WAIS was created in 1955, and there have been many revisions since, including the WAIS-R, WAIS-III, and WAIS-IV. WAIS-R is a revised form of the WAIS and consists of six verbal (information, comprehension, arithmetic, digit span, similarities, vocabulary) and five performance (picture arrangement, picture completion, block design, object assembly, digit symbol) subtests. The current edition, WAIS-IV, includes four core indices measuring verbal comprehension, perceptual reasoning, working memory, and processing speed. The WAIS scales have long been considered the gold standard measure of intellectual functioning and have demonstrated excellent validity and reliability in healthy individuals (Weschler 2008; Denhart 2018).

Amusia

Montreal Battery of Amusia: Is a comprehensive tool used to diagnose individuals with congenital amusia or acquired music cognition deficits. Its components are as follows: a scale test; off-beat test; out-of-key test; questionnaire regarding education, professional background and music experiences; audiometry; melodic organization tests; temporal organization tests; memory recognition test; cognitive deficit screening; pitch discrimination; and pitch production (Vuvan et al. 2018).

Activities of Daily Living

Alzheimer's Disease Cooperative Study, ADLs (ADCS-ADL): Is a measure of informant-based items describing a patient's performance of activities of daily living, used to track decline over time. It is also used in other forms of dementia. It has been shown to be valid and have excellent test-retest reliability. Correlations with Mini Mental State Exam scores and therefore cognitive impairment are moderate-to-high (Galasko et al. 1997).

Alzheimer's Disease Functional Assessment and Change Scale (ADFACS): Is a measure that assesses function based on performance of ADLs and IADLs. It is a 16-item instrument, with each ADL item scored from 0 (no impairment) to 4 (severe impairment) and each IADL item scored from 0 (no impairment) to 3 (severe impairment), for a total possible score of 54. Psychometric tests in a Spanish population showed the ADFACS has very high internal consistency and is strongly correlated with other functional and cognitive measures. It is a reliable, sensitive and valid instrument for detecting cognitive changes in dementia (Manero et al. 2014; Boustani et al. 2003).

Barthel Index (BI): Is a measure of one's ability to perform activities of daily living. The scale consists of 10 items: personal hygiene, bathing, feeding, toilet use, stair climbing, dressing, bowel control, bladder control, ambulation or wheelchair mobility and chair/bed transfers. Each item has a five-stage scoring system and a maximum score of 100 points, where higher scores indicate better performance. The scale is suitable for monitoring on the phone, and is shown to have a high inter-rater reliability (Park 2018).

Disability Assessment for Dementia (DAD): Is a measure of functional disability due to cognitive impairment in dementia. The test is administered in an interview with a caregiver and consists of 40 items: 17 assessing basic self-care and 23 assessing instrumental activities of daily living. The test demonstrates high internal consistency, interrater reliability and test-retest reliability (Gelinas et al. 1999).

Functional Independence Measure (FIM): Is an 18-item outcome measure composed of both cognitive (5-items) and motor (13-items) subscales. Each item assesses the level of assistance required to complete an activity of daily living on a 7-point scale. The summation of all the item scores ranges from 18 to 126, with higher scores being indicative of greater functional independence. This measure has been shown to have excellent reliability and concurrent validity in its full form (Granger et al. 1998, Linacre et al. 1994; Granger et al. 1993).

Lawton Instrumental Activities of Daily Life Scale: Is a measure of functional impairment in more complex daily living skills (in comparison to basic activities of daily living). The scale examines 8 domains of function: ability to use the telephone, shopping, food preparation, housekeeping, laundry, transportation, responsibility for medications, and finances. 1 point is given if the patient is independent and capable in each domain, for a total possible score ranging from 0 (low function and dependent) to 8 points (high function and independent). The scale is a valid and accepted test of functional status and has good interrater reliability (Graf, 2008; Lawton & Brody, 1969).

Stroke Impact Scale (ADL Subsection): Is a patient-reported measure of multi-dimensional stroke outcomes. The measure consists of 59 functional tasks (e.g. dynamometer, reach and grab, walking, reading out loud, rating emotional regulation, word recall, number of

tasks completed, and shoe tying). These tasks are then divided into 8 distinct subscales which include: strength, hand function, mobility, communication, emotion, memory, participation and activities of daily living (ADL). Each task is measured on a 5-point scale (1=an inability to complete the task, 5=not difficult at all). The measure has been shown to have good reliability and validity (Mulder et al. 2016; Richardson et al. 2016).

<u>Introduction</u>

Defining cognitive impairment post-stroke

Cognition includes multiple domains (Sachdev et al. 2014; Cummings et al. 2013):

- Attention, which can be broadly defined as focusing, shifting, dividing, or sustaining attention on a particular stimulus or task.
- Executive function which is involved in planning, abstract thinking, organization of thoughts, inhibition and conflict monitoring.
- Visuospatial ability which describes one's aptitude to visual search or scan for information, to draw or recreate visual images, and mentally manipulate objects two- and three-dimensional objects.
- Learning and memory describes one's ability to recall and recognition of visual and verbal information, be it episodic or semantic.
- Language which is the ability to express and be receptive of oneself through language through writing and reading comprehension.
- Social cognition which is the recognition of one's own and other's emotional state, and an understanding of the theory of mind.

Importantly these domains are not independent of each other.

Over the past years, the definition and nomenclature describing cognitive impairments have changed to include a vast yet specific selection of cognitive disorders. Today, the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V defines neurocognitive disorders (NCD) as a group of acquired disorders with a primary cognitive deficit that alters one's level of functioning. NCDs are further classified into mild or major subtypes: major but not mild NCDs reach the threshold for diagnosis of dementia. However, this threshold is difficult to define since both types of NCDs exist on a continuum of cognitive/functional impairment and the distinction between the two NCD types is often arbitrary (Simpson, 2014).

The DSM-V diagnostic criteria for mild NCDs include (Simpson, 2014):

1. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on:
   a. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   b. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
2. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills

or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required.)

Vascular cognitive impairment (VCI) refers to a heterogenous group of conditions (including: mild neurocognitive disorder, dementia, vascular dementia and mixed dementia) in which vascular lesions cause or contribute to impaired cognitive function (Barbay et al. 2017). Currently, there are three terms used to describe VCI.

- VCI-no dementia (VCI-ND) describes individuals "whose symptoms are not associated with substantial functional impairment, including a high proportion with subcortical ischemia with cognitive impairment of presumed vascular cause" (Moorhouse & Rockwood, 2008).
- Vascular dementia is defined as a loss of cognitive function resulting from ischemic, hypoperfusive, or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology (Roman, 2003) and includes disorders that are in the original vascular dementia construct, such as post-stroke dementia and multi-infarct dementia (Moorhouse & Rockwood, 2008).
- Mixed dementia describes the "presentation of individuals with clinical, and commonly neuro pathological, features of Alzheimer's disease and vascular dementia" (Moorhouse & Rockwood, 2008).

Clinical presentation of VCI commonly includes decreased executive functioning, mental slowing, and impairment of goal formulation, initiation, planning, organizing, sequencing, executing, abstracting and attention (Lesniak et al. 2008; Roman 2003; Srikanth et al. 2003; Desmond et al. 1999; Looi & Sachdev 1999; Hochstenbach et al. 1998). Memory, however, may be relatively preserved (Roman 2003; Desmond et al. 1999; Looi & Sachdev 1999). In a study of elderly residents, Rao et al. (1999) found that individuals with VCI displayed significantly poorer performance than controls on abstract thinking, attention, calculation, language, memory, orientation, perception, praxis, and Mini Mental State Examination (MMSE) scores.

As suggested by Rockwood et al. (2000), the concept of VCI-ND is useful in identifying patients with stroke at risk for developing vascular dementia. Ballard et al. (2003; 2002) reported that a third of elderly stroke survivors who were free of dementia at 3 months post-stroke met the criteria for VCI-ND. Compared to elderly controls, the stroke survivors with VCI-ND had greater impairments of attention and executive function but had preservation of memory compared to those with dementia.

Issues in diagnosis and assessment of cognitive impairment

At present, there is no gold standard for the diagnosis of VCI. While some have used the MMSE or the modified version to demonstrate cognitive decline (Wentzel et al., 2001), others have used the Montreal Cognitive Assessment (MoCA) (Prokopenko et al., 2013) or the Cambridge Examination for Mental Disorders in the Elderly - Cognitive Subscale (CAMCOG) (O'Brien et al., 2003) that has been adapted to include VCI-ND (Szatmari et al., 1999). Both the MOCA and MMSE have been shown to have similar capabilities in detecting cognitive impairment post-stroke (Barbay et al. 2017). Recently the Groupe de reflexion pour l'evaluation cognitive vasculaire (GRECOGVASC) battery has been proposed an international standardized cognitive assessment. The GRECOGVASC encompasses a variety of tests in addition to the MMSE and the MOCA, assessing language, visuospatial, memory, executive function, neuropsychiatric symptoms and disability (Barbay et al. 2017).

Based on a consensus meeting sponsored by the National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network, Hachinski et al. (2006) produced a set of harmonized criteria for cognitive screening and assessment to define the spectrum of VCI subtypes. The authors proposed that the following neuropsychological domains be examined: executive function, attention, memory, visuospatial, language, depression, and pre-morbidity. They produced screening and assessment methods for the identification of individuals with possible cognitive and behavioural impairment to establish minimum datasets for clinical practice and research studies of VCI. The recommended 5-minute neuropsychological protocol included selected subtests of the MoCA (5-word memory, 6-item orientation, and 1-letter phonemic fluency), which could be supplemented with other tasks (e.g. cube and clock drawing, short trail-making test). Given more time, the full trail-making test, a semantic fluency test, or the MMSE could be added, but only if administered more than one hour following the protocol. Inclusion of the MMSE in the abbreviated assessment was rejected, as it lacks sufficient assessment of executive function and is relatively insensitive to mild memory impairment. Further 30-minute and 60-minute neuropsychological testing protocols were recommended for more extended assessment.

Prevalence and natural history of cognitive impairment post-stroke

According to the Canadian Study of Health and Aging, it is estimated that 5% of all people over the age of 65 years have evidence of vascular cognitive impairment (VCI) (Rockwood et al., 2000). Forty-four percent of these individuals developed dementia over a 5-year period (Ingles et al., 2002). The risk for cognitive impairment or decline is augmented by a history of stroke. In a UK-based population study of 4,075 individuals aged 65 and older, stroke was significantly associated with an increased risk for the development of dementia (OR=2.1, 95%CI 1.1-4.2) (Yip et al., 2006).

Patel et al. (2003) reported prevalence rates of VCI have varied substantially from 15-20% in various clinical settings to 39%, 35%, 30% and 32% at 3 months, 1 year, 2 years, and 3 years post-stroke, respectively. These latter rates are similar to the 31% reported at 15 months post-stroke by Ballard et al. (2003) and at 3 months by Sundar & Adwani (2010).

The risk for cognitive impairment is greater following stroke and, while not all individuals with cognitive impairment have dementia, post-stroke cognitive impairment is associated with an increased risk for dementia. Linden et al. reported that, overall, cognitive impairments were more common among patients with stroke than in age and gender matched controls (61% vs. 31%, OR=3.5) (Linden et al., 2004). The increased risk for cognitive impairment attributable to stroke was most marked among patients less than 80 years of age (OR=8.5). Another study reported that, in a sample of 327 patients with stroke, 12.6% had VCI-no dementia (VCI-ND) prior to stroke (Serrano et al., 2007). Using a consistent method of assessment, the frequency of VCI-ND was 26.9% at 3 months, 39.5% at 12 months and 36.6% at 24 months post-stroke. While cognitive impairment was more common than dementia in patients with stroke, patients with VCI-ND were at least 8 times more likely to develop delayed dementia than those without VCI-ND.

Stroke may be a major risk factor for the conversion of existing mild cognitive impairment (MCI) to dementia. Gamaldo et al. (2006) demonstrated that, in a sample of 335 individuals enrolled in the Baltimore Longitudinal Study of Aging (mean age 75 years at study entry), stroke was associated with an increased risk for dementia when compared to individuals who did not experience stroke (OR=5.55, 95%CI 2.76-11.4). Of the individuals who were diagnosed with dementia following stroke, the majority (14/19) had evidence of MCI prior to the stroke event. The odds ratio for developing dementia in those individuals with MCI prior to stroke was reported to be 12.4 (95%CI 1.5-9.9) (Gamaldo et al., 2006).

Impact of cognitive impairment on rehabilitation outcomes

It has been suggested that cognitive abilities such as abstract thinking, judgment, short-term verbal memory, comprehension and orientation are important in predicting the stroke survivor's functional status at discharge (Jongbloed, 1986; Mysiw et al., 1989; Tatemichi et al., 1994). Reduced cognition has been associated with a decreased ability to perform activities of daily living (ADL), with poorer physical functioning at discharge and with a greater likelihood of mortality within 1 year of discharge (Arfken et al. 1999; Prencipe et al. 1997; Desmond et al. 2000; Lin et al. 2003; Claesson et al. 2005; Leys et al. 2005; Hinkle 2006; Cederfeldt et al. 2010; Lichtenberg et al. 1994; Tatemichi et al. 1994; Ruchinskas & Curyto 2003). Narasimhalu et al. (2011) found post-stroke cognitive impairment to be predictive of dependency and Zinn et al. (2004) reported fewer discharges home among patients with cognitive impairment than among cognitively intact patients (85.9% vs. 93.4%, p=0.07). A recent 15-year longitudinal study found that, on average, the relative risk of disability following stroke was twice as high for those with cognitive impairment than in those without: 3-month RR=2.4, 95%CI 1.93-3.08; 1-year RR=1.9, 95%CI 1.38-2.6; 5- year RR=1.8, 95%CI 1.27-2.55 (Douiri et al., 2013).

Although the presence of cognitive impairment may be associated with decreased ADL function, it has been demonstrated that it is not a significant predictor of ADL function at 6 months post-stroke (Zinn et al., 2004). Rather, instrumental function may be more severely impacted by the presence of cognitive ability. At 6 months post-stroke, the presence of cognitive impairment was associated with and predictive of decreased instrumental ADL (IADL) function (Zinn et al., 2004). Similarly, Mok et al. (2004) determined that higher levels of cognitive impairment post-stroke were associated with greater deficits in IADL function and greater levels of pre-stroke cognitive decline. Identified predictors of IADL performance were stroke severity, executive dysfunction, age and pre-stroke cognitive decline (Mok et al., 2004).

Patients with cognitive impairments may require more therapy over a longer period of time (Zinn et al., 2004). In addition, participation in rehabilitation may be adversely affected by the presence of attention and executive dysfunction (Robertson et al., 1997; Skidmore et al., 2010). However, this is associated with greater expenditure of healthcare resources (Claesson et al. 2005).

Cognitive rehabilitation

Cognitive rehabilitation involves "a systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient's brain-behavioural deficits" (Cicerone et al., 2000). Various interventions aim to:
1) reinforce, strengthen or re-establish previously learned patterns of behaviour;
2) establish new patterns of cognitive activity through compensatory cognitive mechanisms for impaired neurological systems;
3) establish new patterns of activity through external compensatory mechanisms such as personal orthoses or environmental structuring and support; and
4) enable persons to adapt to their cognitive disability.

Accordingly, cognitive rehabilitation directs itself to several areas of cognition such as attention, concentration, perception, memory, comprehension, communication, reasoning, problem-solving, judgement, initiation, planning, self-monitoring and awareness (Cumming et al., 2013).

Attentional Training

Attention is a cognitive function that will ultimately affect all aspects of cognition and processing. No matter the nature of a task, attention is required to pick out salient information, and ignore non-relevant stimuli. For this reason, training attention specifically can improve a variety of mental processes and training effects can ideally permeate to almost all levels of cognitive functioning. Training of attention can take on two very broad classifications. One way is repetition of task-specific activities that require an attention network (network training). Another is through activities like meditation and mindfulness training that seek to change the brain's overall state (state training) (Posner, Rothbart & Tang, 2015).

Four RCTs were found evaluating attentional training for cognitive rehabilitation. Two RCTs examined attentional training programs to standard care (Barker-Collow et al. 2009; Giaguinto & Fraigli, 2003). Two RCTs compared attentional training to other computerized training (Mazer et al. 2003; Strum et al. 1997).

The methodological details and results of all four RCTs are presented in Table 1.

Table 1. RCTs evaluating attentional training interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Attentional training compared to standard care		
Barker-Collow et al. (2009) RCT (8) N$_{Start}$=78 N$_{End}$=66 TPS=Acute	E: Attention Process Training C: Usual care Duration: 1hr/d, 5d/wk for 4 wk	• Integrated Visual and Auditory Continuous Performance Test (+exp) • Trail-Making Test A (-) • Trail-Making Test B (-) • Paced Auditory Serial Addition Test (-)
Giaquinto & Fraioli (2003) RCT (5) N$_{Start}$=60 N$_{End}$=60 TPS=Acute	E: Daily attention training (computerized discrimination task + cutaneous electrical stimulation) C: Untrained Duration: 40min, 5d/wk for 3wk	• EEG Signals Detecting N140 at 3 wks (+exp) • Functional Independence Measure (-)
Attentional training compared to other standard cognitive training programs		
Mazer et al. (2003) RCT (7) N$_{Start}$=97 N$_{End}$=84 TPS=Subacute	E: Useful Field of View (UFOV) training C: Traditional computerized training Duration: 30-60min/session, 2-4 sessions/wk until 20 sessions	• Useful Field of View (-) • Functional Independence Measure (-) • Test of Everyday Attention (-) • Motor-Free Visual Perception Test (-) • Money Road Map Test of Direction Sense (-) • Trail-Making Test A (-) • Trail-Making Test B (-) • Charron Test (-) • On-road Evaluation (-)
Sturm et al. (1997) RCT Crossover (3) N$_{Start}$=38 N$_{End}$=37 TPS=Chronic	E: Computerized Adaptive Attention Testing for specific disorders C: Standardized attention test battery Duration: 14 1-hr sessions	• Alertness Training Task (+exp) • Vigilance Training Task (+exp) • Selective Attention Training Task (-) • Divided Attention Training Task (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about attentional training

ATTENTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Attentional training** may produce greater improvements in attention than **standard care**.	2	Barker-Collow et al. 2009; Giaguinto & Fraioli, 2003
1b	**Attentional training** may not have a difference in efficacy when compared to **other standard cognitive training** for improving attention.	2	Mazer et al. 2003; Sturm et al. 1997

EXECUTIVE FUNCTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Attentional training** may not have a difference in efficacy when compared to **standard care** for improving executive function.	1	Barker-Collow et al. 2009
1b	**Attentional training** may not have a difference in efficacy when compared to **other standard cognitive training** for improving executive function.	1	Mazer et al. 2003

LEARNING AND MEMORY			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Attentional training** may not have a difference in efficacy when compared to **standard care** for improving learning and memory.	1	Barker-Collow et al. 2009

VISUOSPATIAL PERCEPTION AND ORIENTATION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Attentional training** may not have a difference in efficacy when compared to **other standard cognitive training** for improving visuospatial perception and orientation.	1	Mazer et al. 2003

ACTIVITIES OF DAILY LIVING			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Specialize attentional training** may not have a difference in efficacy when compared to **other standard cognitive training** for improving activities of daily living.	1	Mazer et al. 2003
2	**Attentional training** may not have a difference in efficacy when compared to **standard care** for improving activities of daily living.	1	Giaguinto & Fraioli, 2003

Key Points

Attentional training may not be helpful for improving cognitive rehabilitation

Memory Training
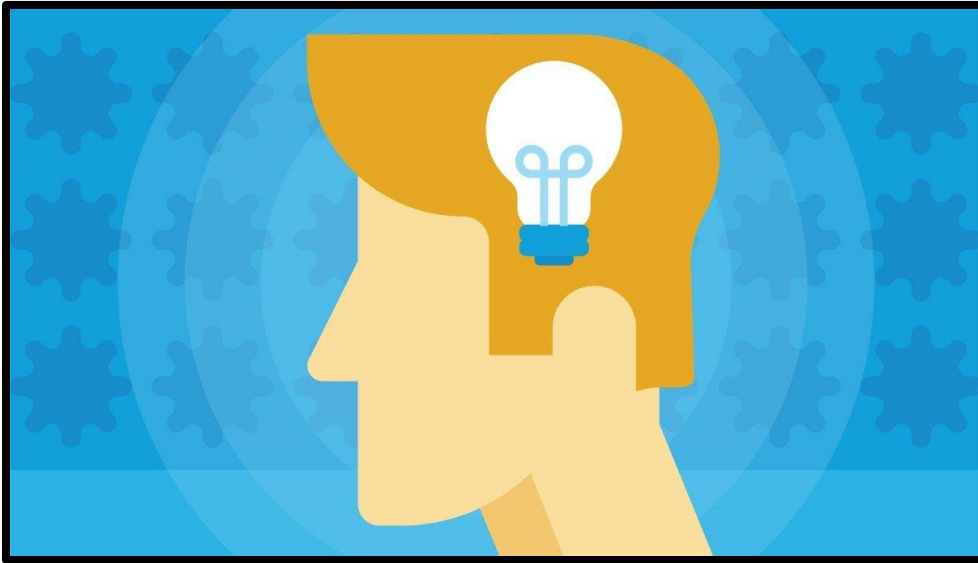
There are many different types of memory, and therefore many types of memory training. Most of the research available tends to focus on training working memory, but other methods are available for training semantic or episodic memory as well. Because all types of memory play such a crucial role in our ability to live independent lives, it is a major target for rehabilitation in those affected by memory deficits. Although the nature of the tasks may differ, training generally consist of a learning phase of some form where the information is intended to be encoded, and a recall phase. In addition, training certain strategies as opposed to simply task-specific repetition is also another way to ameliorate memory deficits (Zarit, Cole & Guider, 1981).

Five RCTs were found evaluating memory training for cognitive rehabilitation. One RCT examined memory training against no treatment (Westerberg et al. 2007). Two RCTs examined specialized memory training against rote training (Chen et al. 2012; Doornhein & De Haan, 1998). One RCT examined process-oriented memory training against strategy based, and a lose dose training regime (Hildebrandt et al. 2006). One RCT examined memory self-efficacy training against an educational program (Aben et al. 2014).

The methodological details and results of the five RCTs evaluating are presented in Table 2.

Table 2. RCTs evaluating memory training interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Memory training compared to no training		
Westerberg et al. (2007) RCT (6) N$_{Start}$=21 N$_{End}$=18 TPS=Chronic	E: Computerized working memory training C: No treatment Duration: 40min/d, 5d/wk for 5wks	• Stroop Interference Test (-) • Claeson-Dahl Test (-) • Digit Span from WAIS R (+exp) • Raven's Progressive Matrices (-) • Word List Delayed Recall (-) • Paced Auditory Serial-Addition - A (+exp) • RUFF 2&7 Serial Cancellation Test (+exp) • Cognitive failure Questionnaire (+exp)
Specialized memory strategy training compared to rote training		
Chen et al. (2012) RCT (5) N$_{Start}$=11 N$_{End}$=9 TPS=Subacute	E: Global processing training (global to local encoding) C: Rote repetition training (no encoding strategy) Duration: 4 sessions over 4wk	• Immediate Recall of Rey-Osterrieth Complex Figure (+exp) • Delayed Recall of Rey-Osterrieth Complex Figure (-)
Doornhein & De Haan (1998) RCT (4) N$_{Start}$=12 N$_{End}$=12 TPS=Subacute	E: Memory strategy training C: Drill and practice exercises, no strategy training Duration: 2 sessions/wk for 4wk	• Name-face Paired Association Task (+exp) • Stylus Maze Task (+exp) • List Learning Task (-) • Oxford Recurring Faces Test (-) • Memory Questionnaire (subjective judgement) (-)
Process-oriented training vs strategy-based training vs a low dose regime		
Hildebrandt et al. (2006) RCT (6) N$_{Start}$=62 N$_{End}$=62 N$_{Stroke}$=41 N$_{TBI}$=7 N$_{Other}$=14 TPS=Subacute	E1: Process-oriented memory training E2: Strategy-based memory training C: Low dose memory training Duration: 1hr/d, 5d/wk for 5wk	E1 vs C: • Rivermead Behavioural Memory Test (-) • California Verbal Learning Test (+exp$_1$) • Text Reproduction (+exp$_1$) • Categorical Word Fluency (+exp$_1$) • Map Learning (-) • Digit Span Test (-) E2 vs C: • Rivermead Behavioural Memory Test (-) • California Verbal Learning Test (-) • Text Reproduction (+exp$_2$) • Categorical Word Fluency (+exp$_2$) • Map Learning (-) • Digit Span Test (-)
Memory self-efficacy training vs educational programs		
Aben et al. (2014) RCT (8) N$_{Start}$=153 N$_{End}$=139 TPS=Chronic	E: Memory self-efficacy training program C: Educational program Duration: 9 sessions, 1hr/session, 2 sessions/wk	• Auditory verbal Learning Test (-) • Rivermead Behavioural Memory Test (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about memory training

LoE	ATTENTION		
LoE	Conclusion Statement	RCTs	References
1b	**Memory training** may produce greater improvements in attention than **standard care**.	1	Westerberg et al. 2007

LoE	EXECUTIVE FUNCTION		
LoE	Conclusion Statement	RCTs	References
1b	**Process-oriented training** and **strategy-based training** may produce greater improvements in executive function than **low does training**.	1	Hildebrandt et al. 2006
1b	**Memory training** may not have a difference in efficacy when compared to **standard care** for improving executive function.	1	Westerberg et al. 2007

LoE	LEARNING AND MEMORY		
LoE	Conclusion Statement	RCTs	References
1b	There is conflicting evidence about the effect of **memory training** to improve learning and memory when compared to **standard care.**	1	Westerberg et al. 2007
1b	**Process-oriented training** and **strategy-based training** may not have a difference in efficacy when compared to **low dose training** for improving learning and memory.	1	Hildebrandt et al. 2006
1b	**Memory self-efficacy training** may not have a difference in efficacy when compared to **educational programs** for improving learning and memory.	1	Aben et al. 2014
2	**Specialized memory training** may not have a difference in efficacy when compared to **rote training** for improving learning and memory.	2	Chen et al. 2012; Doorhein & De Haan, 1998

LoE	VISUOSPATIAL PERCEPTION AND ORIENTATION		
LoE	Conclusion Statement	RCTs	References
2	**Specialized memory training** may produce greater improvements in visuospatial perception and orientation than **rote training**.	1	Chen et al. 2012

LoE	GLOBAL COGNITION		
LoE	Conclusion Statement	RCTs	References
1b	There is conflicting evidence about the effect of **memory training** to improve global cognition when compared to **standard care.**	1	Westerberg et al. 2007

Key Points

> The literature is mixed regarding memory training for cognitive rehabilitation

Mental Imagery
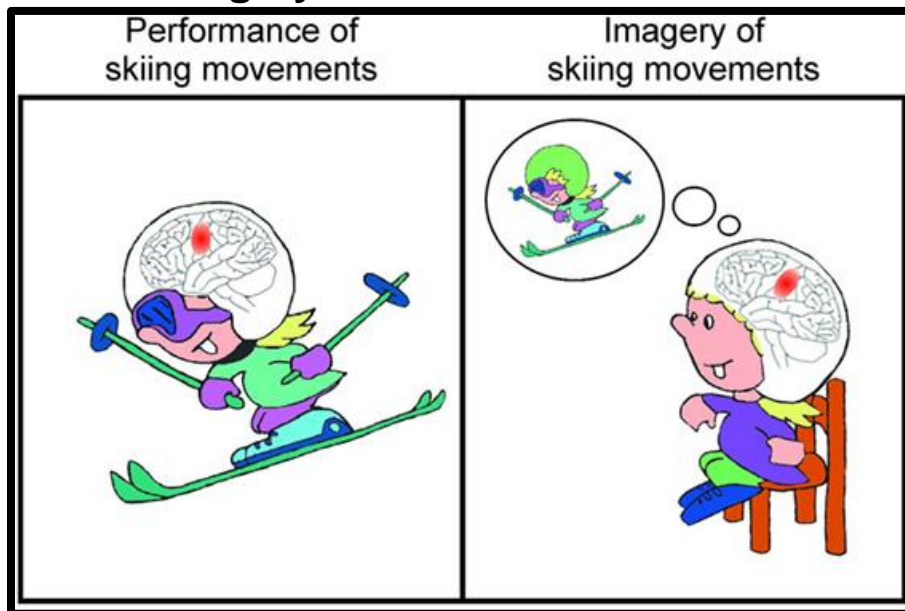
Mental practice as the name suggests, involves cognitively rehearsing a specific task by repetitively imagining oneself performing the precise movements involved in the task in the absence of performing the physical movement (Page et al. 2014). Mental practice is speculated to be effective because of its ability to use the same motor schema as when physically practicing the same task through the activation of similar neural regions and networks during mental practice (Page et al. 2014). The use of mental practice was Adopted from the field of sports psychology where the technique has been shown to improve athletic performance, when used as an adjunct to standard training methods (Page et al. 2014). There has also been a large amount of work done showing imagery's ability to improve memory recall, and learning (Bower, 1970). Therefore, this technique could be used to not only enhance memory, but other functions as well.

Three RCTs were found evaluating mental imagery for cognitive rehabilitation. One RCT examined mental imagery against functional rehabilitation (Li et al. 2004), and the other RCT compared it to rote memory tactics (Gasparrini & Satz, 1979).

The methodological details and results of all three RCTs are presented in Table 3.

Table 3. RCTs evaluating mental imagery for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Mental imagery compared to functional rehabilitation		
Liu et al. (2009) RCT (4) N$_{Start}$=35 N$_{End}$=33 TPS=Acute	E: Mental imagery training C: Functional rehabilitation Duration: 1hr/d, 5d/wk for 3wk	• Score of 5 Trained Tasks in Training Environment (+exp) • Score of 5 Trained Tasks in Novel Environment (+exp) • Score of 3 Untrained Tasks in Novel Environment (+exp)
Liu et al. (2004) RCT (6) N$_{Start}$=49 N$_{End}$=46 TPS=Acute	E: Mental imagery training C: Functional rehabilitation Duration: 1hr/d, 5d/wk for 3wk	• Score of Trained Tasks at 3wk (+exp) • Score of Untrained Tasks (+exp) • Color Trails Test (+exp)
Mental imagery compared to rote memory		
Gasparrini & Satz (1979) RCT (5) N$_{Start}$=30 N$_{End}$=30 TPS=Chronic	Experiment #1 E: Visual imagery mnemonic technique C: Rote memory Duration: 2-3 sessions over 1wk	• Teaching Paired Associates (+exp) • Change in Paired Associates (-) • Long-term Memory for Paired Associates (-) • Word List Memory (-) • Sentences Memory (-)
	Experiment # 2 (Crossover RCT) E: Visual imagery mnemonic technique C: Verbal mediation technique Duration: NR	• Paired Associates Test (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about mental imagery training

	ATTENTION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Mental imagery training** may produce greater improvements in attention than **standard care**.	1	Liu et al. 2004

	LEARNING AND MEMORY		
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Mental imagery training** may not have a difference in efficacy when compared to **rote memory** for improving learning and memory.	1	Gasparrini & Satz, 1997

	ACTIVITIES OF DAILY LIVING		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Mental imagery training** may produce greater improvements in activities of daily living than **standard care**.	2	Liu et al. 2009; Liu et al. 2004

Key Points

Mental imagery may be beneficial for improving attention, and activities of daily living

Mental imagery may not be beneficial for improving learning and memory

Cognitive-motor Interference

Adopted from: https://dribbble.com/shots/4508119-Walking-and-texting
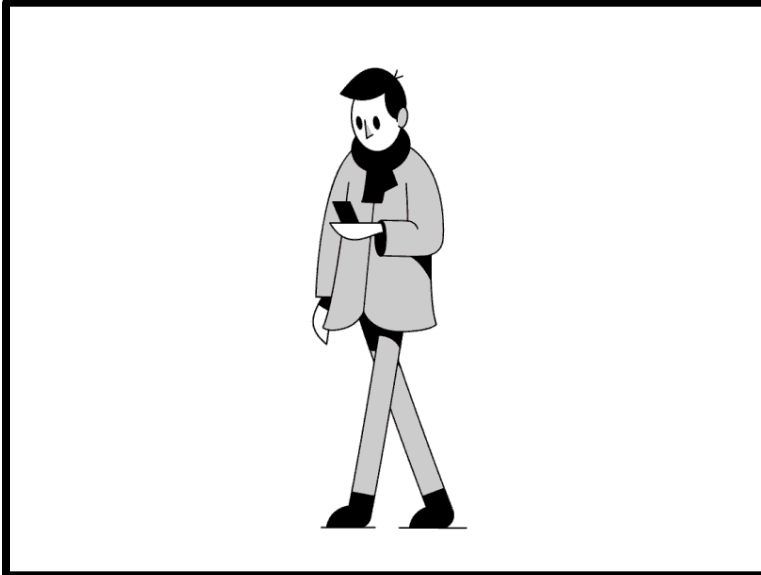
Dual-tasking training requires subjects to simultaneously perform complex tasks, such as cognitive and motor tasks, allowing them to improve their coordination of various tasks (Kim et al. 2014). Cognitive-motor tasks are important for various activities of daily living, such as walking while holding a conversation (Liu et al. 2017). Additionally, dual tasks can be two motor tasks to allow for different motor processes to occur simultaneously to further stimulate the damaged brain.

Three RCTs were found evaluating cognitive-motor interference training for cognitive rehabilitation. One RCT examined a cognitive-motor dual task with auditory motor synchronization compared to the cognitive-motor dual task alone (Park et al. 2018). One RCT examined a Wii Fit, and Tetrax biofeedback compared to conventional weight-shift training (Hung et al. 2017). One RCT compared self-regulation of cognitive-motor functions to functional rehab (Liu et al. 2014).

The methodological details and results of all three RCTs are presented in Table 4.

Table *. RCTs evaluating cognitive-motor interference interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Cognitive-motor interference training with auditory motor synchronization vs standard cognitive-motor training		
Park et al. (2018) RCT (8) N$_{Start}$=30 N$_{End}$=30 TPS=Subacute	E: Cognitive-Motor Dual-Task Training and Auditory Motor Synchronization Training (30min/d x 3d/wk) C: Cognitive-Motor Dual-Task Training only Duration: 6wk	• Trail Making Test A (+exp) • Trail Making Test B (-) • Digit Span Test Forward (+exp) • Digit Span Test Backward (+exp) • Stroop Test-word (+exp) • Stroop test-colour (-)
Wii fit vs tetrax biofeedback and standard cognitive motor training		
Hung et al. (2017) RCT (7) N$_{Start}$=43 N$_{End}$=37 TPS=Chronic	E1: Wii Fit (30min, 2d/wk) E2: Tetrax biofeedback (30min, 2d/wk) C: conventional weight-shifting training (30min, 2d/wk) Duration: 12wk	E1 vs E2: • Cognitive Abilities Screening Instrument Chinese Version - executive domain (+exp1) E1 vs C: • Cognitive Abilities Screening Instrument Chinese Version – executive domain (+exp1) E1 vs E2/C: • Cognitive Abilities Screening Instrument Chinese Version – other domains (-)
Cognitive-motor interference vs standard care		
Liu et al. (2014) RCT (7) N$_{Start}$=46 N$_{End}$=44 TPS=Acute	E: Self-regulation of motor and cognitive performance C: Functional rehabilitation Duration: five 1hr sessions	• Tasks of Daily Living (+exp) • Functional Independence Measure-Cognition (-) • Color Trails Test (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about cognitive-motor interference training

LoE	ATTENTION		
	Conclusion Statement	**RCTs**	**References**
1b	**Cognitive-motor interference training with auditory motor synchronization** may produce greater improvements in attention than to **standard cognitive-motor training**.	1	Park et al. 2018
1b	**Cognitive-motor interference training** may not have a difference in efficacy when compared **standard care** for improving attention.	1	Liu et al. 2014

LoE	EXECUTIVE FUNCTION		
	Conclusion Statement	**RCTs**	**References**
1b	**Wii Fit training** may produce greater improvements in executive function than **textrax biofeedback,** or **conventional weight-shift training**.	1	Hung et al. 2017
1b	There is conflicting evidence about the effect of **Cognitive-motor interference training with auditory motor synchronization** to improve executive function when compared to **standard cognitive-motor training**.	1	Park et al. 2018

LoE	LEARNING AND MEMORY		
	Conclusion Statement	**RCTs**	**References**
1b	**Cognitive-motor interference training with auditory motor synchronization** may produce greater improvements in learning and memory than to **standard cognitive-motor training**.	1	Park et al. 2018

LoE	GLOBAL COGNITION		
	Conclusion Statement	**RCTs**	**References**
1b	**Wii Fit training** may not have a difference in efficacy when compared than **textrax biofeedback,** or **conventional weight-shift training** for improving global cognition.	1	Liu et al. 2014
1b	**Cognitive-motor interference training** may produce greater improvements in global cognition than to **standard care.**	1	Liu et al. 2014

LoE	ACTIVITIES OF DAILY LIVING		
	Conclusion Statement	**RCTs**	**References**
1b	**Cognitive-motor interference training** may not have a difference in efficacy when compared **standard care** for improving activities of daily living.	1	Mazer et al. 2003

Key Points

The literature is mixed regarding cognitive-motor interference for cognitive rehabilitation

Exercise Programs

Exercise can be defined as planned physical activity that is structured and repetitive and is performed deliberately with the intention of improving physical fitness. Major factors of physical fitness are cardiovascular fitness, strength and power. After stroke, individuals are impaired on all three of these attributes, to significant but varying degrees (Saunders, Greig & Mead, 2014). Physiotherapy and exercise are the primary method for regaining any of these deficits experienced after the injury. Although it is well known that physiotherapy and exercise are effective for rehabilitation, it is still not clear as to what type is most effective (Langhorne, Wagenaar & Patridge, 1996; Cho & Cha, 2016). Besides the more obvious physical benefits associated with exercise, psycho-social benefits also exist, and attempts are made to maximize these residual benefits as well (Saunders, Greig & Mead, 2014). Many studies have shown how aerobic exercise can help improve cognitive function, and importantly protect it through ageing in healthy individuals (Quaney et al. 2009).

Nine RCTs were found evaluating physical exercise for cognitive rehabilitation. Six RCTs compared an exercise program to standard care (Kim et al. 2017; Swatridge et al. 2017; Lui-Ambrose & Eng, 2015, Calabro et al. 2015; Moore et al. 2015; Quaney et al. 2009). Three RCTs compared a higher intensity workout program to a lower intensity one (Tang et al. 2016; Fernandez-Gonzalo et al. 2016; Ploughman et al. 2008).

The methodological details and results of all nine RCTs are presented in Table 5.

Table 5. RCTs evaluating exercise interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Exercise compared to conventional care and/or simple stretching		
Kim et al. (2017) RCT PEDro=5 N$_{Start}$=30 N$_{End}$=29 TPS = Chronic	E1: exercise protocol hand grip training (15 min/session), treadmill-based weight loading training (30 min/session) (3 sessions/d x 6wk) and conventional therapy (60min/d x 6wk) C: conventional therapy.	• Korean Montreal Cognitive Assessment (+exp) • Stroop Test: Simple Interference (-) • Trail Making Test A (-) • Trail Making Test B (-)
Swatridge et al. (2017) RCT (6) Nstart = 9 Nend = 9 TPS = Subacute	E: Moderate Intensity exercise (20min) C: No exercise Duration: 2 sessions	• Modified Eriksen Flanker task (-) • P300 EEG Detection (+exp)
Liu-Ambrose & Eng (2015) RCT (9) N$_{Start}$=28 N$_{End}$=24 TPS=Chronic	E: Exercise sessions with a key focus on resistance, balance and aerobic training C: Waiting list, no treatment Duration: 2 exercise sessions + 1 leisure activity/wk for 6mo	• Stroop Test (+exp) • Trail-Making Test A (-) • Trail-Making Test B (-) • Verbal Digits Backwards Test (+exp) • Verbal Digits Forwards Test (+exp)
Calabro et al. (2015) RCT (8) N$_{Start}$=20 N$_{End}$=20 TPS=Subacute	E: Patients received standard physical exercise plus 30 sessions of robotic tilt table training C: Patients received standard physical exercise plus verticalization training by a physiotherapist Duration: 30min/d, 5d/wk for 6wk	• Raven Colored Progressive Matrices (+exp) • Paired Associative Stimulation Protocol (+exp)
Moore et al. (2015) RCT (7) N$_{Start}$=40 N$_{End}$=40 TPS=Chronic	E: Structured exercise C: Standard care + stretching Duration: 45-60min/d, 3d/wk for 19wks	• Addenbrooke's Cognitive Scale (+exp) Quality of Life: Stroke Impact Scale: • Memory (-) • ADLs (-) •
Quaney et al. (2009) RCT (5) N$_{Start}$=40 N$_{End}$=38 TPS=Chronic	E: Progressive, resistive aerobic exercise program C: Stretching exercises program Duration: 45min/d. 3d/wk for 8wk	• Serial Reaction Time Task (+exp) • Wisconsin Card Sorting Task (-) • Trail-Making Test A (-) • Trail-Making Test B (-) • Stroop Test (-)
Higher intensity exercise programs vs lower intensity exercise programs		
Tang et al. (2016) RCT (6) N$_{Start}$=50 N$_{End}$=47 TPS=Chronic	E: High intensity aerobic exercise C: Balance/Flexibility Control Group Duration: 60min/d, 3d/wk for 6mo	• Verbal Digit Span (-) • Stroop Test (-)
Fernandez-Gonzalo et al. (2016) RCT (4) N$_{Start}$=32 N$_{End}$=29 TPS=Chronic	E: ECC-overload flywheel leg press, 2 times a week for 12 weeks. C: Daily routine Duration: 2 sessions/wk for 12wk	• Talking-While-Walking Test Circuit Time (+exp) • Talking-While-Walking Test Cost of Walking (+exp) • Digits Span Forward (+exp) • Digits Span Backward (+exp) • Rey Auditory Verbal Learning Test Learning (-) • Rey Auditory Verbal Learning Test Long-term Recall (-) • Continuous Performance Task (-)

		• Spatial Span Forward (-) • Spatial Span Backward (-) • Stroop Word (-) • Stroop Color (+exp) • Stroop Word and Color (-) • Trail-Making Test-A (-) • Trail Making Test-B (-) • Verbal Fluency Test (+exp)
Ploughman et al. (2008) RCT Crossover (6) N_{Start}=21 N_{End}=21 TPS=Chronic	E: Bodyweight-support Treadmill Training C: Home exercise program Duration: 20min/session, 2 sessions separated by 7-10d	• Trail-Making Test A (-) • Trail-Making Test B (-) • Symbol Digit Substitution Test (-) • Paced Auditory Serial Addition Test (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp2 indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about exercise programs

ATTENTION

LoE	Conclusion Statement	RCTs	References
1a	**Exercise programs** may not have a difference in efficacy when compared to **standard care or stretching** for improving attention.	4	Kim et al. 2017; Swatridge et al. 2017; Liu-Ambrose & Eng, 2015; Quaney et al. 2009
1b	**High intensity exercise programs** may not have a difference in efficacy when compared to **lower intensity exercise** for improving attention.	2	Fernandez-Gonzalo et al. 2016; Ploughman et al. 2008

EXECUTIVE FUNCTION

LoE	Conclusion Statement	RCTs	References
1a	**Exercise programs** may not have a difference in efficacy when compared to **standard care or stretching** for improving executive function.	4	Kim et al. 2017; Swatridge et al. 2017; Liu-Ambrose & Eng, 2015; Quaney et al. 2009
1a	**Higher intensity exercise programs** may not have a difference in efficacy when compared to **lower intensity exercise** for improving executive function.	3	Fernandez-Gonzalo et al. 2016; Tang et al. 206; Ploughman et al. 2008

LEARNING AND MEMORY

LoE	Conclusion Statement	RCTs	References
1a	**Exercise programs** may produce greater improvements in learning and memory than **standard care or stretching**.	4	Calabro et al. 2015; Moore et al. 2015; Liu-Ambrose & Eng, 2015; Quaney et al. 2009
1a	**Higher intensity exercise programs** may not have a difference in efficacy when compared to **lower intensity exercise** for improving learning and memory.	3	Fernandez-Gonzalo et al. 2016; Tang et al. 206; Ploughman et al. 2008

GLOBAL COGNITION

LoE	Conclusion Statement	RCTs	References
1a	**Exercise programs** may produce greater improvements in global cognition than **standard care or stretching**.	3	Kim et al. 2017; Calabro et al. 2015; Moore et al. 2015;

ACTIVITIES OF DAILY LIVING

LoE	Conclusion Statement	RCTs	References
1b	**Exercise programs** may not have a difference in efficacy when compared to **standard care or stretching** for improving activities of daily living.	1	Moore et al. 2015

Key Points

Exercise may be beneficial for improving learning and memory, and overall cognitive abilities

Exercise may not be beneficial for improving attention or executive function

Higher intensity exercises may not be more beneficial than lower intensity exercises for improving cognition

Multimodal

Multimodal training refers to combinations of various types of interventions used simultaneously to produce better outcomes than the individual interventions could alone.

Five RCTs were found that used multimodal interventions. Two RCTs compared a combination physical exercise and cognitive training, to no additional training (Cheng et al. 2018; Matz et al. 2015). Two RCTs compared a combination of physical exercise and cognitive training to physical exercise alone (Bo et al. 2018; Kongkasuwan et al. 2016). One RCT compared home visits from nurses and mailed information to mailed information alone (Ostwald et al. 2014).

The methodological details and results of all fiveRCTs are presented in Table 6.

Table 6. RCTs evaluating multimodal interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Physical exercise + cognitive training vs standard care/no training		
Cheng et al. (2018) RCT (6) N$_{Start}$=168 N$_{End}$=136 TPS=Acute	E: Comprehensive rehabilitation therapy (patient and family education, cognitive training, rehabilitation training, regular check-ups) C: Conventional therapy Duration: 4 wks	• Montreal Cognitive Assessment (+exp) • Mini-Mental State Examination (-)
Matz et al. (2015) RCT (7) N$_{Start}$=202 N$_{End}$=146 TPS=Subacute	E: Motivational therapy + healthy diet + physical activity + cognitive training C: Standard care Duration: 24mo	• Alzheimer Disease Assessment Scale (-)
Physical exercise + cognitive training vs physical exercise alone		
Bo et al. (2018) RCT (6) Nstart = 225 Nend = 178 TPS = Subactue	E1: Computer-assisted cognitive training + physical exercise (3x/wk) E2: computer-assisted cognitive training (60min 3x/wk) E3: physical exercise (50min 3x/wk) C: Control (45min video documentaries, 3x/wk) Duration: 12 wks	E1 vs C: • Trail Making B (+exp1) • Stroop Test (+exp1) • Forward Digit Span (+exp1) • Mental Rotation Test (+exp1) E1 vs E2: • Trail Making B (-) • Stroop Test (-) • Forward Digit Span (-) • Mental Rotation Test (+exp1) E1 vs E3: • Trail Making B (-) • Stroop Test (-) • Forward Digit Span (+exp1) • Mental Rotation Test (+exp1)
Kongkasuwan et al. (2016) RCT (6) N$_{Start}$=118 N$_{End}$=113 TPS=NR	E: Physical therapy and art therapy C: Physical therapy only Duration: 1-2hr/d, 5d/wk for 4wk	• Abbreviated Mental Test (-) • Barthel Index (+exp)
Ostwald et al. (2014) RCT (5) N$_{Start}$=159 N$_{End}$=134 TPS=Chronic	E: Home visits from nurses and therapists, plus mailed letters containing information and resources C: Mailed letters containing information and resources only Duration: 70min/session, 16 sessions over 6mo	• Stroke Impact Scale Memory (-) • Functional Independence Measure-Cognitive (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about multimodal training

	EXECUTIVE FUNCTION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Exercise and cognitive training** may produce greater improvements in executive function than **standard care**.	1	Bo et al. 2018
1b	**Exercise and cognitive training** may not have a difference in efficacy when compared to **exercise alone, or cognitive training alone** for improving executive function.	1	Bo et al. 2018

	LEARNING AND MEMORY		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Exercise and cognitive training** may produce greater improvements in executive function than **standard care**.	1	Bo et al. 2018
1b	**Exercise and cognitive training** may produce greater improvements in executive function than **physical exercise alone**.	1	Bo et al. 2018
1b	**Exercise and cognitive training** may not have a difference in efficacy when compared to **cognitive training alone** for improving learning and memory.	1	Bo et al. 2018

	VISUOSPATIAL PERCEPTION AND ORIENTATION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Exercise and cognitive training** may produce greater improvements in visuospatial perception and orientation than **exercise alone, cognitive training alone, or standard care**.	1	Bo et al. 2018

	GLOBAL COGNITION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1a	**Exercise and cognitive training** may not have a difference in efficacy when compared to **standard care** for improving global cognition.	2	Cheng et al. 2018; Matz et al. 2015
1b	**Exercise and cognitive training** may not have a difference in efficacy when compared to **physical therapy alone** for improving global cognition.	1	Kongkasuwan et al. 2016

	ACTIVITIES OF DAILY LIVING		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Exercise and cognitive training** may produce greater improvements in activities of daily living than **exercise alone**.	1	Kongkasuwan et al. 2016

Key Points

The literature is mixed regarding multimodal interventions for improving cognitive rehabilitation

Music Therapy

Adopted from: https://steinhardt.nyu.edu/site/ataglance/2017/03/music-therapy-helps-with-recovery-post-stroke.html

Previous work has shown that an enriched multimodal environment produces better motor and cognitive outcomes post-stroke than an enriched motor environment alone (Maegele et al. 2005). In animal studies, they have found that an enriched auditory environment can produce enhanced cognitive functions such as learning and memory (Chikahisa et al. 2006). For humans, listening to music activates a wide array of brain regions past the auditory cortex, including frontal, parietal, temporal and subcortical structures (Sarkamo et al. 2008). For this reason, further enriching a stroke survivors' environment with music could help to improve several cognitive functions.

One RCT was found evaluating music therapy for cognitive rehabilitation. The RCT examined music therapy compared to only language listening and a no listening condition (Sarkamo et al. 2008)

The methodological details and results of the single RCT are presented in Table 7.

Table 7. RCTs evaluating music therapy interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Sarkamo et al. (2008) RCT (6) N$_{Start}$=60 N$_{End}$=54 TPS=Acute	E1: Music listening (≥1hr/d) E2: Language listening C: No listening material Duration: 6mo	• Rivermead Behavioural Memory Test (+exp$_1$) • Auditory List-Learning Task (-) • Digit Span Test (-) • Memory Interference Task (-) • Verbal Fluency Test (-) • Clock Drawing Test (-) • Benton Visual Retention Test (-) • Montreal Battery of Evaluation of Amusia (-) Frontal Assessment Battery (FAB): • Stroop Subtest and Mental Subtraction Test of FAB – Summed Correct Responses (+exp$_1$) • Stroop Subtest and Mental Subtraction Test of FAB – Reaction Times (-) • Vigilance Subtest of FAB – Correct Responses (-) • Simple Reaction Time Subtest of FAB – Reaction Time (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about music therapy

ATTENTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Music therapy** may not have a difference in efficacy when compared to **standard care** for improving attention.	1	Sarkamo et al. 2008

EXECUTIVE FUNCTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Music therapy** may not have a difference in efficacy when compared to **standard care** for improving executive function.	1	Sarkamo et al. 2008

LEARNING AND MEMORY			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Music therapy** may not have a difference in efficacy when compared to **standard care** for improving learning and memory.	1	Sarkamo et al. 2008

VISUOSPATIAL PERCEPTION AND ORIENTATION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Music therapy** may not have a difference in efficacy when compared to **standard care** for improving visuospatial perception and orientation.	1	Sarkamo et al. 2008

GLOBAL COGNITION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Music therapy** may not have a difference in efficacy when compared to **standard care** for improving global cognition.	1	Sarkamo et al. 2008

AMUSIA			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Music therapy** may not have a difference in efficacy when compared to **standard care** for improving amusia.	1	Sarkamo et al. 2008

Key Points

Music therapy may not be helpful for improving cognitive rehabilitation

Social and behavioural strategies
Board Games

Adopted from: https://www.sciencenews.org/article/subatomic-genius-games-chemistry-teacher-john-coveyou

Simple, cost effective, non-invasive, non-pharmacological interventions are constantly being sought after in a rehabilitation setting. The intervention in question should engage patients in verbal, sensory, motor and cognitive skills to help improve their recovery. Board games and puzzles are in fact able to satisfy these conditions. There are generally rules and strategies to consider, a motor component of physically playing, and often a social communication component as well. These types of activities effectively require a number of cognitive domains, and so theoretically could be used as therapy to help stroke survivors rehabilitate functions which have been impacted.

One RCT was found evaluating board games and puzzles for cognitive rehabilitation. The single RCT compared organized activity sessions and usual care to usual care alone (Rice et al. 2017).

The methodological details and results of the single RCT are presented in Table 8.

Table 8. RCTs evaluating board games and puzzles for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Rice et al. (2017) RCT (6) N$_{start}$=134 N$_{end}$=125 TPS =Acute Note: delirium population	E: board games/puzzles (15min, 2X/d) + standard care C: usual standardized care. Duration: 14d	• Montreal Cognitive Assessment (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about board games and puzzles

GLOBAL COGNITION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Board games and puzzles** may not have a difference in efficacy when compared to **standard care** for improving global cognition.	1	Rice et al. 2017

Key Points

Board games and puzzles may not be helpful for improving global cognition

Pager Prompting System

Adopted from: https://www.cbc.ca/news/technology/telus-may-be-closing-its-pager-network-but-the-beeper-isn-t-dead-yet-1.2929237

With respect to cognitive rehabilitation, the majority of the interventions can be seen as compensatory as opposed to restorative. External strategies and aids can be used in conjunction with any internal strategies and ongoing cognitive rehabilitation to further ameliorate the everyday consequences of the deficits. Electronic aids such as phone calendars, reminders and alarms can be extremely effective, and have increased in availability. Pagers, although falling out of use, are the simplest form of electronic memory aid, and can be used even with significantly impaired individuals. Paging systems have been found to be effective memory aids in impaired individuals (Wilson et al, 2001), but their efficacy with respect to stroke specifically has not been firmly established.

One RCT was found evaluating a pager prompting system for cognitive rehabilitation. The single RCT compared the pager system to standard rehabilitation (Fish et al. 2008).

The methodological details and results of the single RCT are presented in Table 9.

Table 9. RCTs evaluating pager prompting systems for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Fish et al. (2008) RCT Crossover (5) N$_{Start}$=36 N$_{End}$=36 TPS=Chronic (this is a follow-up analysis of Wilson et al.2001)	E: Pager prompting system C: Waiting list/No pager Duration: 11wks	• Personalized Target Behaviours (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about pager prompting systems

	ACTIVITIES OF DAILY LIVING		
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Pager prompting systems** may produce greater improvements in activities of daily living than **usual care**.	1	Fish et al. 2008

Key Points

Pager prompting systems may be beneficial for improving activities of daily living

Occupational Workplace Intervention

After a stroke, returning to work is no easy task. For many younger, previously working stroke survivors, returning to work is of significant importance for quality of life, and life satisfaction (Vestling, Tufvesson & Iwarsson, 2003). Standard rehabilitation usually consists of occupational therapy in some capacity, for those patients who would benefit from it. Much of the therapy consists within a hospital, care center or patient's home. Alternatively, occupational therapy occurring at the workplace, provides an environment where training can be directly transferred to the workplace.

One RCT was found evaluating direct occupational workplace interventions. The single RCT compared this occupational workplace therapy to standard care (Ntsiea et al. 2015).

The methodological details and results of the single RCT are presented in Table 10.

Table 10. RCTs evaluating occupational workplace interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Ntsiea et al. (2015) RCT (6) N$_{Start}$=80 N$_{End}$=72 TPS=Acute	E: Occupational workplace intervention C: Standard care Duration: tailored to patient	• Return to Work (+exp) • Barthel Index (-) • Montreal Cognitive Assessment (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about occupational workplace interventions

	GLOBAL COGNITION		
LoE	Conclusion Statement	RCTs	References
1b	**Occupational workplace interventions** may not have a difference in efficacy when compared to **standard care** for improving global cognition.	1	Ntsiea et al. 2015

|	ACTIVITIES OF DAILY LIVING		
LoE	Conclusion Statement	RCTs	References
1b	**Occupational workplace interventions** may not have a difference in efficacy when compared to **standard care** for activities of daily living.	1	Ntsiea et al. 2015

Key Points

Occupational workplace intervention may be beneficial for improving activities of daily living, but not global cognition

Error and Errorless training
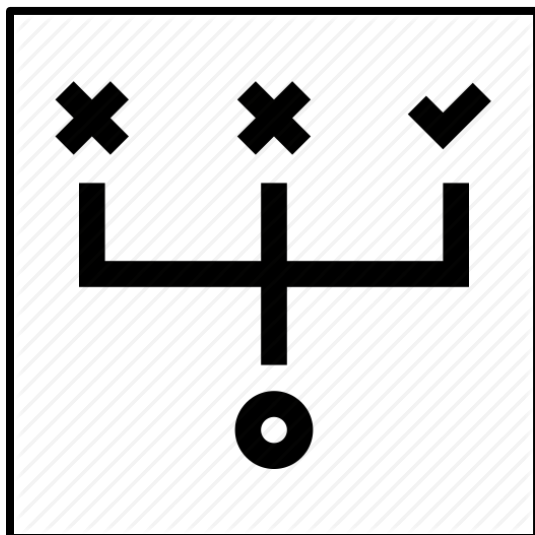
Adopted from: https://www.iconfinder.com/icons/500159/choice_issue_solving_strategy_tactic_trial_and_error_workflow_icon

One can categorize a given training regime into one of two types. Some training is trial and error, where errors are not only acceptable but are often seen as the actual point of learning. On the contrast, training can be errorless, where the nature of the tasks does not allow for errors to made, and instead correct methods are explained thoroughly and attempted every time. Previous work on non-stroke related populations have shown that errorless training appears to be more effective when training people with pre-existing cognitive deficits. By learning more about which methods of training are more effective specifically within a stroke population, care workers can hopefully improve cognitive rehabilitation and increase its effectiveness.

One RCT was found evaluating error training compared to errorless training for cognitive rehabilitation (Mount et al. 2007).

The methodological details and results of the single RCT are presented in Table 11.

Table 11. RCTs evaluating trial and error interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Mount et al. (2007) RCT Crossover (4) N$_{Start}$=47 N$_{End}$=33 TPS=Acute	E1: Trial and error training E2: Errorless training Duration: 2 sessions/d for 7d	• Incidence Rate of Retention (-) • Carry-over for Wheelchair Task (-) • Carry-over for Sock Donning Task (+exp1)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about trial and error training

	LEARNING AND MEMORY		
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Trial and error training** may not have a difference in efficacy when compared to **errorless training** for improving learning and memory.	1	Mount et al. 2007

	ACTIVITIES OF DAILY LIVING		
LoE	**Conclusion Statement**	**RCTs**	**References**
2	There is conflicting evidence about the effect of t**rial and error learning** to improve activities of daily living when compared to **errorless training**.	1	Mount et al. 2007

Key Points

Trial and error training may not have greater efficacy than errorless training for improving cognitive rehabilitation

Problem solving therapy

Problem solving therapy is a psychosocial intervention that can be used to help an individual better cope with their environment. The therapy revolves around creating strategies that focus on how to break down complex tasks into smaller, manageable parts. This can be particularly successful for those individuals who have experienced a cognitive deficit post-stroke, and whose ability to perform complex tasks has been disrupted. Although this therapy is not restorative of cognitive function, it could help an individual functionally cope better with the challenges they may face throughout their day.

One RCT was found evaluating problem solving therapy for cognitive rehabilitation. The single RCT compared problem solving therapy to a standard care group (Hadidi et al. 2015)

The methodological details and results of the single RCT are presented in Table 12.

Table 12. RCTs evaluating problem solving therapy for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Hadidi et al. (2015) RCT (8) N$_{Start}$=22 N$_{End}$=22 TPS=Acute	E: Problem-solving therapy C: No additional therapy Duration: 1.5hr/wk for 10wk	• Functional Independence Measure (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
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+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about problem solving therapy

	ACTIVITIES OF DAILY LIVING		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Problem solving therapy** may not have a difference in efficacy when compared to **usual care** for improving activities of daily living.	1	Hadidi et al. 2015

Key Points

Problem solving therapy may not be beneficial for improving activities of daily living

Computer-based Cognitive Training

Adopted from: https://news.northwestern.edu/stories/2019/03/stroke-rehab-game/

Traditionally, therapist's physical interactions with a patient were necessary for rehabilitating several different functions. As the strain on hospital resources continues to grow, having physical interactions with a therapist become more difficult, and patient care subsequently suffers. As technology continues to progress, more opportunities are available to use this technology to aid in therapy and rehabilitation as an adjunct or replacement for a human interaction. A computer-based approach is generally more accessible and cost-effective than the same session under the direction of a human therapist. For this reason, computer-based rehabilitation can free up more hospital resources and allow patients to begin rehabilitation as quickly as possible. Furthermore, patients can take a more involved role in their own care, and training can theoretically be performed as often, and whenever the patient wants..

Seven RCTs were found evaluating computer-based interventions for cognitive rehabilitation. Four of these RCTs compared computer-based rehabilitation to usual care or no treatment (van de Ven et al. 2017a; van de Ven et al. 2017b; Zucchella et al. 2014; Prokopenko et al. 2013). Three RCT compared a computer-based rehabilitation to a non-computer-based therapy (De Luca et al. 2018; Poulin et al. 2016; Wentink et al. 2016).

The methodological details and results of all seven RCTs are presented in Table 13.

Table 13. RCTs evaluating computer-based interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Computer-based therapy vs standard care		
van de Ven et al. (2017a) RCT (7) N$_{Start}$=97 N$_{End}$=80 TPS=Chronic	E: Computer-based cognitive flexibility tasks (30min 5X/wk) C1: Mock training (tasks with no expected cognitive benefit) C2: Waiting list group (usual care) Duration: 12 wks	• Trail Making Test B (-) • Category Fluency and Letter Fluency Tasks (-) • Tower of London (-) • Letter-Number Sequencing (-)
van de Ven et al. (2017b) RCT (7) N$_{Start}$=97 N$_{End}$=80 TPS=Chronic	E: Computer-based cognitive flexibility tasks (30min 5X/wk) C1: Mock training (tasks with no expected cognitive benefit) C2: Waiting list group (usual care) Duration: 12 wks	• Cognitive Failure Questionnaire (-) • Dysexecutive Functioning Questionnaire (-) • Lawton and Brody Instrumental Activities of Daily Living Scale (-)
Zucchella et al. 2014 RCT (7) N$_{start}$= 92 N$_{end}$= 87 TPS=Acute	E: Therapist guided computer exercises (1hr sessions, 4x/wk) C: Sham training Duration: 4 weeks	• Mini-mental state examination (+exp) • Digit span (-) • Corsi's test (-) • Rey Auditory verbal learning test (immediate recall) (-) • Rey Auditory verbal learning test (delayed recall) (+exp) • Logical memory (immediate recall) (+exp) • Logical memory (delayed recall) (+exp) • Progressive matrices 47 (-) • Frontal assessment battery (-) • Trail making test A (+exp) • Trail making test B (+exp) • Attentive matrices (+exp) • Phonological fluency (-) • Semantic fluency (-) • Rey-Osterrieth figure copy (-) • Functional independence measure (-)
Prokopenko et. Al. (2013) RCT (7) N$_{Start}$=43 N$_{End}$=43 TPS=Acute	E: Computer-based training + Standard care C: Standard care Duration: 25-35min/d for 14d	• Frontal Assessment Battery (+exp) • Clock Drawing Test (+exp) • Schulte's Tests (+exp) • Mini Mental State Exam (-) • Montreal Cognitive Assessment (-)
Computer-based training vs non-computer-based cognitive training		
De Luca et al. (2018) RCT (6) N$_{Start}$=35 N$_{End}$ =35 TPS=Subacute	E: computer assisted cognitive rehabilitation + standard cognitive rehabilitation (45 min sessions 6x/wk) C: standard cognitive rehabilitation Duration: 8 wks	• Mini-mental State Examination (-) • Semantic Verbal Fluency (-) • Phonemic Verbal Fluency (-) • Attentive Matrices (-) • Rey Auditory Visual Learning Immediate (-) • Rey Auditory Visual Learning Delayed (-) • Digit Span (-) • Ravens Colored Progressive Matrices (-)
Poulin et al. (2016) RCT (6) N$_{Start}$=11 N$_{End}$=9 TPS=Chronic	E1: Cognitive Orientation to daily Occupational Performance (CO-OP) (1hr sessions 2x/wk) E2: Computerized executive function training (1hr sessions 2x/wk) Duration: 8 wks	• Trail Making Test A (-) • Trail Making Test B (-) • Colour-Word Interference Test (-) • Digit Span Sequencing (-) • Digit Span Forward (-) • Digit Span Backward (-)

Wentink et al. (2016) RCT (10) N_{Start}=115 N_{End}=107 TPS=Chronic	E: Luminosity computer training C: Stroke Info group Duration: 15-20min/d, 5d/wk for 8wk	• Corsi Forward Block Span (Block Tapping) Test (+exp) • Corsi Backward Block Span (Block Tapping) Test (-) • Forward Digit Span Test (-) • Backwards Digit Span Test (-) • Trail-making Test A (-) • Trail-making Test B (-) • Flanker Task Congruent Reaction Time (-) • Flanker Task Incongruent Reaction Time (+exp) • Raven's Progressive Matrices (-) • Cognitive Failures Questionnaire (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
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- indicates no statistically significant between groups differences at α=0.05

Conclusions about computer-based cognitive training

ATTENTION

LoE	Conclusion Statement	RCTs	References
1a	**Computer-based therapy** may produce greater improvements in attention than **standard care**.	2	Zucchella et al. 2014; Prokopenko et al. 2013
1a	**Computer-based therapy** may not have a difference in efficacy when compared to **non-computer-based cognitive therapy** for improving attention.	3	De Luca et al. 2018; Poulin et al. 2016; Wetnik et al. 2016

EXECUTIVE FUNCTION

LoE	Conclusion Statement	RCTs	References
1a	**Computer-based therapy** may not have a difference in efficacy when compared to **standard care** for improving executive function.	4	Van de Ven et al. 2017; Van de Ven et al. 2017b; Zucchella et al. 2014; Prokopenko et al. 2013
1a	**Computer-based therapy** may not have a difference in efficacy when compared to **non-computer-based cognitive therapy** for improving executive function.	3	De Luca et al. 2018; Poulin et al. 2016; Wetnik et al. 2016

LEARNING AND MEMORY

LoE	Conclusion Statement	RCTs	References
1b	There is conflicting evidence about the effect of **Computer-based therapy** to improve learning and memory when compared to **standard care.**	1	Zucchella et al. 2014;
1a	**Computer-based therapy** may not have a difference in efficacy when compared to **non-computer-based cognitive therapy** for improving learning and memory.	3	De Luca et al. 2018; Poulin et al. 2016; Wetnik et al. 2016

VISUOSPATIAL PERCEPTION AND ORIENTATION

LoE	Conclusion Statement	RCTs	References
1a	**Computer-based therapy** may not have a difference in efficacy when compared to **standard care** for improving visuospatial perception and orientation.	1	Zucchella et al. 2014

GLOBAL COGNITION

LoE	Conclusion Statement	RCTs	References
1a	**Computer-based therapy** may not have a difference in efficacy when compared to **standard care** for improving global cognition.	3	Van de Ven et al. 2017b; Zucchella et al. 2014; Prokopenko et al. 2013
1a	**Computer-based therapy** may not have a difference in efficacy when compared to **non-computer-based cognitive therapy** for improving global cognition.	2	De Luca et al. 2018; Wetnik et al. 2016

ACTIVITIES OF DAILY LIVING			
LoE	**Conclusion Statement**	**RCTs**	**References**
1a	**Computer-based therapy** may not have a difference in efficacy when compared to **standard care** for improving activities of daily living.	2	Van de Ven et al. 2017b; Zucchella et al. 2014

Key Points

The literature is mixed regarding computer-based training for improving attention

Computer -based training may not be helpful for improving executive function or global cognition

Virtual Reality Training

Adopted from https://www.hvhcc.com/services

Virtual reality (VR) is a technology that allows individuals to experience and interact with virtual environments, often through a game. VR simulates life-like learning and can be used to increase intensity of training while providing three-dimensional feedback of a visual, sensory, and auditory nature (Saposnik et al. 2010). VR tools are classified as either immersive (i.e. three-dimensional environment via head-mounted display) or non-immersive (i.e. two-dimensional environment via conventional computer monitor or projector screen). Customized VR programs have been created and tested in rehabilitation research, although commercial gaming consoles (e.g. Nintendo Wii) have also been used to deliver VR training.

Four RCTs were found evaluating virtual reality for cognitive rehabilitation. Two RCTs examined virtual reality compared to standard care (Faria et al. 2018; Gamito et al. 2017). One RCT examined virtual reality with computer training compared to computer training alone (Kim et al. 2011). One RCT looked at active participation within the virtual environment compared to passive (Rose et al. 1999).

The methodological details and results of all four RCTs evaluating virtual reality are presented in Table 14.

Table 14. RCTs evaluating virtual reality interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Virtual reality vs conventional therapy		
Faria et al. (2018) RCT (3) N$_{Start}$=32 N$_{End}$=24 TPS=Chronic	E: Virtual reality (Reh@Task) + conventional therapy (45min X 3/wk) C: Conventional therapy. Duration: 1mo	• Montreal Cognitive Assessment (-) • Barthel Index (-)
Gamito et al. (2017) RCT (3) N$_{Start}$=20 N$_{End}$=20 TPS=Subacute	E: 60-min sessions of a virtual reality-based cognitive training (cognitively demanding tasks in immersice virtual environment). C: No training Duration: 2-3 sessions/ wk, 4-6 wks	• Wechsler Memory Scale – 3rd edition (+exp) • Rey Complex Figure (-) • Toulouse–Pieron Test (-)
Virtual reality vs computer-based training		
Kim et al. (2011) RCT (5) N$_{Start}$=28 N$_{End}$=28 TPS=Acute	E: Virtual reality training (IREX System ®)+ Computer-based training C: Computer-based training only Duration: 30min/d, 5d/wk for 4wk	• Korean Mini Mental State Exam (-) • Visual Continuous Performance Test (+exp) • Auditory Continuous Performance Test (-) • Word of Color Word in Word-color Test (-) • Color of Color Word in Word-color test (-) • Forward Digit Span Test (-) • Backward Visual Span Test (+exp) • Visual & Verbal Learning Tests (-) • Trail-making Test A (-) • Tower of London test (-) • Korean Modified Barthel Index (-)
Active vs passive participation in virtual environment		
Rose et al. (1999) RCT crossover (5) N$_{Start}$=96 N$_{End}$=96 TPS=NR	E: Stroke, active participation in virtual environment training (exploring a bungalow to find an object) C: Stroke, passive participation in virtual environment training (observing the bungalow to find an object) Duration: 1 session	• Spatial Layout (+exp) • Object Recognition (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
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- indicates no statistically significant between groups differences at α=0.05

Conclusions about virtual reality training

<table>
<tr><td colspan="4">**ATTENTION**</td></tr>
<tr><td>**LoE**</td><td>**Conclusion Statement**</td><td>**RCTs**</td><td>**References**</td></tr>
<tr><td>**2**</td><td>**Virtual reality** may not have a difference in efficacy when compared to **computer-based therapy** for improving attention.</td><td>1</td><td>Kim et al. 2011</td></tr>
</table>

<table>
<tr><td colspan="4">**EXECUTIVE FUNCTION**</td></tr>
<tr><td>**LoE**</td><td>**Conclusion Statement**</td><td>**RCTs**</td><td>**References**</td></tr>
<tr><td>**2**</td><td>**Virtual reality therapy** may not have a difference in efficacy when compared to **computer-based training** for improving executive function.</td><td>1</td><td>Kim et al. 2011</td></tr>
</table>

<table>
<tr><td colspan="4">**LEARNING AND MEMORY**</td></tr>
<tr><td>**LoE**</td><td>**Conclusion Statement**</td><td>**RCTs**</td><td>**References**</td></tr>
<tr><td>**2**</td><td>**Virtual reality therapy** may produce greater improvements in learning and memory than **standard care**.</td><td>1</td><td>Gamito et al. 2017</td></tr>
<tr><td>**2**</td><td>**Active virtual reality participation** may not have a difference in efficacy when compared to **passive virtual reality participation** for improving learning and memory.</td><td>1</td><td>Rose et al. 1999</td></tr>
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<tr><td>**2**</td><td>**Active virtual reality therapy participation** may produce greater improvements in visuospatial perception and orientation than to **passive virtual reality participation**.</td><td>1</td><td>Rose et al. 1999</td></tr>
<tr><td>**2**</td><td>**Virtual reality therapy** may not have a difference in efficacy when compared to **standard care** for improving visuospatial perception and orientation.</td><td>1</td><td>Gamito et al. 2017</td></tr>
<tr><td>**2**</td><td>**Virtual reality therapy participation** may not have a difference in efficacy when compared to **computer-based training** for improving visuospatial perception and orientation.</td><td>1</td><td>Kim et al. 2011</td></tr>
</table>

GLOBAL COGNITION			
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Virtual reality therapy** may not have a difference in efficacy when compared to **standard care** for improving global cognition.	1	Faria et al. 2018
2	**Virtual reality therapy** may not have a difference in efficacy when compared to **computer-based training** for improving global cognition.	1	Kim et al. 2011

ACTIVITIES OF DAILY LIVING			
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Virtual reality therapy** may not have a difference in efficacy when compared to **standard care** for improving activities of daily living.	1	Faria et al. 2018
2	**Virtual reality therapy** may not have a difference in efficacy when compared to **computer-based training** for improving activities of daily living.	1	Kim et al. 2011

Key Points

Virtual reality may not be beneficial for improving cognition

Repetitive Transcranial Magnetic Stimulation (rTMS)

Transcranial magnetic stimulation is a painless and non-invasive method of affecting neural activity through the exogenous generation of an electromagnetic field through a coil placed on the scalp, that consequently induces a change in the electrical fields of the brain (Peterchev et al. 2012). The voltage and current of the electromagnetic field generated are dependent on the parameters of the stimulation device, which is not distorted by the biological tissues in which it is applied in (Peterchev et al. 2012). The neuromodulatory effects of transcranial magnetic stimulation are attributed largely to neural membrane polarization shifts that can lead to changes in neuron activity, synaptic transmission, and activation of neural networks (Peterchev et al. 2012). Repetitive transcranial magnetic stimulation (rTMS) is the application of repetitive trains of transcranial magnetic stimulation at regular intervals.

After a stroke, interhemispheric competition is altered; with cortical excitability increasing in the unaffected hemisphere and decreasing in the affected hemisphere (Zhang et al. 2017). rTMS can be used to help modulate this interhemispheric competition, with low stimulation frequencies (≤1Hz) decreasing cortical excitability and inhibiting activity of the contralesional hemisphere, while high frequency (>1Hz) stimulation increases excitability and have a facilitatory effect on activity of the ipsilesional hemisphere (Dionisio et al. 2018).

Three RCTs were found evaluating rTMS for cognitive rehabilitation. Two RCTs examined rTMS compared to a sham condition (Lu et al. 2015; Kim et al. 2010). One RCT compared rTMS over prefrontal cortex versus rTMS over motor cortex (Rektorova et al. 2005)

The methodological details and results of all three RCTs are presented in Table 15.

Table 15. RCTs evaluating rTMS interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
rTMS compared to sham		
Lu et al. (2015) RCT (6) N$_{Start}$=54 N$_{End}$=50 TPS=Subacute	E: Low-frequency (1Hz) rTMS C: Sham therapy Duration: 1 session/d, 5d/wk for 4wk	• Montreal Cognitive Assessment (+exp) • Loewenstein Occupational Therapy Cognitive Assessment (+exp) • Rivermead Behavior Memory Test (+exp)
Kim et al. (2010) RCT (8) N$_{Start}$=18 N$_{End}$=18 TPS=Subacute	E1: High-frequency rTMS (10Hz) E2: Low-frequency rTMS (1Hz) C: Sham rTMS Duration: 5 sessions/wk for 5wk	E1 vs E2/C: • Tower of London Test (-) • Forward Digit Span (-) • Backward Digit Span (-) • Verbal Learning Test (-) • Visual Learning Test (-) • Auditory Continuous Performance Test (-) • Visual Continuous Performance Test (-) • Word of Color Word Test (-) • Color of Color Word Test (-) • Modified Barthel Index (-) E2 vs C: • Tower of London Test (-) • Forward Digit Span (-) • Backward Digit Span (-) • Verbal Learning Test (-) • Visual Learning Test (-) • Auditory Continuous Performance Test (-) • Visual Continuous Performance Test (-) • Word of Color Word Test (-) • Color of Color Word Test (-) • Modified Barthel Index (-)
rTMS over prefrontal cortex vs motor cortex		
Rektorova et al. (2005) RCT crossover (6) N$_{Start}$=7 N$_{End}$=7 TPS=Chronic	E1: High-frequency rTMS over left dorsolateral prefrontal cortex E2: High-frequency rTMS over left motor cortex Duration: 1 session in each condition, 4d apart	• Stroop Test (+exp$_1$) • Wechsler Adult Intelligence Scale-R (-) • Trail-Making Test A (-) • Rey-Osterrieth Complex Figure Test – Copy (-) • Rey-Osterrieth Complex Figure Test – Immediate recall (-) • Rey-Osterrieth Complex Figure Test – Delayed Recall (-) • Trail-Making Test B (-) • Letter Verbal Fluency Test (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about rTMS

ATTENTION

LoE	Conclusion Statement	RCTs	References
1b	**High frequency and low frequency rTMS** may not have a difference in efficacy when compared to **usual care** for improving attention.	1	Kim et al. 2010
1b	**rTMS over dorsolateral prefrontal cortex** may not have a difference in efficacy when compared to **rTMS over motor cortex** for improving attention.	1	Rektorova et al. 2005

EXECUTIVE FUNCTION

LoE	Conclusion Statement	RCTs	References
1b	**High frequency and low frequency rTMS** may not have a difference in efficacy when compared to **usual care** for improving executive function.	1	Kim et al. 2010
1b	**rTMS over dorsolateral prefrontal cortex** may not have a difference in efficacy when compared to **rTMS over motor cortex** for improving executive function.	1	Rektorova et al. 2005

LEARNING AND MEMORY

LoE	Conclusion Statement	RCTs	References
1a	There is conflicting evidence about the effect of **High frequency and low frequency rTMS** to improve learning and memory when compared to **usual care**.	2	Lu et al. 2015; Kim et al. 2010
1b	**rTMS over dorsolateral prefrontal cortex** may not have a difference in efficacy when compared to **rTMS over motor cortex** for improving learning and memory.	1	Rektorova et al. 2005

VISUOSPATIAL PERCEPTION AND ORIENTATION

LoE	Conclusion Statement	RCTs	References
1b	**rTMS over dorsolateral prefrontal cortex** may not have a difference in efficacy when compared to **rTMS over motor cortex** for improving visuospatial perception and orientation.	1	Rektorova et al. 2005

GLOBAL COGNITION

LoE	Conclusion Statement	RCTs	References
1b	**Low frequency rTMS** may produce greater improvements in global cognition than **standard care**.	1	Lu et al. 2015
1b	**rTMS over dorsolateral prefrontal cortex** may not have a difference in efficacy when compared to **rTMS over motor cortex** for improving global cognition.	1	Rektorova et al. 2005

ACTIVITIES OF DAILY LIVING			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**High frequency and low frequency rTMS** may not have a difference in efficacy when compared to **usual care** for improving activities of daily living.	1	Kim et al. 2010

Key Points

rTMS may not be beneficial for improving cognitive rehabilitation

Transcranial Direct-current Stimulation (tDCS)

Adopted from: https://tryniakaufman.com/2018/01/11/transcranial-direct-current-stimulation-the-drug-of-the-future/
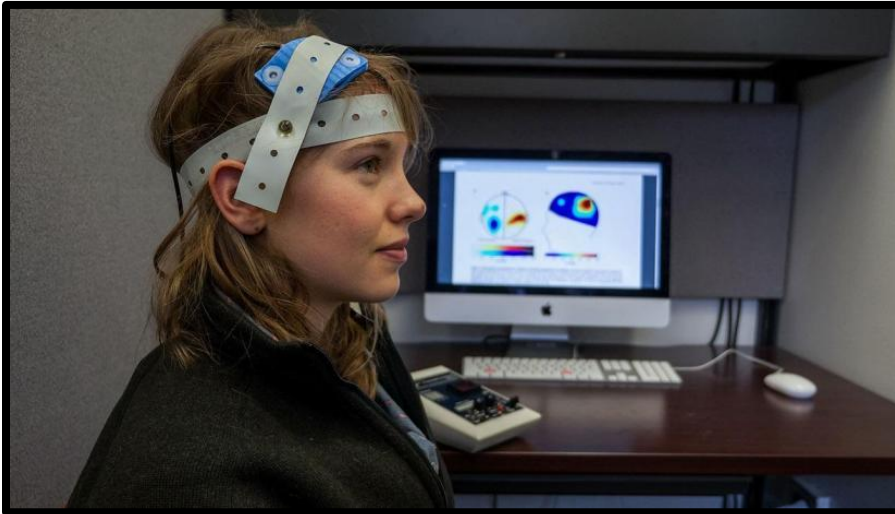
Another form of non-invasive brain stimulation is transcranial direct-current stimulation (tDCS). This procedure involves the application of mild electrical currents (1-2 mA) conducted through two saline-soaked, surface electrodes applied to the scalp, overlaying the area of interest and the contralateral forehead above the orbit. Anodal stimulation is performed over the affected hemisphere and increases cortical excitability, while cathodal stimulation is performed over the unaffected hemisphere and decreases cortical excitability (Alonso-Alonso et al. 2007). Additionally, tDCS can be applied on both hemispheres concurrently, this is known as dual tDCS. In contrast to transcranial magnetic stimulation, tDCS does not induce action potentials, but instead modulates the resting membrane potential of the neurons (Alonso-Alonso et al. 2007).

Two RCTs were found evaluating tDCS for cognitive rehabilitation. The two RCTs examined anodal tDCS compared to a sham condition (Kang et al. 2009; Jo et al. 2009)

The methodological details and results of the two RCTs are presented in Table 16.

Table 16. RCTs evaluating tDCS interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Kang et al. (2009) RCT Crossover (8) N$_{Start}$=20 N$_{End}$=20 TPS=Variable	E: Anodal tDCS C: Sham tDCS Duration: 1 session in each condition, ≥2d apart	• Go/No Go Test Response Accuracy (-) • Go/No Go Test Correct Responses (-)
Jo et al. (2009) RCT crossover (7) N$_{Start}$=10 N$_{End}$=10 TPS=Subacute	E: Anodal tDCS C: Sham tDCS Duration: 30min/session, 1 session in each condition, 48hr apart	• Working Memory Task Accuracy (+exp) • Working Memory Task Response Time (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about tDCS

EXECUTIVE FUNCTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**tDCS** may not have a difference in efficacy when compared to **usual care** for improving executive function.	1	Kang et al. 2009

LEARNING AND MEMORY			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	There is conflicting evidence about the effect of **tDCS** to improve learning and memory when compared to **usual care**.	1	Jo et al. 2009

Key Points

tDCS may not be beneficial for improving cognitive rehabilitation

Pharmaceuticals

Antihypertensives

Many blood pressure reduction trials have been conducted and, while some report the effects of treatment on cognition outcomes, cognition is typically treated as a secondary outcome or project. In the Epidemiology of Vascular Aging Study, Tzourio et al. (1999) reported that 8.5% of participants experienced cognitive decline over the 4-year study period. The odds for cognitive decline were almost three times greater among individuals with high blood pressure than among normotensive participants. In a study of a sample of 2,212 community dwelling African Americans aged 65 years and older, Richards et al. (2000) determined that antihypertensive medications alone were associated with a significant reduction in the risk for cognitive impairment with the exception of centrally-acting sympatholytics. This particular class of drugs was associated with a significant increase in the risk for cognitive impairment. Results from the Honolulu Asia Aging Study, Peila et al. (2006) demonstrated that, in hypertensive men, duration of treatment is also associated with reduction in risk for incident dementia. The contribution of hypertension to the risk for dementia post-stroke may be masked, in part, by its large contribution to the risk for stroke. The slow development of cognitive impairment related to the presence of hypertension is greatly augmented by the presence of stroke. Reduction of hypertension could reduce the risk for cognitive decline by preventing further cardio or cerebrovascular disease (Mackowiak-Cordoliani et al. 2005; Williams, 2004).

Six RCTs were found evaluating antihypertensive medications for cognitive rehabilitation. Four RCTs compared antihypertensive medication to a placebo, or usual care (Bu et al. 2016; Ihle-Hansen et al. 2014; Diener et al. 2008; Tzourio et al. 2003). One RCT examined antihypertensive medication against cholesterol lowering medication (Bath et al. 2017). One RCT examined one antihypertensive (nitrendipine) against another (eprosartan) (Schrader et al. 2005).

The methodological details and results of all six RCTs are presented in Table 17.

Table 17. RCTs evaluating antihypertensive interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Antihypertensive medication compared to placebo or standard care		
Bu et al. (2016) RCT (8) N$_{Start}$=660 N$_{End}$=638 TPS=Acute	E: Antihypertensive treatment while in hospital C: Discontinuation of antihypertensive treatment while in hospital Duration: 3mo	• Mini-mental State Examination (-) • Montreal Cognitive Assessment (-)
Ihle-Hansen et al. (2014) RCT (8) N$_{Start}$=195 N$_{End}$=178 TPS=Acute	E: Pharmacological support including antihypertensive, anti-diabetic, statin, and vitamin B complex prescriptions; nutritional advice and optimised medical treatment C: Usual Care Duration: 1yr	• Trail-Making Test A (-) • 10 Word Recall Test (-)
PRoFESS Study Group Diener et al. (2008) RCT (10) N$_{Start}$=20332 N$_{End}$=18712 TPS=Subacute	E1: Telmisartan (80mg/d) + Aspirin (25mg 2/d) + Extended-release Dipyridamole (200mg 2/d) E2: Telmisartan (80mg/d) + Clopidogrel (75mg/d) E3: Placebo + Aspirin (25mg 2/d) + Extended-release Dipyridamole (200mg 2/d) E4: Placebo + Clopidogrel (75mg/d) Duration: 2.5yr	• Mini Mental State Exam (-) • Barthel Index (-)
PROGRESS Tzourio et al. (2003) RCT (8) N$_{Start}$=6105 N$_{End}$=5888 TPS=Chronic	E: Perindopril (4mg/d) (+ Indapamide 2-2.5mg/d) C: Placebo Duration: 3.9yr	• Mini Mental State Exam (+exp)
Antihypertensive medication compared to cholesterol medication		
Bath et al. (2017) RCT (6) N$_{Start}$=83 N$_{End}$=83 TPS= chronic	E1: intensive blood pressure lowering (target SBP <125 mmHg) via oral medication E2: guideline blood pressure lowering (target SBP <140 mmHg) via oral medication. E3: intensive lipid lowering (target LDL-cholesterol <1.3mmol/l) via oral medication E4: guideline lipid lowering (target LDL-c <3.0) via oral medication. Duration: 6mo Of note: E3 and E4 are given to a subset of the study population with ischemic stroke, and they receive both anti-hypertensive and lipid lowering therapy.	E1 and E2 (BP Group) vs E3 and E4 (Lipid Group): • Addenbrooke's Cognitive Examination-Revised (-) E1 vs. E2: • Addenbrooke's Cognitive Examination-Revised (-) • Stroop test (-) • Trail-Making Tests A (-) • Trail-Making Tests B (-) • Category Fluency (animal naming) (-) • Mini-Mental State Examination (-) • Telephone Interview for Cognition Scale-Modified (-) • Informant Questionnaire for Cognitive Decline in the Elderly (-) • Barthel index (-) E3 vs. E4: • Addenbrooke's Cognitive Examination-Revised (-) • Stroop test (+exp3) • Trail-Making Tests A (+exp3) • Trail-Making Tests A (-) • category fluency (+exp3) • Mini-Mental State Examination (-) • Telephone Interview for Cognition Scale-Modified (-)

		• premorbid cognitive function assessed in an informant interview using the IQCODE (-) • Barthel index (-)
Nitrendipine compared to Eprosartan		
MOSES Schrader et al. (2005) RCT (8) N_{Start}=1405 N_{End}=1352 TPS=Chronic	E1: Nitrendipine (10mg/d) E2: Eprosartan (600mg/d) Duration: 2.5yr	• Mini Mental State Exam (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.

+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group

+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group

+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group

- indicates no statistically significant between groups differences at α=0.05

Conclusions about antihypertensives

LoE	Conclusion Statement	RCTs	References
ATTENTION			
1b	**Intensive lipid lowering** may produce greater improvements in attention than **guideline lipid lowering**.	1	Bath et al. 2017
1b	**Intensive blood pressure lowering** may not have a difference in efficacy when compared to **guideline blood pressure lowering** for improving attention.	1	Bath et al. 2017
1b	**Antihypertensive medication** may not have a difference in efficacy when compared to **usual care** for improving attention.	1	Ilhe-Hansen et al. 2014

LoE	Conclusion Statement	RCTs	References
EXECUTIVE FUNCTION			
1b	**Intensive lipid lowering** may produce greater improvements in executive function than **guideline lipid lowering**.	1	Bath et al. 2017
1b	**Intensive blood pressure lowering** may not have a difference in efficacy when compared to **guideline blood pressure lowering** for improving executive function.	1	Bath et al. 2017

LoE	Conclusion Statement	RCTs	References
LEARNING AND MEMORY			
1b	**Antihypertensive medication** may not have a difference in efficacy when compared to **usual care** for improving learning and memory.	1	Ilhe-Hansen et al. 2014

LoE	Conclusion Statement	RCTs	References
GLOBAL COGNITION			
1b	**Nitrendipine** may not have a difference in efficacy when compared to **eprosartan** for improving global cognition.	1	Schrader et al. 2005
1a	**Antihypertensive medication** may not have a difference in efficacy when compared to **usual care** for improving global cognition.	3	Bu et al. 2016; Diener et al. 2008; Tzourio et al. 2003
1b	**Intensive blood pressure and lipid lowering** may not have a difference in efficacy when compared to **guideline blood pressure and lipid lowering** for improving global cognition.	1	Bath et al. 2017

ACTIVITIES OF DAILY LIVING			
LoE	Conclusion Statement	RCTs	References
1b	**Antihypertensive therapy** may not have a difference in efficacy when compared to **a placebo** for improving activities of daily living.	1	Diener et al. 2008
1b	**Intensive blood pressure and lipid lowering** may not have a difference in efficacy when compared to **guideline blood pressure and lipid lowering** for improving activities of daily living.	1	Bath et al. 2017

Key Points

Intense lipid lowering may be beneficial for improving attention and executive function.

Antihypertensive medication may not be beneficial for improving cognitive rehabilitation

Actovegin

Actovegin is a protein free hemodyslate that is extracted from calf's blood via ultrafiltration. The drug is produced by an Austrian pharmaceutical company Nymngen. Although not approved by the FDA and other drug-related health and safety administrations, it has been used in many post-Soviet countries and China for over half a century (Lee et al. 2011). In the literature, Actovegin has shown to increase oxygen absorption and utilization (Obermaier-Kusser et al. 1989; Buchmayer et al. 2011) synergistic increases in cell proliferation and activity (Schönwald et al. 1991), increased glucose transport and subsequent metabolism and insulin like activity (Jacob et al. 1996) and neuroprotective features (Derev'yannykh et al. 2008). Because of this profile, it has been used to treat cerebrovascular disorders, such as dementia (Schaffler, Wauschkuhn, & Häuser, 1991). In one study on a rat model of ischemic stroke, actovegin shorted the restoration period for many major reflexes, spontaneous respiration and motor activity compared to untreated rats (Boyarinov et al. 1998). Another study on stroke survivors in the acute phase found Actovegin reduced motor disorders and increased cognitive assessment scores to a greater degree than the nootropic piracetam (Derev'yannykh et al. 2008).

One RCT was found evaluating Actovegin for cognitive rehabilitation. Guekht et al (2017) compared Actovegin to a placebo.

The methodological details and results of the single RCT are presented in Table 18.

Table 18. RCTs evaluating Actovegin for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Guekht et al. (2017) RCT (9) N$_{Start}$=503 N$_{End}$=433 TPS = Acute	E: Intravenous Actovegin at (2000mg/250mL/d) followed by 1200mg/d orally (two 200mg tablets X 3/d) C: placebo Duration: 6mo	• Alzheimer's Disease Assessment Scale: Cognitive Subscale (+exp) • Montreal Cognitive Assessment (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about actovegin

GLOBAL COGNITION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1a	**Actovegin** may produce greater improvements in global cognition than **a placebo**.	1	Guekht et al. 2017

Key Points

Actovegin may be beneficial for improving global cognition
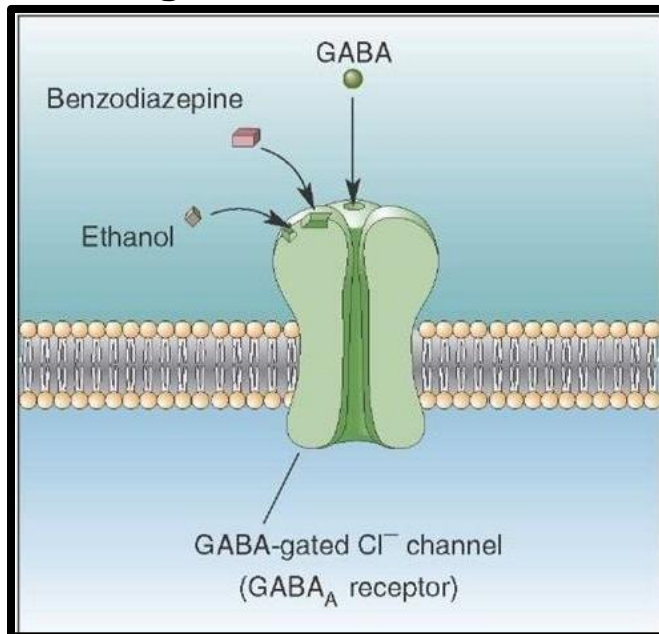
Gaba Agonists

GABA agonists such as phosphodiesterase inhibitors have been shown to promote functional recovery in rodent models of artery occlusion as well as upregulated neurogenesis, synaptogenesis and regional blood flow (Bednar, 2008; Menniti et al. 2009). Although the mechanism by which these effects take place is not yet well understood there are clear clinical implications for the use of GABA agonists in the cognitive rehabilitation of post-stroke patients.

One RCT was found evaluating a GABA agonist for cognitive rehabilitation. Di Cesare et al (2016) compared a phosphodiesterase-5 inhibitor to a placebo.

The methodological details and results of the single RCT are presented in Table 19.

Table 19. RCTs evaluating GABA agonists for cognitive rehabilitation.

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Di Cesare et al. (2016) RCT (9) N$_{Start}$=139 N$_{End}$= 137 TPS=Acute	E: Phosphodiesterase-5 inhibitor (6mg/d) C: Placebo Duration: 90d	Repeatable Battery Assessment of Neuropsychological Status: • Coding Subtest (-) • Recognition Memory Subtest (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about GABA agonists

ATTENTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**GABA agonists** may not have a difference in efficacy when compared to **a placebo** for improving attention.	1	Di Cesare et al. 2016

LEARNING AND MEMORY			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**GABA agonists** may not have a difference in efficacy when compared to **a placebo** for improving learning and memory.	1	Di Cesare et al. 2016

Key Points

GABA agonists may not be beneficial for improving cognitive rehabilitation

Nimodipine

Adopted from: https://www.webmd.com/drugs/2/drug-10951/nimodipine-oral/details and https://en.wikipedia.org/wiki/Nimodipine

Nimodipine is a calcium channel blocker that will preferentially dilate cerebral blood vessels. After ischemic injury it also can provide a cytoprotective effect by preventing large swings in intracellular calcium concentration (Trust Study Group, 1990). Most of the research surrounding nimodipine for stroke recovery is focused on acute stroke patients. When a bleed occurs, the bodies natural response is to constrict blood flow to prevent further blood loss. In the brain however, this decrease in blood flow can damage the tissue and exacerbate the injury. The rational is that by administering nimodipine soon after the cerebrovascular event, blood flow will not be as restricted in the brain and subsequent damage will be minimized. Nimodipine's efficacy is often assessed via functional measures and activities of daily living scales, but its effects on cognitive outcomes post-stroke specifically is comparatively less (Mohr et al. 1994). More research is needed to make clear the efficacy of nimodipine for cognitive recovery and rehabilitation.

One RCT was found evaluating nimodipine for cognitive rehabilitation. Sze et al. (1998) compared nimodipine to a non-treatment group.

The methodological details and results of the single RCT are presented in Table 20.

Table 20. RCTs evaluating nimodipine for cognitive rehabilitation.

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Sze et al. (1998) RCT (6) N$_{Start}$=100 N$_{End}$=92 TPS=Acute	E: Nimodipine (90mg/d) C: No treatment Duration: 12wk	• Fuld Object-Memory Evaluation (+exp) • Mini Mental State Exam (+exp) • Barthel Index (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about nimodipine

<table>
<tr><td colspan="4" align="center">LEARNING AND MEMORY</td></tr>
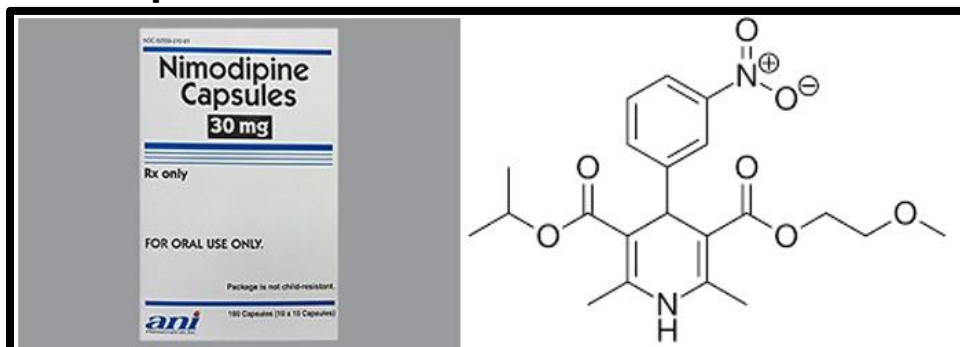<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Nimodipine may produce greater improvements in learning and memory than usual care.</td><td>1</td><td>Sze et al. 1998</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">GLOBAL COGNITION</td></tr>
<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Nimodipine may produce greater improvements in global cognition than usual care.</td><td>1</td><td>Sze et al. 1998</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">ACTIVITIES OF DAILY LIVING</td></tr>
<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Nimodipine may not have a difference in efficacy when compared to usual care for improving activities of daily living.</td><td>1</td><td>Sze et al. 1998</td></tr>
</table>

Key Points

Nimodipine may be beneficial for improving learning and memory, and global cognition

Nimodipine may not be beneficial for improving activities of daily living

Vinpocetine
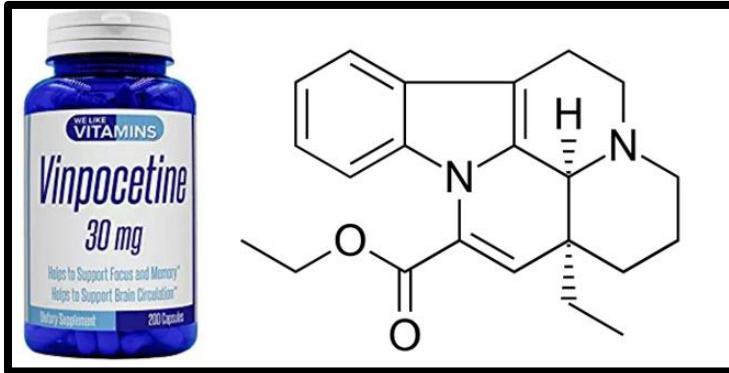
Vinpocetine is a man-made derivative of Vincamine, an alkaloid from the common periwinkle plant, and has several known pharmacological actions. It has been shown to increase blood flow to the brain and boost cerebral metabolism (Ogunrin, 2014). In addition, it is also known to increase oxygen utilization, have an inhibitory effect on phosphodiesterase, improve rheological properties of the blood and increase the tolerance of the brain against hypoxia or ischemia (Kiss & Karpati, 1996). From a behavioural standpoint, the drug has been shown to improve cognitive processing with improved memory recall and retention (Ogunrin, 2014). For all of these reasons, there is a potential for its use in rehabilitating cognitive functions post-stroke.

One RCT was found evaluating vinpocetine for cognitive rehabilitation. The single RCT examined vinpocetine in combination with the medications cytidine diphosphate (citicoline) and aspirin or clopidogrel, compared to the other medications alone (Zhang et al. 2016).

The methodological details and results of the single RCT are presented in Table 21.

Table 21. RCTs evaluating vinpocetine interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Zhang et al. (2016) RCT (4) N$_{Start}$=610 N$_{End}$=404 TPS=Acute	E: 30mg of IV vinpocetine + IV 0.4-0.5g cytidine diphosphate + 75-100mg aspirin or clopidogrel 75mg daily for 7 days C: IV 0.4-0.5g cytidine diphosphate + 75-100mg aspirin or clopidogrel 75mg daily for 7 days Duration: 90d	• Mini Mental State Examination (+exp) • Barthel Index (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about vinpocetine

GLOBAL COGNITION			
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Vinpocetine** may produce greater improvements in global cognition than **similar drugs**.	1	Zhang et al.2016

ACTIVITIES OF DAILY LIVING			
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Vinpocetine** may produce greater improvements in activities of daily living than **similar drugs**.	1	Zhang et al.2016

Key Points

Vinpocetine may be beneficial for improving global cognition, and activities of daily living
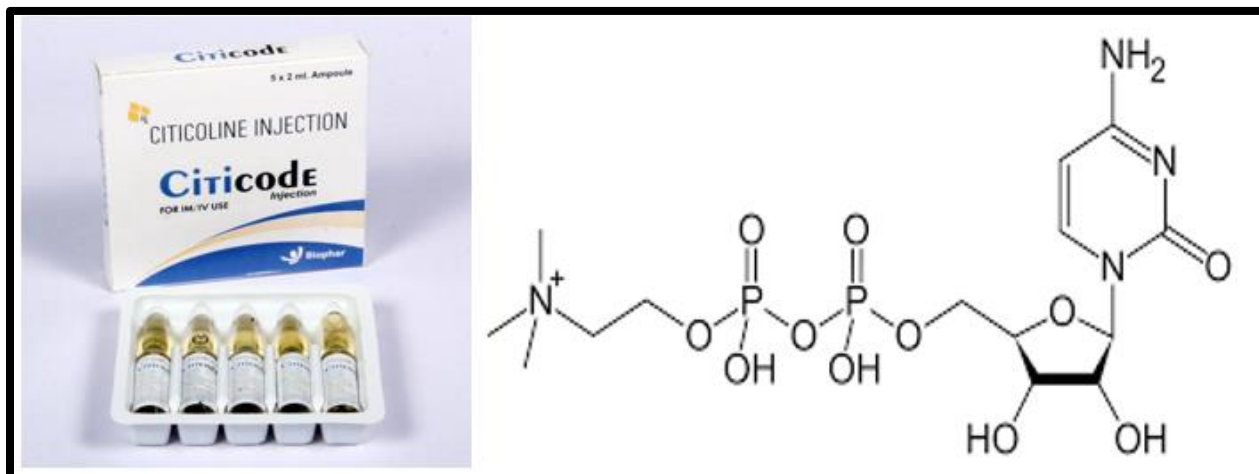
Citicoline

Citicoline, the generic name for cytidine 5'-diphosphocholine, is a naturally occurring chemical in many tissues and is a precursor to phosphotidylcholine. One of the proposed mechanisms of action is its role in protecting cell membranes by promoting resynthesis of phospholipids and preventing the release of free fatty acids form membrane damage (Fioravanti & Yanagi, 2005). The compound has shown to have neuroprotective effects, inhibiting apoptosis in many neurodegenerative disease models, increasing cellular metabolism and protecting mitochondrial function (Secades & Frontera, 1995). It has also been shown to increase dopamine and noradrenaline levels (Secades & Frontera, 1995). Animal model studies have shown efficacy of the drug's ability to improve learning and memory (Gareri et al. 2015). In humans, similar results have been found on its ability to improve memory, particularly in the elderly (Alvarez et al. 1997). More recently, research has examined more specifically its efficacy for stroke rehabilitation.

Two RCTs were found evaluating a citicoline for cognitive rehabilitation. Two RCTs examined citicoline against a placebo (Alvarez-Sabin et al. 2016; Alvarez-Sabin et al. 2013).

The methodological details and results of all two RCTs are presented in Table 22.

Table 22. RCTs evaluating citicoline for cognitive rehabilitation.

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Alvares-Sabin et al. (2016) RCT (4) N$_{Start}$=163 N$_{End}$=163 TPS=Subacute	E: Citicoline (1g/d) C: Standard care Duration: 2yr	• Global Cognitive Impairment (+exp)
Alvarez-Sabin et al. (2013) RCT (7) N$_{Start}$=347 N$_{End}$=199 TPS=Subacute	E: Citicoline (1g/d) C: Placebo Duration: 12mo	• Attention and Executive Function Battery (+exp) • Benton's Temporal Orientation (+exp) • Memory Battery scores (-) • Judgement of Line Orientation (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about citicoline

	EXECUTIVE FUNCTION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Citicoline** may produce greater improvements in executive function than **a placebo**.	1	Alvarez-Sabin et al. 2013

	LEARNING AND MEMORY		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Citicoline** may not have a difference in efficacy when compared to **a placebo** for improving learning and memory.	1	Alvarez-Sabin et al. 2013

	VISUOSPATIAL PERCEPTION AND ORIENTATION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	There is conflicting evidence about the effect of **citicoline** to improve visuospatial perception and orientation when compared to **a placebo.**	1	Alvarez-Sabin et al. 2013

	GLOBAL COGNITION		
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Citicoline** may not have a difference in efficacy when compared to **standard care** for improving global cognition.	1	Alvarez-Sabin et al. 2016

Key Points

Citicoline may be beneficial for improving executive function, but not learning and memory or global cognition

Antidepressants

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are used in the treatment of depression following stroke. Depression is one of many possible symptoms displayed post-stroke but is often in conjunction with cognitive impairment. The frequency and severity of cognitive impairment has been positively correlated with the presence of depression immediately after injury (Downhill & Robinson, 1994). In addition, depressive symptoms can persist longer into recovery if the individual also has cognitive impairment, and cognitive impairment will last longer if the individual is depressed (Robinson et al. 1986). Given the association between the presence of depression and cognitive dysfunction, studies have investigated the effect of antidepressants on cognition post-stroke.

Two RCTs were found evaluating an antidepressant for cognitive rehabilitation. All two RCTs compared an antidepressant to a placebo. One used escitalopram, an SSRI (Jorge et al. 2010), and one used nortriptyline, a TCA (Kimura et al. 2000)

The methodological details and results of all twoRCTs are presented in Table 23.

Table 23. RCTs evaluating antidepressants for cognitive rehabilitation.

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Jorge et al. (2010) RCT (7) N$_{Start}$=129 N$_{End}$=110 TPS=Subacute	E: Escitalopram (10mg/d) C: Placebo Duration: 12mo	• Repeatable Battery for the Assessment of Neuropsychological Status Total Score (+exp) RBANS Subcategories: • Delayed Memory (+exp) • Immediate Memory (+exp) • Attention (-) • Visuospatial/Constructional (-) • Trail-Making Tests A (-) • Trail-Making Test B (-) • Controlled Oral Word Association Test Raw Scores (-) • Stroop Test (-) • Wechsler Adult Intelligence Scale-III Similarities Scores (-)
Kimura et al. (2000) RCT (8) N$_{Start}$=106 N$_{End}$=47 TPS=Subacute	E: Nortriptyline (≤100mg/d, titrated) C: Placebo Duration: 6wk	• Mini Mental State Exam (among patients who responded to treatment only) (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about antidepressants

	ATTENTION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Antidepressants** may not have a difference in efficacy when compared to a **placebo** for improving attention.	1	Jorge et al. 2010

	EXECUTIVE FUNCTION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Antidepressants** may not have a difference in efficacy when compared to a **placebo** for improving executive function.	1	Jorge et al. 2010

	LEARNING AND MEMORY		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Antidepressants** may produce greater improvements in learning and memory than a **placebo**.	1	Jorge et al. 2010

	VISUOSPATIAL PERCEPTION AND ORIENTATION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Antidepressants** may not have a difference in efficacy when compared to a **placebo** for improving visuospatial perception and orientation.	1	Jorge et al. 2010

	GLOBAL COGNITION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	There is conflicting evidence about the effect of **antidepressants** to global cognition when compared to a **placebo.**	1	Jorge et al. 2010

Key Points

Antidepressants may be beneficial for improving learning and memory but may not be beneficial for improving other cognitive outcomes
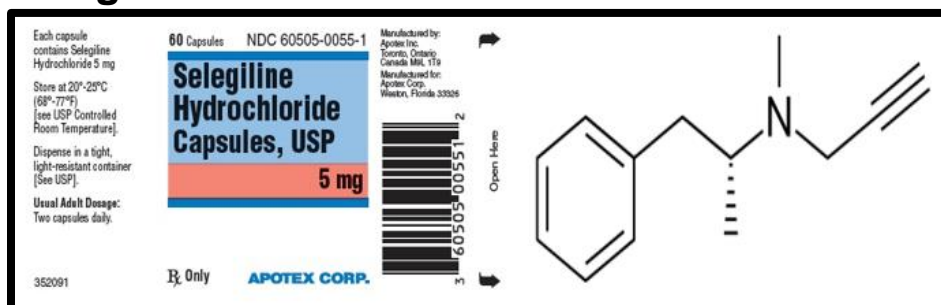
Selegiline

Selegiline (L-Deprenyl) is monoamine oxidase (MAO) inhibitor, the enzyme responsible for breaking down dopamine, noradrenaline and serotonin. By administering selegiline greater concentrations of these neurotransmitters persist in the synapse and contribute to a greater signal strength. The drug is most commonly used to treat Parkinson's disease, but the literature regarding selegiline and cognitive function post-stroke is limited. Freedman et al. (1998) tested the efficacy of selegiline on patients with Alzheimer's disease, but reported no significant differences in measures of cognition compared to a control group. Sivenius et al. (2001) found positive improvements among patients with stroke following a course of selegiline, including stroke severity, motor function, activities of daily living, quality of life, and depression. However, the authors reported a lack of statistically significant findings, and cognitive outcomes were not measured.

One RCT was found evaluating selegiline compared to a placebo for cognitive rehabilitation (Bartolo et al. 2015).

The methodological details and results of the single RCT are presented in Table 24.

Table 24. RCTs evaluating selegiline for cognitive rehabilitation.

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Bartolo et al. (2015) RCT (8) N$_{Start}$=47 N$_{End}$=44 TPS=Acute	E: Selegiline (10mg/d) C: Placebo Duration: 6wk	• Mini Mental State Exam (-) • Frontal Assessment Battery (-) • Montreal Cognitive Assessment (+exp) • Rey Auditory Verbal Learning Test (-) • Logical Memory Immediate Recall (+exp) • Logical Memory Delayed Recall (-) • Digit Span (+exp) • Corsi Block Tapping Test (-) • Attentive Matrices (+exp) • Trail-Making Test A (+exp) • Trail-Making Test B (+exp) • Stroop Tests T & E (+exp) • Symbol Digit (-) • Rey-Osterrieth Figure, Copy (-) • Raven's Colored Progressive Matrices 47 (-) • Phonological Fluency (-) • Semantic Fluency (-) • Hamilton Depression Rating Scale (-) • Functional Independence Measure (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about selegiline

<table>
<tr><td colspan="4" align="center">ATTENTION</td></tr>
<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Selegiline may produce greater improvements in attention than a placebo.</td><td>1</td><td>Bartolo et al. 2015</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">EXECUTIVE FUNCTION</td></tr>
<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Selegiline may not have a difference in efficacy when compared to a placebo for improving executive function.</td><td>1</td><td>Bartolo et al. 2015</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">LEARNING AND MEMORY</td></tr>
<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Selegiline may not have a difference in efficacy when compared to a placebo for learning and memory.</td><td>1</td><td>Bartolo et al. 2015</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">VISUOSPATIAL PERCEPTION AND ORIENTATION</td></tr>
<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Selegiline may not have a difference in efficacy when compared to a placebo for visuospatial perception and orientation.</td><td>1</td><td>Bartolo et al. 2015</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">GLOBAL COGNITION</td></tr>
<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Selegiline may not have a difference in efficacy when compared to a placebo for global cognition.</td><td>1</td><td>Bartolo et al. 2015</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">ACTIVITIES OF DAILY LIVING</td></tr>
<tr><td>LoE</td><td>Conclusion Statement</td><td>RCTs</td><td>References</td></tr>
<tr><td>1b</td><td>Selegiline may not have a difference in efficacy when compared to a placebo for improving activities of daily living.</td><td>1</td><td>Bartolo et al. 2015</td></tr>
</table>

Key Points

Selegiline may be beneficial for improving attention, but not other cognitive outcomes

Rivastigmine
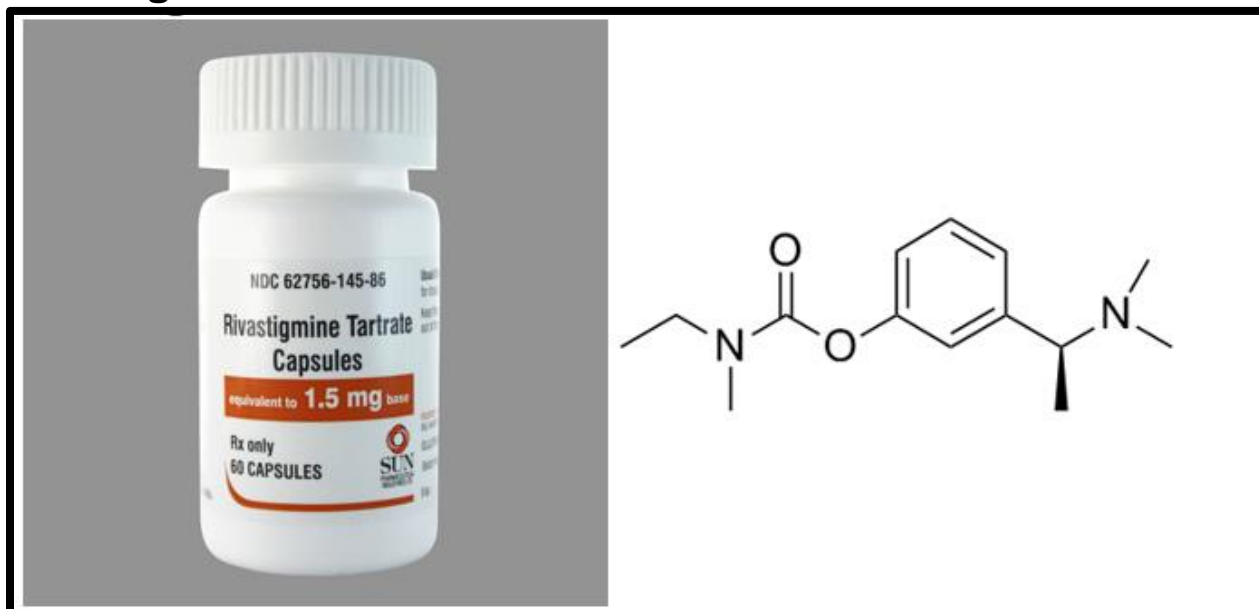
Rivastigmine is a cholinesterase inhibitor, affecting both butylcholinesterase and acetylcholinesterase. It is most often used to treat Alzheimer's and Parkinson's disease. It works by preventing the breakdown of acetylcholine, and therefore increasing the amount available in the synapse for signalling. The efficacy of the drug has been established for the treatment of Alzheimer's, improving cognitive functions like memory along with physiological ones, such as cerebral blood flow (Vinerri et al. 2002). It has been demonstrated that the benefits derived from treatment are greater among patients with concurrent vascular risk, such as hypertension, than among patients without such vascular risk factors (Erkinjuntti et al. 2003; Kumar et al. 2000). Because it is successful in improving cognitive functioning in other neurological conditions, it could be efficacious for improving cognitive recovery post-stroke.

One RCT was found evaluating rivastigmine compared to a placebo for cognitive rehabilitation (Narasimhalu et al. 2018).

The methodological details and results of the single RCT are presented in Table 25.

Table 25. RCTs evaluating rivastigmine for cognitive rehabilitation.

Authors (Year) Study Design (PEDro Score) Sample Size_start_ Sample Size_end_ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Narasimhalu et al. (2018) RCT (10) N_Start_=50 N_End_=36 TPS=Subacute	E: rivastigmine (initial dose 1.5mg, 3mg after 4wks at lower dose, 4.5mg after 4wks at lower dose, 2x/d) C: placebo Duration: 6mo	• Clock Drawing (-) • Color trails 1 & 2 (-) • Alzheimer's Disease Cooperative Study-ADL (-) • Symbol digit modalities (-) • Digit cancellation (-) • Maze (-) • Verbal fluency animals (+exp) • Verbal fluency food (-) • Visual memory (immediate recall) (-) • Visual memory (delayed recall) (-) • Visual memory (recognition) (-) • Frontal assessment battery (-) • ADAS-Cog (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp₂ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about rivastigmine

<table>
<tr><td colspan="4" align="center">**ATTENTION**</td></tr>
<tr><td>**LoE**</td><td>**Conclusion Statement**</td><td>**RCTs**</td><td>**References**</td></tr>
<tr><td>**1b**</td><td>**Rivastigmine** may not have a difference in efficacy when compared to **a placebo** for improving attention.</td><td>1</td><td>Narasimhalu et al. 2018</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">**EXECUTIVE FUNCTION**</td></tr>
<tr><td>**LoE**</td><td>**Conclusion Statement**</td><td>**RCTs**</td><td>**References**</td></tr>
<tr><td>**1b**</td><td>**Rivastigmine** may not have a difference in efficacy when compared to **a placebo** for improving executive function.</td><td>1</td><td>Narasimhalu et al. 2018</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">**LEARNING AND MEMORY**</td></tr>
<tr><td>**LoE**</td><td>**Conclusion Statement**</td><td>**RCTs**</td><td>**References**</td></tr>
<tr><td>**1b**</td><td>**Rivastigmine** may not have a difference in efficacy when compared to **a placebo** for improving learning and memory.</td><td>1</td><td>Narasimhalu et al. 2018</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">**GLOBAL COGNITION**</td></tr>
<tr><td>**LoE**</td><td>**Conclusion Statement**</td><td>**RCTs**</td><td>**References**</td></tr>
<tr><td>**1b**</td><td>**Rivastigmine** may not have a difference in efficacy when compared to **a placebo** for improving global cognition.</td><td>1</td><td>Narasimhalu et al. 2018</td></tr>
</table>

<table>
<tr><td colspan="4" align="center">**ACTIVITIES OF DAILY LIVING**</td></tr>
<tr><td>**LoE**</td><td>**Conclusion Statement**</td><td>**RCTs**</td><td>**References**</td></tr>
<tr><td>**1b**</td><td>**Rivastigmine** may not have a difference in efficacy when compared to **a placebo** for improving activities of daily living.</td><td>1</td><td>Narasimhalu et al. 2018</td></tr>
</table>

Key Points

Rivastigmine may not be beneficial for improving cognitive rehabilitation

Alternative and complementary medicine

Traditional Chinese Medicine

Adopted from: https://myherb.store/de-ji-xue-shuan-xin-mai-ning-jiao-nang-for-stroke-0-5g-36-capsules/

Traditional Chinese and Japanese herbal medicine are complementary and alternative forms of medicine that have been utilized as a healthcare system in Asian countries for hundreds of years and are widely used for stroke treatment today (Tsai et al. 2017; Han et al. 2017). Different herbal medicines have various beneficial properties such as anti-inflammation, increasing cerebral blood flow velocity, inhibiting platelet aggregation, increasing tissue tolerance to hypoxia, etc. (Han et al. 2017). Chinese and Japanese herbal medicines commonly used for stroke rehabilitation generally consist of a mixture of different plant and animal extracts with these varying properties (Han et al. 2017).

The medicine used in the following study is called Xueshuan xinmai. It contains Radix Salviae Miltiorrhizae (red sage) and ginsenosides. Radix Salviae Miltiorrhizae is known to promote blood flow and is often used to treat vascular diseases (Lin & Hsieh, 2010). Ginsenosides are the main component of ginseng and have a large range of pharmacological activities.

One RCT was found evaluating traditional Chinese medicine for cognitive rehabilitation. The single RCT compared Xeushuan xinmai to a placebo (Wei et al. 2015).

The methodological details and results of the single RCT are presented in Table 26.

Table 26. RCTs evaluating traditional Chinese medicine interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Wei et al. (2015) RCT (9) N$_{Start}$=28 N$_{End}$=27 TPS=Subacute	E: Xueshuan xinmai tablets (0.8g, 3/d) C: Placebo Duration: 3mo	• Auditory Verbal Learning Test (+exp) • Rey-Osterrieth Complex Figure Delayed Recall (+exp) • Rey-Osterrieth Complex Figure Copy (-) • Digit Span (-) • Clock Drawing Test (-) • Mini Mental Status Exam (-) • Stroop Color and Word Test (-) • Symbol Digit Modalities Test (-) • Boston Naming Test (-) • Category Verbal Fluency Test (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.

+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group

+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group

+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group

- indicates no statistically significant between groups differences at α=0.05

Conclusions about traditional Chinese medicine

	ATTENTION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Xueshuan xinmai** may not have a difference in efficacy when compared to **a placebo** for improving attention.	1	Wei et al. 2015

	EXECUTIVE FUNCTION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Xueshuan xinmai** may not have a difference in efficacy when compared to **a placebo** for improving executive function.	1	Wei et al. 2015

	LEARNING AND MEMORY		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Xueshuan xinmai** may produce greater improvements in learning and memory than **a palcebo**.	1	Wei et al. 2015

	VISUOSPATIAL PERCEPTION AND ORIENTATION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Xueshuan xinmai** may not have a difference in efficacy when compared to **a placebo** for improving visuospatial perception and orientation.	1	Wei et al. 2015

	GLOBAL COGNITION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Xueshuan xinmai** may not have a difference in efficacy when compared to **a placebo** for improving global cognition.	1	Wei et al. 2015

Key Points

Xueshuan xinmai may be beneficial for improving learning and memory, but not other cognitive outcomes
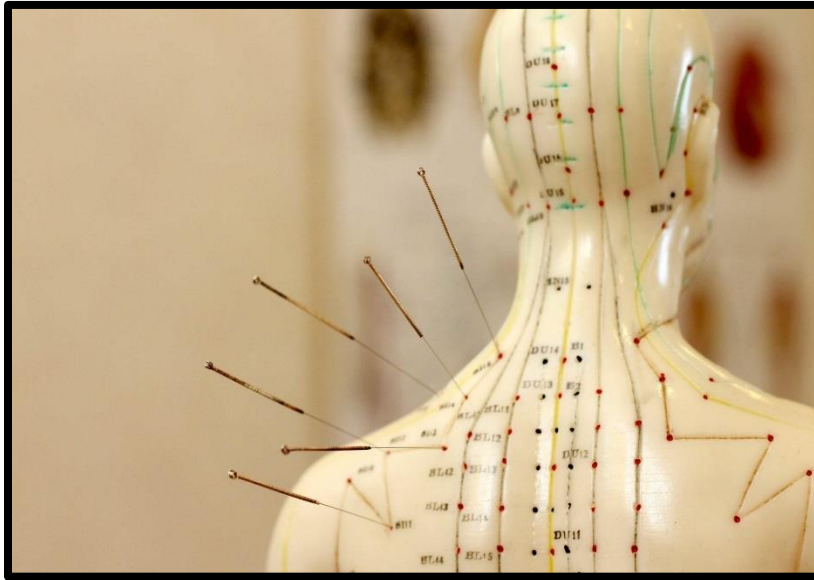
Acupuncture

The use of acupuncture has recently gained attention as an adjunct to stroke rehabilitation in Western countries even though acupuncture has been a primary treatment method in China for about 2000 years (Baldry, 2005). In China, acupuncture is an acceptable, time-efficient, simple, safe and economical form of treatment used to ameliorate motor function, sensation, verbal communication and additional neurological functions in post-stroke patients," (Wu et al. 2002). According to Rabinstein and Shulman (2003), "Acupuncture is a therapy that involves stimulation of defined anatomic locations on the skin by a variety of techniques, the most common being stimulation with metallic needles that are manipulated either manually or that serve as electrodes conducting electrical currents". There is a range of possible acupuncture mechanisms that may contribute to the health benefits experienced by stroke patients (Park et al. 2006). For example, acupuncture may stimulate the release of neurotransmitters (Han & Terenius, 1982) and influence the deep structure of the brain (Wu et al. 2002). Lo et al. (2005)found that, when acupuncture was applied for at least 10 minutes, led to long-lasting changes in cortical excitability and plasticity even after the needle stimulus was removed. With respect to stroke rehabilitation, the benefit of acupuncture has been evaluated most frequently for pain relief and recovery from motor deficits, but some research has examined its effectiveness in improving cognitive outcomes.

Four RCTs were found evaluating acupuncture for cognitive rehabilitation. Two RCTs compared acupuncture to standard care (Yang et al. 2017; Chen et al. 2016). Two RCTs also compared acupuncture in combination with another therapy to the alternative therapy (Jiang et al, 2016; Wang et al. 2016).

The methodological details and results of all four RCTs are presented in Table 27.

Table 27. RCTs evaluating acupuncture for cognitive rehabilitation.

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
**Acupuncture compared to standard care**	
Yang et al. (2017) RCT (4) N$_{Start}$=60 N$_{End}$=60 TPS = Acute	E: Baihui acupoint acupuncture (24 hours with needles in, 3d/wk) C: conventional therapy Duration: 6mo	• Mini-Mental State Examination (+exp)
Chen et al. (2016) RCT (8) N$_{Start}$=250 N$_{End}$=241 TPS=Acute	E: Acupuncture therapy C: Standard rehabilitation care Duration: 30min/d, 6d/wk for 3wk	• Montreal Cognitive Assessment (+exp) • Mini Mental State Exam (+exp)
**Acupuncture alone, and in combination with computer-based cognitive therapy**	
Jiang et al. (2016) RCT (5) N$_{Start}$=240 N$_{End}$=204 TPS=Subacute	E1: Acupuncture therapy E2: Computer-based cognitive therapy E3: Acupuncture + Computer-based cognitive therapy C: Standard care Duration: 30min/d, 5d/wk for 12wk	E1 vs C: • Mini Mental State Exam (+exp$_1$) • Montreal Cognitive Assessment (+exp$_1$) • Functional Independence Measure (+exp$_1$) E2 vs C: • Mini Mental State Exam (+exp$_2$) • Montreal Cognitive Assessment (+exp$_2$) • Functional Independence Measure (+exp$_2$) E1 vs E2: • Mini Mental State Exam (-) • Montreal Cognitive Assessment (-) • Functional Independence Measure (-) E3 vs E1/E2/C: • Mini Mental State Exam (+exp$_3$) • Montreal Cognitive Assessment (+exp$_3$) • Functional Independence Measure (+exp$_3$)
Wang et al. (2016) RCT (7) N$_{Start}$=126 N$_{End}$=119 TPS=Subacute	E1: Nimodipine (30mg 3/d) E2: Acupuncture E3: Acupuncture + nimodipine (30mg 3/d) Duration: 30min, 6d/wk for 3mo	E1 vs E2: • Montreal Cognitive Assessment (-) E1 vs E3: • Montreal Cognitive Assessment (-) E2 vs E3: • Montreal Cognitive Assessment (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about acupuncture

| LoE	GLOBAL COGNITION		
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Acupuncture** may produce greater improvements in global cognition than **usual care**.	2	Yang et al. 2017; Chen et al. 2016
2	**Acupuncture with computer-based cognitive therapy** may produce greater improvements in global cognition than **usual care, or either therapy independently**.	1	Jiang et al. 2016
1b	**Acupuncture with nimodipine** may not have a difference in efficacy when compared to **either therapy alone** for improving global cognition.	1	Wang et al. 2016

LoE	ACTIVITIES OF DAILY LIVING		
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Acupuncture with computer-based cognitive therapy** may produce greater improvements in activities of daily living than **usual care, or either therapy independently**.	1	Jiang et al. 2016

Key Points

Acupuncture may be beneficial for improving global cognition and activities of daily living

Electroacupuncture

Adopted from: https://www.promotionhealthcare.com/electroacupuncture-treatment-pain-injuries/
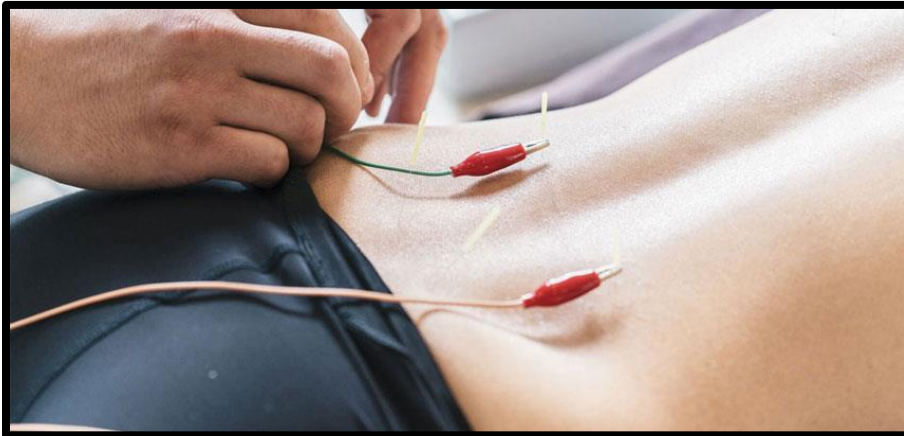
Electroacupuncture is a variant of acupuncture techniques practiced in traditional Chinese medicine, the difference being that a minute electrical current of similar intensity to that of a bioelectric current produced endogenously in the body is applied to the needles used (Wang et al. 2014). The needle is often placed on meridian points throughout the body (Wang et al. 2014). The treatment has been found to ameliorate several cognitive deficits in rodent models of stroke, epilepsy and Alzheimer's disease (Feng et al. 2013; dos Santos et al. 2005; Li et al. 2014). Further investigation will be needed to see if these results will translate into humans.

2 RCTs were found evaluating electroacupuncture for cognitive rehabilitation. 1 RCT evaluated electroacupuncture compared to usual care and a sham condition (Chou et al. 2009). 1 RCT compared electroacupuncture to both high-intensity TENS stimulation and low intensity TENS stimulation (Rorsman & Johansson, 2006).

The methodological details and results of all two RCTs are presented in Table 28.

Table 28. RCTs evaluating electroacupuncture interventions for cognitive rehabilitation

Authors (Year) Study Design (PEDro Score) Sample Size_start Sample Size_end Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Electroacupuncture compared to standard care		
Chou et al. (2009) RCT (6) N_Start=38 N_End=33 TPS=Chronic	E: Electroacupuncture C: Usual care with sham TENS Duration: 20min/d, 2d/wk for 8wk	Loewenstein Occupational Therapy Cognitive Assessment-Geriatric (LOTCA-G): • LOTCA-G Orientation (+exp) • LOTCA-G Perception (+exp) • LOTCA-G Attention (+exp) • LOTCA-G Thinking Operation (-) • LOTCA-G Visuomotor Organization (-) • LOTCA-G Memory (-)
Electroacupuncture vs Transcutaneous Electrical Nerve Stimulation (TENS)		
Rorsman & Johansson (2006) RCT (6) N_Start=54 N_End=51 TPS=Acute	E1: Electroacupuncture E2: High-intensity low-frequency TENS C: Low-intensity high-frequency TENS Duration: 30min/d, 2d/wk for 10wk	• Mini Mental State Exam (-) • Rey Auditory Verbal Learning Test (-) • Facial Recognition Memory (-) • Word Fluency (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp_2 indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about electroacupuncture

ATTENTION

LoE	Conclusion Statement	RCTs	References
1b	**Electroacupuncture** may produce greater improvements in attention than **usual care**.	1	Chou et al. 2009

EXECUTIVE FUNCTION

LoE	Conclusion Statement	RCTs	References
1b	**Electroacupuncture** may not have a difference in efficacy when compared to **standard care** for improving executive function.	1	Chou et al. 2009
1b	**Electroacupuncture** may not have a difference in efficacy when compared to **high or low frequency TENS** for improving executive function.	1	Rorsman and Johansson, 2006

LEARNING AND MEMORY

LoE	Conclusion Statement	RCTs	References
1b	**Electroacupuncture** may not have a difference in efficacy when compared to **standard care** for improving learning and memory.	1	Chou et al. 2009
1b	**Electroacupuncture** may not have a difference in efficacy when compared to **high or low frequency TENS** for improving learning and memory.	1	Rorsman and Johansson, 2006

VISUOSPATIAL PERCEPTION AND ORIENTATION

LoE	Conclusion Statement	RCTs	References
1b	**Electroacupuncture** may produce greater improvements in visuospatial perception and orientation than **usual care**.	1	Chou et al. 2009

GLOBAL COGNITION

LoE	Conclusion Statement	RCTs	References
1b	**Electroacupuncture** may not have a difference in efficacy when compared to **high or low frequency TENS** for improving global cognition.	1	Rorsman and Johansson, 2006

Key Points

Electroacupuncture may be beneficial for improving attention, and visuospatial perception and orientation, but not other cognitive outcomes

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