Matthew W McDonald, Sandra Black, Dale Corbett, Rick M Dijkhuizen, Tracy D Farr, Matthew S Jeffers, Rajesh N Kalaria, Alexander P Leff, Jess Nithianantharajah, Sarah Pendlebury, Terence J Quinn, Andrew N Clarkson' Michael J O'Sullivan

Cognition in Stroke Rehabilitation and Recovery Research:

Consensus-based Core Recommendations from the Stroke Recovery and Rehabilitation Roundtable

Matthew W McDonald[1,3*]

Sandra Black[2,3]

Dale Corbett[1,3]

Rick M Dijkhuizen[4]

Tracy D Farr[5]

Matthew S Jeffers[1,3*]

Rajesh N Kalaria[6]

Alexander P Leff[7]

Jess Nithianantharajah[8]

Sarah Pendlebury[9]

Terence J Quinn[10]

Andrew N Clarkson[11,‡]

Michael J O'Sullivan[12,‡]

(NOT YET FINALISED – PLEASE ADD A **SINGLE** AFFILIATIONS BELOW (double affiliations limited to recognition of funders of SRRR, as I understand it))

1. Department of Cellular and Molecular Medicine, University of Ottawa, Canada
2.

3. Canadian Partnership for Stroke Recovery, University of Ottawa, Canada
4. Center for Image Sciences, University Medical Center Utrecht and Utrecht University, Utrecht, Netherlands
5.
6. Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK
7. Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, London, UK.
8.
9.
10. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
11. The Department of Anatomy, Brain Health Research Centre and Brain Research New Zealand, University of Otago, Dunedin, New Zealand
12. University of Queensland Centre for Clinical Research, Faculty of Medicine, University of Queensland, Brisbane, Australia

Keywords

cognitive function; animal models; stroke; rehabilitation; recovery; consensus

Abstract

Cognitive impairment is common and associated with poor quality of life after stroke and therefore, an important target for rehabilitation. Cognitive impairment can also be an obstacle to rehabilitation of movement and other functions, given that current approaches often engage learning mechanisms. Cognitive function was identified as an important, but relatively neglected target during the first Stroke Recovery and Rehabilitation Roundtable (SRRR I) and a Cognition Working Group was convened as part of SRRR II. There is currently insufficient evidence to build consensus on specific approaches to cognitive rehabilitation. However, consideration of cognition in recovery studies more broadly is important. We present recommendations on the integration of cognition into stroke rehabilitation studies generally and define priorities for ongoing and future research in the field of stroke recovery and rehabilitation. A number of promising interventions are ready to be taken forward to trials to tackle the gap in evidence for cognitive rehabilitation and some of the most promising of these approaches are discussed as part of mapping future directions for cognitive recovery research.

Background

Epidemiology and Importance

SRRR I[1] focussed on motor recovery since it was most developed in terms of mechanistic understanding and readiness for clinical trials. Cognitive function was not considered in SRRR I but was identified as a future priority. The definition of post-stroke cognitive impairment that we use here is a new cognitive deficit that develops in the first 3 months following stroke onset and persists for a minimum duration of six months from outset, which is not explained by any other condition or disease, e.g. metabolic and endocrine disorders, or depression[13].

Neuropsychological testing 3 weeks after stroke reveals cognitive deficits in 30-40% of individuals[2], across a broad range of domains such as executive function, visuospatial cognition, episodic and working memory[3]. Furthermore, cognitive, affective and behavioural consequences of stroke are more strongly associated with quality of life than measures of physical disability[4]. The risk of dementia after stroke is high, with a post-event incidence of 34% one year after either stroke or TIA[5]. Stroke survivors highlight cognitive disturbance as an area of unmet need: difficulties with memory, concentration and fatigue were the leading areas reported as unmet needs in the UK Stroke Survivor Survey[6]. Existing international guidelines for stroke rehabilitation highlight the lack of evidence for specific approaches for rehabilitation of cognitive function[7], so defining priorities to fill gaps in existing evidence was a major element of the SRRR II effort to generate research alignment.

Mechanisms of Impairment and Recovery

Cognitive function relies on effective signalling between cortical and subcortical brain regions. Lesions may disrupt network structure and function by direct or indirect injury to grey matter regions or white matter connections that form cognitive networks. Secondary mechanisms of injury include degeneration of connected structures and secondary injury that results from the cascade of pathological events triggered by strokes such as, reactive astrogliosis, infiltration of immune cells, and activation of programmed cell death. Alterations in structural connectivity can be evaluated non-invasively by diffusion MRI, or invasively (in animal models) using neuroanatomical tracing. Functional connectivity can be measured with electrophysiological approaches including EEG/MEG and functional MRI. ~~Cognitive impairments are in part mediated by changes in functional connectivity, as has been shown for frontal brain regions that are involved in executive function[8].~~ Whilst there are available methods to assess structural and functional connectivity changes after stroke, longitudinal studies are needed to fully understand the evolution of post-stroke cognitive impairment.

Mechanisms of recovery are likely to include synaptic and experience-dependent plasticity of damaged and undamaged circuits[11], which supports the acquisition of new cognitive skills. Neurogenesis is now thought to occur throughout adult life and is also implicated in some aspects of cognition[9]. The role of neurogenesis in cognitive recovery after stroke remains unknown, but immature neurons migrate to sites of ischaemic injury[10]. The potential role of immune and glial cells in recovery of function is also an area of active interest, with chronic reactive astrogliosis in white matter tracts linked to delayed impairment in memory.

Challenges in Recovery and Rehabilitation Research

Cognition is multi-dimensional. The DSM-5 approach to neurocognitive disorders recognises six major domains, each having multiple subdomains[12]. A proper account of the consequences of damage to specific domains requires an understanding of the distributed neural networks that span cortical and subcortical structures that underpin the neurocognitive domains (**Figure 1**). As a consequence, at the typical spatial scale of stroke, multiple networks are affected to varying degrees. This heterogeneity, along with a vast range of approaches for testing cognition, creates difficulties in defining consistent measurement approaches for use in rehabilitation trials. The vast array of cognitive testing approaches is replicated in behavioural paradigms for animal model research. Additionally, cognitive impairments can be delayed and, acutely, apparent impairments can be exaggerated by systemic factors, such as acute infection and delirium. Another complicating factor is the lack of information on pre-morbid cognitive status.

Context and Scope

The SRRR meetings have been firmly anchored around recovery from stroke, as a discrete clinical event defining the start of a period for rehabilitation. Previous studies adopt a design that included stroke as an index event, such as studies of cognition in hospital-based cohorts or studies in a stroke rehabilitation setting.

There have been a number of initiatives to develop consistency of approach and consensus in relation to clinical entities that overlap or can co-exist with acute stroke, such as cerebral small vessel disease and *vascular cognitive impairment (VCI)*[14].

More recently, the Vascular Impairment of Cognition Classification Consensus Study[15] agreed on guidelines for diagnosis and reiterated support for standardised neuropsychological and imaging approaches, previously proposed by the National Institute of Neurological Disorders and Canadian Stroke Network (the VCI Harmonization Standards[16]). A recent UK initiative is seeking to build consensus around functional assessment for animal models of VCI[17]. Efforts to drive research alignment in VCI are relevant to the Cognition theme of SRRR II and share features, notably the emphasis on translation and new therapies. The SRRR II Cognition Working Group was focussed primarily on the setting of stroke rehabilitation, and rehabilitation trials. Aspects of VCI other than acute stroke, such as silent infarction or insidious small vessel disease, were not within the group's scope.

Developing interventions that interfere with mechanisms of delayed injury or enhance intrinsic mechanisms of neural adaptation is at the heart of rehabilitation research. Animal models provide a means to explore basic mechanisms and possible interventions. The two-way interaction between preclinical and clinical research was therefore viewed as central to cognitive recovery research and a core component of the working group's mission. The group sought to make recommendations that span preclinical and clinical research and that will foster more effective translation.

Methods and Participants

The Cognition Working Group gathered experts from a diverse range of fields. A group (n=7) met in person at the SRRR II meeting in Saint-Sauveur, Canada in

October 2018. A wider advisory group was also established to provide additional expertise. Overall, expertise in clinical stroke, rodent models of stroke, neuroimaging of humans and animal models, neuropsychology, including cross-species approaches, the neurobiology of language and cognitive rehabilitation were represented.

In advance of SRRR II, a structured survey was sent to the participants and from this, a list of the major challenges in cognition in relation to stroke recovery and rehabilitation was defined, and an agenda formed for the working group meeting. In a number of areas, it was recognized that there was inadequate evidence to support alternative approaches to develop consensus. In these areas, the methodology shifted to definition of the major priorities for research in post-stroke cognition.

Cognition in Rehabilitation Research: Generic Recommendations

An essential aspect of function to be incorporated into the design of a stroke rehabilitation study might be defined as one that: is likely affected by stroke; is sensitive to therapy; and has importance relative to overall outcome. Therapeutic approaches are often not specific to motor function (e.g. systemically administered drugs) so that cognitive improvement may be part of a therapeutic effect. Furthermore, cognitive impairment is an important determinant of quality of life after stroke. Therefore, the collective view was that cognitive function meets the criteria to be evaluated in all trials and observational studies of stroke recovery. This should include assessment of cognition at entry and as an outcome measure. The need to develop recommendations for outcome measurements of cognition for stroke trials is

something that was recognised during the SRRR in 2016[18]. The Montreal Cognitive Assessment is currently the most extensively evaluated, in terms of sensitivity and cultural validity, but alternatives are needed. A separate working group is currently undertaking a prioritisation method using Value Focused Thinking Methodology to rank the psychometric properties of cognitive screening tools against pre-determined desirable properties of measurement tools, across stroke recovery time points (acute, sub-acute and chronic).

The systematic exclusion of patients with aphasia from recovery studies was identified as a major concern, both in terms of generalisability and equitable access to treatments that are shown to work in non-aphasic individuals. A consensus recommendation of the group is that a scientifically robust approach is required to participant selection on this basis (**Table 1**).

Research Priorities: Enhancing the translational potential of preclinical cognitive recovery research

Most preclinical stroke recovery research has focussed on the motor system. This work has identified critical periods of sensorimotor recovery and cellular mechanisms that govern neural repair following stroke[10, 19]. Previous consensus recommendations for the alignment of preclinical and clinical stroke recovery research from SRRR I focussed on sensorimotor recovery, although many of these guidelines could be applied to cognitive recovery. The recommendations emphasised the importance of using sensitive outcome measures that are in close

association with human stroke to best capitalise on the potential of experimental models.

Traditionally, research has utilised models such as the middle cerebral artery occlusion (MCAo) model, which have limited value for studying cognition as the injury primarily impacts sensorimotor circuits. Greater priority should be given to replicating behavioural impairments observed in the clinical setting using photothrombosis, endothelin-1, and microvascular emboli models that can produce targeted damage to brain regions, with no (or limited) motor deficits. Additionally, efforts should be made to employ models that exhibit cognitive deficits in a variety of domains, particularly higher-order processes commonly impacted in human stroke (e.g. attention, executive function, speed of processing, dual-tasking, and cognitive flexibility). These domains can be examined in the rodent; however, few preclinical stroke models have employed such measures, with studies largely focussing on using relatively easy to study spatial memory deficits (e.g. Morris water maze, Radial arm Maze, etc.), which are not dramatically impacted by MCAo. While traditional paradigms to assess cognition still have merit, greater emphasis should be placed on cognitive tasks that directly translate across species (**Table 2**). This may be achieved through utilisation of new technologies, such as touch-screen tablets, that allow the delivery of testing paradigms in rodents that mirror the conditions that humans would also be tested under[20, 21]. It can be argued that a significant component of stroke rehabilitation is relearning of many tasks of daily life; therefore, preclinical studies should consider the addition of relearning paradigms in their experiments. We also know that cognitive deficits following a discrete and identifiable stroke do not occur in isolation and may be modulated by underlying cognitive risk

factors. Therefore, preclinical studies should also incorporate increasing age, cardiovascular and metabolic comorbidities (diabetes, diet, etc.), and microvascular injury.

There are a number of ways in which preclinical research can significantly contribute to our understanding of post-stroke cognitive recovery. Effort should be made to monitor longer-term behavioural changes to reflect chronicity and progressive decline in cognitive function, in combination with structural and functional changes in neural networks (histology, in vivo neuroanatomical tracing, MRI, electrophysiology), in an attempt to identify important epochs and markers of cognitive recovery. In addition, the preclinical environment can serve as a fertile testing ground for validation of novel therapeutic strategies prior to translation to the clinical setting. To maximise the chance of translation, adoption of a level of rigour equivalent to clinical trials in humans is required, including randomisation, blinding and reporting standards. Specific to cognitive function, this includes rigorous standards for selection, execution and reporting of cognitive test paradigms. Preclinical researchers require training and expertise to properly conduct cognitive tests, and experimental procedures should be reported in detail[20].

Research Priorities: Translational and Clinical Research

Recovery epochs, Therapeutic Windows and Biomarkers

The cellular and biochemical changes triggered by stroke include both early and late events that occur both proximal and distal to the site of injury. This heterogeneity suggests that there may be distinct epochs of recovery. The notion of recovery

epochs dominated by one or several cellular or biochemical mechanisms emphasizes the challenge of correct timing of interventions in trials.

One consensus conclusion was that epochs need to be defined mechanistically because mechanistic understanding defines candidate therapies. However, much more data is needed. Major gaps include the lack of detailed longitudinal studies using imaging (structural and functional MRI) and other biomarkers in humans, and a relative paucity of long-term follow up data in animals after stroke. Biomarkers provide promising avenues for the definition of epochs, with the potential to span clinical and preclinical models. For example, PET ligands can track microglial activation along white matter pathways after stroke and label biochemical hallmarks of late neurodegeneration, such as amyloid and tau deposition. Refining definitions of post-stroke cognitive impairment based on biomarkers would parallel the use of biomarkers in recent approaches to the diagnosis of Alzheimer's Disease.

Premorbid Function and Functional Reserve

Pre-stroke cognitive performance is thought to influence cognitive outcome after stroke, including the risk of developing future dementia. However, accurate ascertainment of premorbid ability is challenging and contemporary approaches are limited to methods to infer past performance based on patient and carer responses to questions asked after stroke. There is no validated method to assess cognitive reserve and predict its influence on rehabilitation trajectory. Multivariate approaches to neuroimaging data are beginning to reveal information about overall brain status, such as methods to infer "brain age". Application in a stroke rehabilitation setting is,

however, complicated by the fact that structural and functional alterations after stroke are known to extend well beyond sites of visible infarction.

Integration of Patient and Carer-reported Outcome Measures

Much attention has focussed on defining optimal objective testing approaches to measure post-stroke cognitive impairment, primarily based on trying to capture typical patterns of cognitive impairment. However, more work is required to link this approach to stroke outcome as defined by patients, relatives and carers. Understanding the associations of cognitive function with quality of life after stroke is essential both in setting research priorities – across the translational spectrum – and defining the health economics benefits of new interventions to enhance cognitive recovery after stroke. Technology provides new opportunities for integration of objective, patient and carer-reported outcome measures. For example, tablets and smartphones can deliver cognitive tests and prompt reporting of status by patients and carers. Wearable devices can provide information on natural behaviour (locomotion) and information about factors that modulate cognitive performance, such as sleep. The integration of patient- and carer-reported and technology-derived information with more traditional evaluation of cognition presents a major opportunity for recovery research, with particular relevance for cognition.

Candidate Therapies for Cognitive Rehabilitation

The approaches we are interested in directly target cognitive impairments themselves (e.g. executive functions) and not aids (e.g. pagers, reminders) that improve patients' real-world functioning, but not by directly changing cognitive

processing (when the aid is removed, its therapeutic effects are suddenly lost). There are several detailed reviews relating to this topic[22, 23], so here we confine ourselves to outlining some of the key issues. Firstly, it is difficult to isolate individual cognitive functions in terms of measuring outcomes (e.g. working memory and attention frequently modulate tests of executive function). One promising approach that also does away with the issue of correcting for multiple comparisons across tests that are somewhat collinear, is to perform an omnibus test on two different sets of outcomes; those that represent a range of executive functions and those that do not (e.g. are more sensitive to posterior cortical functions). Love et al. did just this using a Bayesian approach[24]. Secondly, interventions need to be delivered in high enough doses to maximise the likelihood of clinically meaningful gains. A way to do this is to augment therapist-delivered, face-to-face training with digital therapies. This has been carried out successfully in studies designed to improve: working memory[25]; goal processing and sustained attention[26]; and, real-world problem solving, with promising effect sizes[27]. Thirdly, with respect to generating evidence from animal models that will be relevant for human rehabilitation, some aspects of cognition are easier to study than others. For example, there are good measures of working memory and attention (**Table 2**) but less analogous ones for complex decision making. While not all cognitive interventions and tests currently have direct equivalents in animal models, there are synergies in cellular and genetic mechanisms that mediate higher cognitive functions across species. For example, changes in the tonic GABA inhibitory pathway have been implicated in age-related decline of human memory function, including spatial reference and working memory[28]. Stroke induces an elevation in tonic GABA signaling and compounds that dampen this response have shown promise in animal models for motor recovery and

are currently being tested in a Phase II trial (ClinicalTrials.gov ID; Servier RESTORE BRAIN Study - NCT02877615). These compounds have also been recently tested in a preclinical model of VCI and shown to improve both reference and working memory. ~~and there is evidence that GABAergic drug therapy improves some of the attentional and cognitive symptoms of Fragile X-syndrome[29].~~ Similarly, Brain Derived Neurotrophic Factor (BDNF) has been implicated as mediating improved spatial memory in a trial of aerobic exercise training in older adults, where training increased hippocampal volume, effectively reversing age-related loss by 1 to 2 years[30]. A recent phase II clinical trial in patients with post-stroke cognitive impairment, showed that exercise paired with cognitive training did improve fluid intelligence, but the relationship to BDNF was less clear[31]. It is here that animal models provide a much more fine-grained approach to understanding the intricacies of the cellular and genetic substrates that underpin human cognition[32]. Armed with such an understanding, we will be in a better position to test interventions in rehabilitative studies in patients.

Conclusions

Research on cognitive recovery after stroke is at an earlier stage of evolution than research in motor recovery. Nevertheless, international consensus is possible in a number of areas. All stroke recovery studies should consider cognition and integrate cognitive evaluation and outcome into their design. Basic neuroscience is essential to develop new interventions to enhance recovery. In order to achieve this, greater alignment between preclinical and clinical research – and the development of an agenda of shared priorities – is required to accelerate progress towards novel therapies. This is best achieved using a bedside to bench to bedside approach.

Table 1. Consensus Recommendations

Recommendations: Observational Studies and Trials
• All intervention studies and trials should include evaluation of cognition • Cognitive function should be evaluated at study enrolment and as an outcome measure (secondary if not primary) • Wherever possible, studies should include evaluation of other behavioural aspects that are associated with cognition and important for quality of life: e.g. mood, apathy, fatigue, anxiety, sleep. • Selection of participants based on language should utilise a formal assessment of language function, apply clear exclusion criteria and aim to define a minimum scientifically justified rate of exclusion
Developmental Priorities
• Longitudinal studies of cognition, with long follow up periods, in clinical and preclinical research • Identification of biomarkers for processes and epochs of recovery (identification of targets for intervention) • Greater use of cognitive paradigms that translate between clinical and preclinical research (supported by standards for selection, execution and reporting of tests)

Table 2. Cognitive paradigms and translation from models to humans

Neurocognitive Domain (DSM-5)	Subdomain	Human Paradigm	Preclinical Paradigms	Comments
Executive function	Cognitive flexibility	Wisconsin Card Sorting Test Digit Symbol Substitution[33]	Attention set-shift	
	Inhibition/impulsivity	Go no-go tasks	Operant conditioning	
	Working memory	Digit Span Spatial Span	T-maze (Delayed alternation task) Y-maze Radial 8-arm maze Morris water maze Trial-unique delayed non-matching-to-location (TUNL) task	Tasks of spatial working memory translate more easily between humans and models. There are many paradigms that have been studied extensively in humans. Despite this, clinical studies currently often opt for digit or letter span tasks.
Complex Attention	Sustained Attention	**Choice Reaction Time[34, 35]**	**5-choice serial reaction time task[36]** 5-choice continuous performance test Signal detection task Cross-modal stimulus presentations	
	Speed of processing	Reaction time tasks	5-choice serial reaction time task	
	Divided attention	Walking while counting backward	Unclear whether tested in preclinical models	
	Neglect	Cancellation tasks[37] Line bisection	Adhesive strip removal	While the adhesive removal test can assess sensory neglect it is

				a combination of cognitive and motor. While cancellation tasks have used letters, other versions use simple objects, such as stars, would more easily translate between models and humans.
Language				Likely cannot be addressed in preclinical animal models
Perceptual-Motor Function	Object recognition (agnosia)	Visual discrimination Pattern recognition	Pairwise/Visual Discrimination/Reversal tasks	
Learning and Memory	Recognition	**Delayed non-matching to sample** Scene Recognition[38, 39]	**Delayed non-matching to sample**	
	Spatial Memory	**Morris Water Maze (human adaptation)***	**Morris Water Maze**	Tests of verbal recall are common in human studies, but less well-suited than spatial, object-based or perceptual tasks to translation
	Associative Learning	**Paired Associate Learning** **Object-in-Scene memory**	**Paired Associate Learning** **Object-in-Scene memory**	
	Emotional Memory		Fear conditioning	

Social Cognition		Little studied in post stroke setting	Not tested in preclinical stroke models

References

1. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The stroke recovery and rehabilitation roundtable taskforce. *Int. J. Stroke*. 2017;12:444-450
2. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, de Haan EH, Kappelle LJ. Cognitive disorders in acute stroke: Prevalence and clinical determinants. *Cerebrovasc. Dis.* 2007;23:408-416
3. Nys GM, van Zandvoort MJ, de Kort PL, van der Worp HB, Jansen BP, Algra A, et al. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. *Neurology*. 2005;64:821-827
4. Brookes RL, Willis TA, Patel B, Morris RG, Markus HS. Depressive symptoms as a predictor of quality of life in cerebral small vessel disease, acting independently of disability; a study in both sporadic small vessel disease and cadasil. *Int. J. Stroke*. 2013;8:510-517
5. Pendlebury ST, Rothwell PM, Oxford Vascular S. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: Analysis of the population-based oxford vascular study. *Lancet Neurol.* 2019;18:248-258
6. McKevitt C, Fudge N, Redfern J, Sheldenkar A, Crichton S, Rudd AR, et al. Self-reported long-term needs after stroke. *Stroke*. 2011;42:1398-1403
7. Quinn TJ, Paolucci S, Sunnerhagen KS, Sivenius J, Walker MF, Toni D, et al. Evidence-based stroke r-ehabilitation: An expanded guidance document from the european stroke organisation (eso) guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *J. Rehabil. Med.* 2009;41:99-111
8. Veldsman M, Brodtmann A. Disconnectomics: Stroke-related disconnection and dysfunction in distributed brain networks. *Int. J. Stroke*. 2019;14:6-8
9. Clelland CD, Choi M, Romberg C, Clemenson GD, Fragniere A, Tyers P, et al. A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science*. 2009;325:210-213
10. Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: Making waves. *Ann. Neurol.* 2006;59:735-742
11. Ray NJ, Metzler-Baddeley C, Khondoker MR, Grothe MJ, Teipel S, Wright P, et al. Cholinergic basal forebrain structure influences the reconfiguration of white matter connections to support residual memory in mild cognitive impairment. *J. Neurosci.* 2015;35:739-747
12. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: The dsm-5 approach. *Nat. Rev. Neurol.* 2014;10:634-642
13. Hachinski V. Vascular dementia: A radical redefinition. *Dementia*. 1994;5:130-132
14. Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic criteria for vascular cognitive disorders: A vascog statement. *Alzheimer Dis. Assoc. Disord.* 2014;28:206-218
15. Skrobot OA, Black SE, Chen C, DeCarli C, Erkinjuntti T, Ford GA, et al. Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the

vascular impairment of cognition classification consensus study. *Alzheimers Dement*. 2018;14:280-292
16. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National institute of neurological disorders and stroke-canadian stroke network vascular cognitive impairment harmonization standards. *Stroke*. 2006;37:2220-2241
17. Horsburgh K, Wardlaw JM, van Agtmael T, Allan SM, Ashford MLJ, Bath PM, et al. Small vessels, dementia and chronic diseases - molecular mechanisms and pathophysiology. *Clin. Sci. (Lond.)*. 2018;132:851-868
18. Kwakkel G, Lannin NA, Borschmann K, English C, Ali M, Churilov L, et al. Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *Int. J. Stroke*. 2017;12:451-461
19. Murphy TH, Corbett D. Plasticity during stroke recovery: From synapse to behaviour. *Nat. Rev. Neurosci.* 2009;10:861-872
20. Tanila H. Testing cognitive functions in rodent disease models: Present pitfalls and future perspectives. *Behav. Brain Res.* 2018;352:23-27
21. Nithianantharajah J, McKechanie AG, Stewart TJ, Johnstone M, Blackwood DH, St Clair D, et al. Bridging the translational divide: Identical cognitive touchscreen testing in mice and humans carrying mutations in a disease-relevant homologous gene. *Sci. Rep.* 2015;5:14613
22. Weicker J, Villringer A, Thone-Otto A. Can impaired working memory functioning be improved by training? A meta-analysis with a special focus on brain injured patients. *Neuropsychology*. 2016;30:190-212
23. Bogdanova Y, Yee MK, Ho VT, Cicerone KD. Computerized cognitive rehabilitation of attention and executive function in acquired brain injury: A systematic review. *J. Head Trauma Rehabil.* 2016;31:419-433
24. Glass BD, Maddox WT, Love BC. Real-time strategy game training: Emergence of a cognitive flexibility trait. *PLoS One*. 2013;8:e70350
25. Westerberg H, Jacobaeus H, Hirvikoski T, Clevberger P, Ostensson ML, Bartfai A, et al. Computerized working memory training after stroke--a pilot study. *Brain Inj.* 2007;21:21-29
26. Levine B, Schweizer TA, O'Connor C, Turner G, Gillingham S, Stuss DT, et al. Rehabilitation of executive functioning in patients with frontal lobe brain damage with goal management training. *Front. Hum. Neurosci.* 2011;5:9
27. Man DW, Soong WY, Tam SF, Hui-Chan CW. A randomized clinical trial study on the effectiveness of a tele-analogy-based problem-solving programme for people with acquired brain injury (abi). *NeuroRehabilitation*. 2006;21:205-217
28. McQuail JA, Frazier CJ, Bizon JL. Molecular aspects of age-related cognitive decline: The role of gaba signaling. *Trends Mol. Med.* 2015;21:450-460
29. Lozano R, Hare EB, Hagerman RJ. Modulation of the gabaergic pathway for the treatment of fragile x syndrome. *Neuropsychiatr. Dis. Treat.* 2014;10:1769-1779
30. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. U. S. A.* 2011;108:3017-3022
31. Ploughman M, Eskes GA, Kelly LP, Kirkland MC, Devasahayam AJ, Wallack EM, et al. Synergistic benefits of combined aerobic and cognitive training on fluid intelligence and the role of igf-1 in chronic stroke. *Neurorehabil. Neural Repair*. 2019;33:199-212

32. Schmidt-Wilcke T, Fuchs E, Funke K, Vlachos A, Muller-Dahlhaus F, Puts NAJ, et al. Gaba-from inhibition to cognition: Emerging concepts. *Neuroscientist*. 2018;24:501-515
33. O'Sullivan M, Morris RG, Markus HS. Brief cognitive assessment for patients with cerebral small vessel disease. *J. Neurol. Neurosurg. Psychiatry*. 2005;76:1140-1145
34. Bonnelle V, Leech R, Kinnunen KM, Ham TE, Beckmann CF, De Boissezon X, et al. Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. *J. Neurosci.* 2011;31:13442-13451
35. Langner R, Willmes K, Chatterjee A, Eickhoff SB, Sturm W. Energetic effects of stimulus intensity on prolonged simple reaction-time performance. *Psychol. Res.* 2010;74:499-512
36. Grottick AJ, Higgins GA. Assessing a vigilance decrement in aged rats: Effects of pre-feeding, task manipulation, and psychostimulants. *Psychopharmacology (Berl.)*. 2002;164:33-41
37. Li K, Malhotra PA. Spatial neglect. *Pract. Neurol.* 2015;15:333-339
38. Mundy ME, Downing PE, Dwyer DM, Honey RC, Graham KS. A critical role for the hippocampus and perirhinal cortex in perceptual learning of scenes and faces: Complementary findings from amnesia and fmri. *J. Neurosci.* 2013;33:10490-10502
39. Moodley K, Minati L, Contarino V, Prioni S, Wood R, Cooper R, et al. Diagnostic differentiation of mild cognitive impairment due to alzheimer's disease using a hippocampus-dependent test of spatial memory. *Hippocampus*. 2015;25:939-951