AHA Scientific Statement

Cognitive Impairment Following Ischemic and Hemorrhagic Stroke

A Scientific Statement from the American Heart Association/American Stroke Association

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Key words: stroke, cognitive impairment, stroke location, diagnostics, pharmacological, non-pharmacological, risk factors**,** quality of life, post-stroke depression, sleep disorders, post-stroke fatigue, functional outcome, screening

Abstract

Purpose: Cognitive impairment is a common consequence of stroke and has direct implications for post-stroke functioning and quality of life including the ability to maintain a job, live independently, sustain interpersonal relationships, and drive a vehicle. In this scientific statement, we critically appraise the literature on the prevalence, diagnosis and management of post-stroke cognitive impairment (PSCI) and provide a framework for the clinical care of these patients while highlighting gaps that merit further study.

Methods: We performed a scoping literature review of randomized controlled clinical trials, prospective and retrospective cohort studies, case-control studies, clinical guidelines, review articles and editorials concerning the incidence and prevalence, natural history, diagnosis, and management of PSCI. Scoping reviews determine the scope of a body of literature on a given topic to indicate the volume of literature and the studies currently available, as well as to provide an overview of its focus.[1]

Results: PSCI is common after stroke, especially in the first year, and ranges from mild to severe. Even though cognitive impairment is reversible in some cases early after stroke, up to one third of individuals with stroke develop dementia within 5 years. The pathophysiology is not yet fully elucidated but is likely due to an acute stroke precipitating a series of pathological events, often in the setting of preexisting microvascular and neurodegenerative changes. Screening for associated comorbidities and interdisciplinary management are integral components of the care of individuals with PSCI. There is a need for prospective studies evaluating the individual trajectory of PSCI and the role of the acute vascular event in the predisposition for Alzheimer's disease and related dementias as well as high-quality, randomized clinical trials focused on PSCI management.

Acronyms:

AD: Alzheimer's disease

ICH: Intracranial hemorrhage

PSCI: Post-stroke cognitive impairment

SAH: Subarachnoid hemorrhage

VCID: Vascular cognitive impairment and dementia

Introduction:

Post-stroke cognitive impairment (PSCI) ranges in severity from mild to severe and occurs in up to 60% of stroke survivors in the first year after stroke with a higher rate seen acutely after stroke. [2, 3,4,5] Up to 20% of individuals with mild PSCI fully recover with the highest rate of recovery seen shortly after stroke. [6] However, improvement in cognitive impairment without return to pre-stroke levels is more frequent than complete recovery. [7, 8] The risk of developing future dementia is increased after stroke even in those with transient cognitive impairment.[9] The American Heart Association/American Stroke Association statement "Vascular Contributions to Cognitive Impairment and Dementia", published in 2011, addressed the construct of vascular cognitive impairment which captures the entire spectrum of cognitive disorders associated with all forms of cerebral vascular brain injury, with or without a clinical history of stroke, with a focus on the role of vascular contributions to dementia.[10] In 2021, the European Stroke Organization and

European Academy of Neurology published joint guidelines on PSCI based on evidence from randomized controlled trials highlighting areas where robust evidence is lacking and suggesting priority areas for future research.[11] In the current scientific statement, we discuss PSCI defined as cognitive impairment resulting from an overt stroke (ischemic or hemorrhagic), ranging from mild cognitive impairment to dementia and provide an actionable summary that delineates a general framework for PSCI screening, diagnosis and management.

This scientific statement is based on a scoping literature review primarily within the last 10 years of randomized controlled clinical trials, prospective and retrospective cohort studies, case-control studies, clinical guidelines, review articles and editorials concerning the incidence and prevalence, natural history, diagnosis and management of PSCI.

Definitions:

The following are key definitions differentiating vascular cognitive impairment and dementia from post-stroke cognitive impairment and dementia:

Vascular cognitive impairment (VCI) refers to cognitive impairment of any severity associated with cerebrovascular disease irrespective of the occurrence of stroke symptoms.[12] The types of vascular injuries leading to VCID range from an insidious, progressive accumulation of microvascular pathologic changes (such as diffuse white matter injury detected on magnetic resonance neuroimaging as white matter hyperintensities or "leukoaraiosis" , cerebral microbleeds, enlarged perivascular spaces or, cortical microinfarcts) to a single clinical stroke event impacting brain structures critical for cognition.[13]

Vascular dementia (VaD) is the end of a continuum of severity of clinical manifestations of VCI.[7]

Post-stroke cognitive impairment (PSCI) refers to any severity of cognitive impairment, irrespective of cause, noted after an overt stroke.[7, 14]

Post-stroke dementia (PSD) is the end of a continuum of severity of clinical manifestations of PSCI and refers to all types of dementia after stroke.[7]

Prevalence and incidence of post-stroke cognitive impairment

The prevalence of PSCI differs by the timing of assessment, diagnostic criteria, demographics (e.g., age, race or ethnicity) and case-mix (e.g., stroke severity, prior/recurrent stroke, pre-stroke dementia, population vs. hospital based, interval from stroke, inclusion of patients with aphasia), resulting in substantial heterogeneity in reported estimates.[15, 16] PSCI is most common in the first year after stroke occurring in up to 60% (cumulative incidence) of stroke survivors with the highest rate seen acutely after stroke.[5] At 3 months after stroke, 76-83% of stroke survivors are impaired in at least one cognitive domain.[17, 18] The Stroke and Cognition Consortium (STROKOG) harmonized data of neuropsychological test scores in 3,146 participants after stroke (97%) or TIA (3%) from 13 studies based in 8 countries and found that 44% were impaired in global cognition 2 to 6 months after the index event. [4] A large population of stroke survivors have cognitive impairment that is not sufficient to meet diagnostic criteria for dementia, but still impacts quality of life.[19] A systematic review that included 23 studies published between 1995-2017 found a pooled prevalence of PSCI without dementia in the first year after stroke of 38% [95% CI = 32-43%] thus concluding that, 4 in 10 stroke survivors display a level of cognitive impairment that does not meet the criteria for dementia.[20]

In a meta-analysis of 22 hospital-based and eight population-based eligible cohorts (N=7511), the pooled prevalence of pre-stroke dementia was higher (14.4%, 95% CI 12.0-16.8) in hospital-based studies than in population-based studies (9.1%, 95% CI 6.9-11.3). [21] Therefore, in studies where cognitive performance is only assessed after but not before the stroke, the estimates of PSCI may not account for any impairment that may have been present before the stroke onset. For example, in the Norwegian-Cognitive Impairment After Stroke (Nor-COAST) multicenter prospective cohort study of mostly mild stroke (N=617), PSCI (including dementia) was prevalent in 59% of participants at 3 months and 51% at 18 months. [22] In this study, 9% of participants had pre-stroke mild or major cognitive impairment. [22] In another cohort of individuals with mild stroke (N=220) that excluded pre-stroke cognitive impairment, the overall frequency of 3-month PSCI was 47.3%.[3]

The prevalence of PSD varies by stroke severity as well as history of stroke recurrence and occurs less frequently than milder forms of cognitive impairment.[23, 24] In a meta-analysis of 22

hospital-based and eight population-based eligible cohorts (7,511 patients), between 1950 and 2009, PSD rates in the first year after stroke ranged from 7.4% (95% CI 4.8-10.0%) in population-based studies of first-ever stroke in which pre-stroke dementia was excluded to 41.3% (95% CI 29.6-53.1%) in hospital-based studies of recurrent stroke in which pre-stroke dementia was included. About 10% of patients had dementia before first stroke, 10% developed new dementia soon after first stroke, and more than a third had dementia after recurrent stroke. [21]

~~In the~~The population-based Oxford Vascular Study, demonstrated that stroke severity is strongly linked to dementia risk probably accounting for much of the observed differences between hospital-based and population-based studies: the 1-year incidence of dementia was 34.4% (95% CI 29.7-41.5) in patients with severe stroke (NIHSS>10), which is about 47 times higher than that of the background age- and sex-matched population, versus 8.2% (95% CI 6.2-10.2; about 3.5 times that of the background age- and sex-matched population) in those with minor stroke (NIHSS<3).[23] The 5-year cumulative incidence of new PSD was 33.1% (31.7–34.5) after stroke with 51% of dementia diagnosed within the first year with greater front-loading of risk in those with major vs more minor stroke.[23]

Racial differences in the frequency and severity of PSCI have been reported.[25] Stroke in Black patients results in a greater cognitive decline and is more frequently associated with dementia within 5 years of ischemic stroke when compared to White patients, despite Black patients having a younger age at the time of the incident stroke. [26]

Both pre-stroke and post-stroke cognitive impairment and dementia are frequent in patients with intracranial hemorrhage (ICH) and higher in those with lobar ICH.[27, 28] In a prospective observational cohort study of 218 patients without pre-existing dementia, the incidence rate of new-onset dementia at 1 year after ICH was 14.2% (95%CI 10.0-19.3) and 28.3% (22.4-34.5) at 4 years.[28] The incidence of new-onset dementia was more than two times higher in patients with lobar ICH (incidence at 1 year 23·4%,95%CI 14·6-33·3) than for patients with non-lobar ICH (incidence at 1 year 9·2%, 95%CI 5·1-14·7).[28]

In subarachnoid hemorrhage (SAH), impairment in at least one neuropsychological domain is common. Depending on the assessment tool used, the rates of impairment on global mental status testing 3 months after SAH range between 26% to 43%.[29]

Natural history of post-stroke cognitive impairment

The temporal pattern of post-stroke dementia based on clinical observation is variable. It may 1) start at the onset of stroke and stabilize, 2) start at the onset of stroke and progress, 3) develop after recurrent strokes, 4) develop at the onset of stroke in the presence of pre-existing cognitive impairment or 5) develop more than 3-6 months after stroke. [30]

The majority of studies on cognitive impairment after stroke report a prevalence or cumulative incidence of dementia at specific time-points with relatively few data on individual cognitive trajectories. If cognitive assessment is done in the very early period post-stroke, estimates of impairment are even more elevated (up to 91.5% at 2 weeks, in one series). [31] Although early impairment post-stroke is common, PSD may be an inappropriate label for these early fluctuations in cognition because most improvement occurs within the first six months post-stroke.[17, 32-34] However, cognitive recovery may be limited in patients with multiple comorbidities, polypharmacy, older age, and previous cognitive decline.[35]

Data on PSCI in the long-term are sparse. In a small study (N=109) of 7-year stroke and TIA survivors, 37% had mild cognitive impairment, and 22% had dementia.[36] Another study reported cognitive impairment in 22% of survivors at 14 years post-stroke.[2] In the Atherosclerosis Risk in Communities Cohort Study (n=15,379 participants free of stroke and dementia at baseline),the risk of dementia compared to no stroke over a median follow-up of 25.5 years by adjusted hazard ratio was 1.76 (95% CI, 1.49-2.00) for 1 minor to mild stroke, 3.47 (95% CI, 2.23-5.40) for 1 moderate to severe stroke, 3.48 (95% CI, 2.54-4.76) for 2 or more minor to mild strokes, and 6.68 (95% CI, 3.77-11.83) for 2 or more moderate to severe strokes.[24] Additional studies are needed to better characterize these temporal patterns and possible contributing factors. [30]

Delayed onset post-stroke cognitive impairment

While there is no widely accepted consensus definition, late PSCI is usually defined as new cognitive impairment or dementia with onset more than three to six months after the stroke.[37]

The risk factors and pathophysiological mechanisms of late post-stroke cognitive decline and dementia differ from early PSCI. One major risk factor is stroke recurrence although rates of stroke recurrence are low in the context of robust secondary prevention. The incidence of new dementia is much higher after a second stroke.[23,21,24]Among those with late-onset PSCI without recurrent stroke, the progression of cerebral small vessel disease appears to play an important role, although other neurodegenerative diseases such as Alzheimer's disease (AD) also need to be considered.[37] Other risk factors for late post-stroke cognitive decline include older age, baseline cognitive impairment, hypertension, diabetes, and brain atrophy.[37]

In the Reasons for Geographical and Racial Differences in Stroke study (REGARDS) study, incident first-ever stroke was associated with a stepwise immediate decline in cognitive function followed by an accelerated risk for future cognitive decline greater than what was expected for age.[25] This acceleration in cognitive decline was greater in older stroke survivors than younger stroke survivors.[25]A systematic review of population-based and hospital-based cohorts found that the overall incidence of new dementia more than 6 months after stroke was 1.7% per year but varied by stroke severity.[21] In the Framingham Study, the 10-year risk of dementia was 19.3% following stroke and 11.0% without stroke. Incident stroke doubled the risk of dementia even after adjusting for age, sex, education and, stroke risk factors.[38]

Differential diagnosis

In addition to the direct effects of the stroke, cognitive function following stroke can be impacted by other stroke complications (e.g., hyponatremia, delirium, depression), as well as by pre-stroke cognitive decline and coexisting age-related neuropathologies. Delirium is a common complication of stroke, occurring in about 25% of admitted patients, and should be differentiated from PSCI.[39] The clinical hallmarks of delirium are alterations in arousal and attention, cognition, and behavior that arise over a short period of time and are not better explained by a neurodegenerative disorder or PSCI.[40] Delirium is more common in patients with stroke who are older, have more severe stroke, post-stroke infection, pre-stroke cognitive decline, and greater brain atrophy.[41] Furthermore, stroke lesion topography has been linked to delirium in patients hospitalized with stroke.[42] Work-up for delirium should include electrolytes, tests of liver and renal function, assessment for infection, constipation, pain and a review of medications.

To exclude potentially reversible causes of impairment, the clinician should obtain laboratory testing for thyroid stimulating hormone and vitamin B12,[43] as well as consider the potential cognitive effects of mood disorders, sleep disorders including obstructive sleep apnea, sedating and anticholinergic medications and, hearing and vision impairments. Post-stroke depression is common, affecting about one third of persons with stroke.[44] Post-stroke depression is often accompanied by cognitive symptoms which makes differentiating it from primarily PSCI more complex. Because depression-related cognitive symptoms may resolve with treatment of the depression, it is important to screen for post-stroke depression especially when PSCI is suspected. [44] The use of a depression screening tool validated in stroke patients may aid in recognition of depression.[45] Risk factors for post-stroke depression include higher physical disability, pre-stroke history of depression, anxiety, cognitive impairment, and lack of social and family support.[44]

Post-stroke cognitive decline should be differentiated from pre-stroke decline. Questioning the patient and an informant about cognitive-related activities of daily living (such as finances, shopping, and organizing medications) or using a validated questionnaire such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) may determine whether there was cognitive impairment that predated the stroke.[46,47] Causes of cognitive impairment before stroke can include vascular cognitive disorders, such as covert cerebral small vessel disease related to stroke risk factors, as well as comorbid age-related neurodegenerative diseases such as AD. In the elderly, it is common for dementia to have multiple etiologies (also termed “mixed dementia”), most frequently VCID in combination with AD.[10]

Most mixed dementia in the elderly is caused by a combination of vascular disease and irreversible neurodegenerative pathologies, particularly AD. The clinician should consider whether AD or another neurodegenerative disease is present. More research is needed on how to accurately diagnose AD and other neurodegenerative pathologies in the setting of a recent stroke. Biomarkers of the AD pathophysiological process, such as beta-amyloid and tau, can be measured in CSF, blood, or by positron-emission tomography. However, such testing is currently expensive, invasive, or not widely available for routine use.

Symptoms and cognitive domains affected

An individual's cognitive trajectory in the months after stroke might be impacted by multiple factors, including the stroke location, preexisting cognitive impairment, small vessel disease and comorbidities, sociocultural (e.g., socioeconomic status) and demographic characteristics (e.g., age, sex) of the person experiencing the stroke, and the interventions provided. Stroke location has been linked to the type of cognitive deficits observed but is not perfectly predictive of cognitive impairment. Involvement of "strategic" locations, such as the left frontotemporal region, left thalamus, and right parietal lobe,[48] as well as the left middle cerebral artery (MCA) territory, have been associated with increased likelihood of PSCI.[49] Support vector regression-based lesion symptom mapping (SVR-LSM) performed at three to six months after ischemic stroke identified the left angular gyrus, left basal ganglia structures and the white matter around the left basal ganglia as strategic structures for global cognitive impairment after stroke.[50] Larger strokes tend to involve many of these regions, making it hard to differentiate cognitive impairment due to regional involvement versus due to stroke size and severity. Because aphasia is common after left MCA stroke and several commonly used cognitive tests and screening instruments depend on intact language function, the severity of cognitive impairment may be overestimated in individuals with aphasia and with left MCA strokes. Furthermore, some studies explicitly exclude individuals with aphasia, leading to difficulties capturing the true rates of cognitive impairment in the broader stroke population.

Global cognitive deficits have been described in the post-stroke setting,[51] but this global impairment may reflect use of global cognitive measures in many studies.[52] Difficulty with executive function and attention (and in some studies, memory) are common after ischemic stroke,[53] but also have been reported to show the most improvement by 3-6 months post-stroke, whereas impairment in the language domain tends to remain stable over time.[53,54] Patients with ICH show similar cognitive deficits as ischemic stroke patients,[55] with different domains impacted depending on the location (i.e. lobar vs nonlobar) of the ICH.[56]

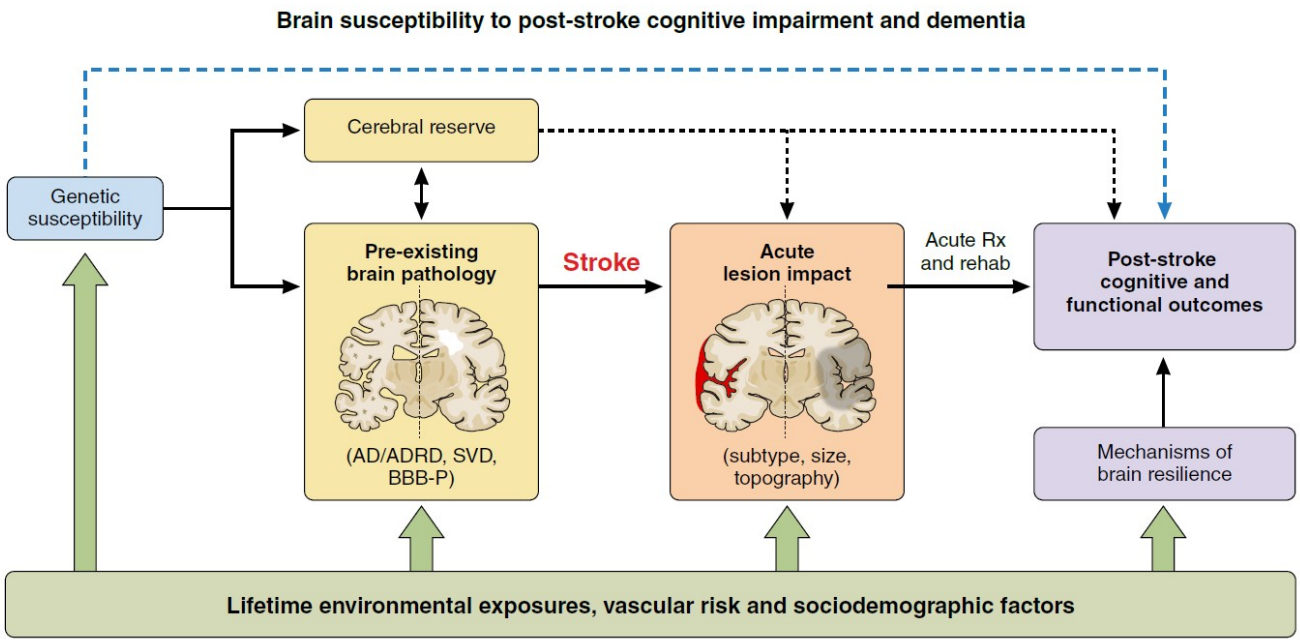
Patients with SAH frequently have less baseline vascular disease or subclinical cerebrovascular disease (both important contributors to PSCI)[56] than other stroke populations. Yet, executive function and processing speed are also impaired in patients with SAH.

Pathophysiology

In the general population, small vessel disease is the biggest contributor to VCID, while in the post-stroke population there is a relatively greater contribution from larger, more destructive embolic infarcts. The exact pathophysiology of PSCI is not well understood given the paucity of knowledge regarding the effects of specific stroke subtypes (i.e. acute ischemia, ICH or, aneurysmal SAH), as well as the variable contributions of the severity of the injury, lesion location, and the interaction between the pre-existing brain pathology and an acute stroke event which may serve as a trigger or accelerate cognitive decline in a vulnerable brain.[14, 57] The constructs of brain reserve and brain resilience as they relate to brain health are evolving.[58 59] Brain reserve is the difference between the degree of brain damage observed in an individual and the clinical manifestation of that damage. Brain resilience is a combination of the brain's capacity to counteract the lifetime accumulation of damage and the compensatory mechanisms that can be used to mitigate the effects of this damage. [58, 59] It is likely that brain reserve and resilience and the factors contributing to them also play a role in the degree of cognitive impairment in the setting of stroke-related brain injury **(Figure 1).**

In most brains affected by stroke, there are diffuse age-related changes involving the smallest building block of the brain parenchyma, the neurovascular unit, which includes neurons, astrocytes, pericytes, microglia and blood vessels.[60] The neurovascular unit is the key structural element of what has been termed "brain health," or the brain's capacity to operate at its optimal state of structural and functional integrity, in the absence of or despite the impact of insidious or precipitous injuries related to cerebrovascular dysfunction, metabolic disarray, proteinopathies, or inflammatory responses.[61-64] The structural elements of the neurovascular unit are often damaged by stroke-related injury possibly leading to PSCI (**Figure 1**).[58, 59] However, the same elements can also be considered as points of intervention for future treatments, rehabilitation and prevention strategies involving lifetime environmental exposures, vascular risk factor modification, and even gene therapies.[65]

Figure 1. Brain Susceptibility to post-stroke cognitive impairment and dementia



Conceptual framework for factors contributing to the pathophysiology of PSCI

Abbreviations: AD/ADRD – Alzheimer's disease and related dementias, BBB-P – blood-brain barrier permeability, Rx – treatment, SVD -small vessel disease

Risk factors

Risk factors for PSCI reflect both pre-existing cerebral vulnerability/reduced reserve and the stroke impact; a minor stroke may precipitate dementia in an older person with a vulnerable brain.[21, 23, 37] Key vulnerability factors include age, cerebral small vessel disease, and neurodegeneration, which may be partially mitigated by higher educational attainment and premorbid intelligence (indicators of "cerebral reserve").[21,23, 37] Co-morbid post-stroke depression is also an important factor associated with PSCI, and the two disorders frequently co-exist possibly through shared mechanisms. The risk associated with late-life vascular factors on early post-stroke cognitive decline is unclear except for diabetes mellitus which has been associated with an increased risk.[66] Pre-stroke cognitive decline which may be assessed using informant questionnaires [e.g., IQCODE or, Eight-Item Informant Interview to Differentiate Aging and Dementia (AD-8)[67]] is an important predictor of PSCI. Strong social networks may be a protective factor although evidence specifically in PSCI is sparse.

PSCI is more common with higher stroke lesion load ie in severe or recurrent strokes.[21, 23,37] The risk of PSCI varies with stroke subtype (higher in hemorrhagic and cardioembolic stroke compared to lacunar stroke), likely partially driven by the corresponding stroke severity. Lesion location is important as risks are higher in stroke affecting specific brain regions (see the previous section on "Symptoms and cognitive domains affected").

In ICH, lobar location carries greater risk than deep location likely because lobar hemorrhages are associated with underlying cerebral amyloid angiopathy.[28, 68, 69] In aneurysmal SAH, delayed cerebral ischemia and chronic hydrocephalus predict PSCI but the underlying biological mechanisms remain poorly understood.[70]

Brain imaging findings (lesion volume, white matter hyperintensities, atrophy) are proxies for stroke severity and brain vulnerability with lobar microbleeds and global small vessel disease burden being important predictors of dementia after hemorrhagic stroke.[28, 68, 69, 71] However, it remains unclear to what extent imaging biomarkers predict PSCI over and above clinical factors including ~~A~~acute cognitive status (delirium, low cognitive test score) which is ~~also~~ a powerful predictor, capturing both pre-stroke decline and lesion impact.[21, 37, 69,] Post-stroke delirium is associated with higher risk for post-stroke dementia as well as lower survival.[72] ApoE-ϵ4

homozygous genotype is a possible risk factor for pre- and post-stroke dementia, accelerating early decline after major stroke and increasing the probability of later dementia after less severe events. [73]

Knowledge gaps remain, particularly in understanding the role of non-cerebral factors including infection, frailty and social factors. Further studies are needed to understand the independent predictors of post-stroke cognitive decline and whether blood and cerebrospinal fluid biomarkers and brain imaging add predictive value over clinical factors.

Association with other post-stroke outcomes

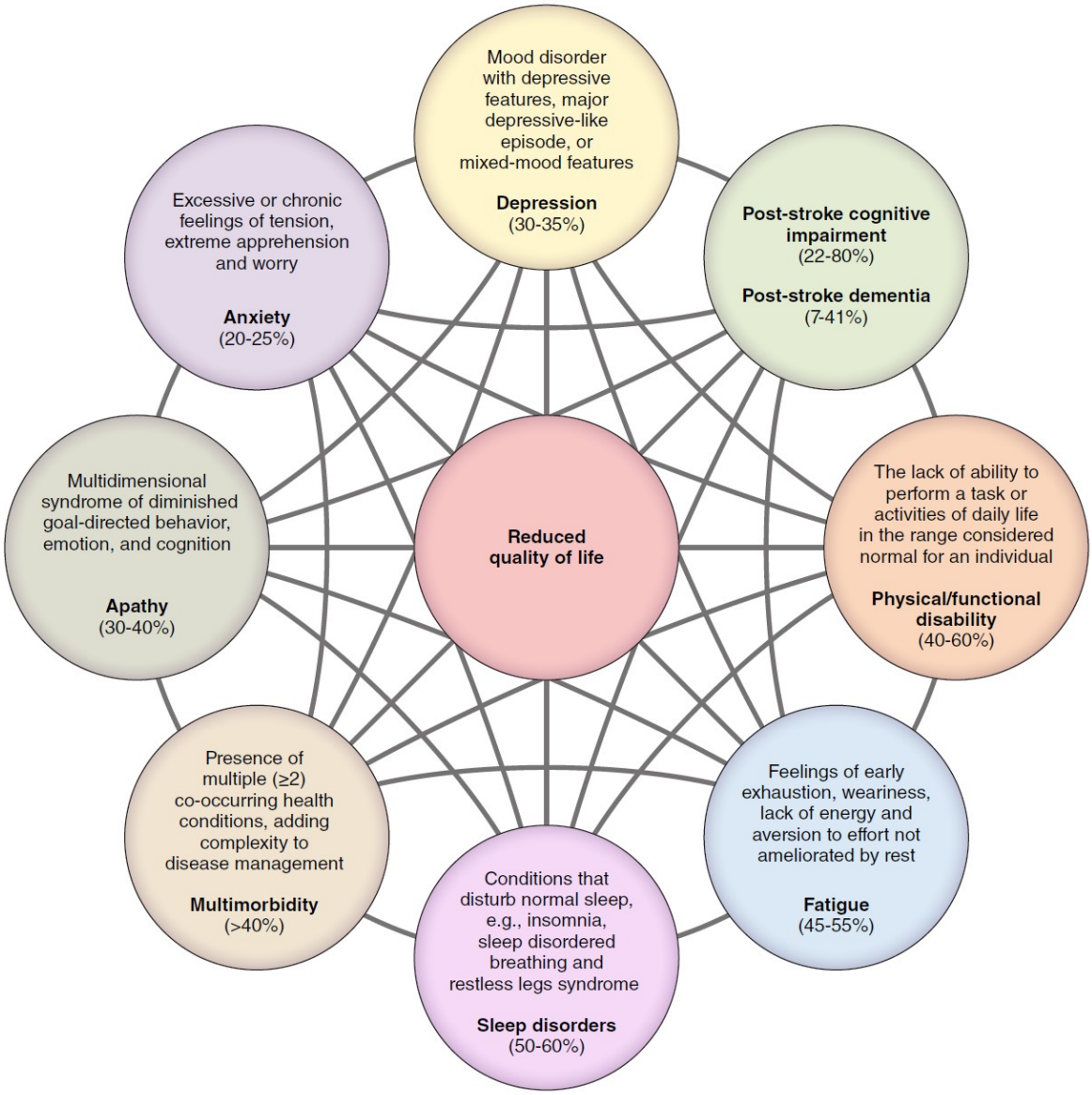
PSCI is associated with other adverse outcomes, including physical disability, sleep disorders, depression, personality and behavioral changes, and other neuropsychological changes, all contributing to a lower quality of life.[74] Independent of the occurrence of PSCI, these outcomes are common after stroke (Figure 2).[44, 74-80] Risk factors also overlap, including older age, stroke severity, history of previous stroke, multiple comorbidities, lower educational attainment, and social isolation.[21, 81] Coexisting adverse post-stroke outcomes and multimorbidity can complicate timely diagnosis and effective treatment,[82] for example the exacerbation of cognitive impairment after stroke due to undiagnosed depression.[16]

In patients with physical deficits after stroke, functional outcomes, measured using the modified Rankin Scale, Barthel Index, or assessment of activities of daily living, are directly affected by cognitive impairment, as patients with PSCI may have difficulty participating in rehabilitation and experiencing the full benefit of a rehabilitation program. Cognitive dysfunction, however, is not conditional on physical disability, as PSCI may occur after mild stroke or transient ischemic attack.[9, 21, 23]

Alongside cognitive assessment post-stroke, patients should be evaluated for problems with physical function, sleep, mood, anxiety, apathy, fatigue, and other personality and behavioral changes both in the acute stage and later during recovery. Although the association between these conditions and PSCI is incompletely understood, they all contribute to reduced quality of life in stroke survivors. (Figure 2). Poor access to resources and stigma surrounding diagnoses of dementia, disability, and depression may impede care.[83]

Robust clinical trial data on the impact of neuropsychological treatments or sleep interventions on PSCI are lacking although improving physical activity [84] and antidepressant use[85] may provide small or short-term benefits in specific cognitive domains. Further research is needed to understand the effect of sleep interventions, such as continuous positive airway pressure for sleep apnea on post-stroke cognitive outcomes.[86] Research is also needed to determine the frequency of co-occurrence of these sleep-related conditions in patients with PSCI.

Figure 2. Comorbid conditions occurring in patients with post-stroke cognitive impairment and dementia contribute to reduced quality of life. Definitions of post-stroke outcomes and their approximate incidence or prevalence (%) within 12 months after stroke



Screening and diagnostic modalities in the clinic

Cognitive complaints, or subjective reports of cognitive decline, are common in patients after stroke,[87, 88] and are linked to objective cognitive impairment as determined by performance-based, standardized measures of cognitive function.[88-90] Yet, several factors impact patients'

report of cognitive problems beyond the presence of objective cognitive dysfunction. Higher psychological distress (e.g., depression, negative affect) has been linked to increased report of cognitive difficulties post-stroke, independent of the severity of objective cognitive impairment.[87, 91] Anosognosia or lack of awareness of the presence or severity of a person's own cognitive deficits often results in underreporting of cognitive problems.[92] Additional information can be gathered from collateral sources, such as family members or caregivers. Informant report is specific, but insensitive to PSCI and can be impacted by interpersonal and cultural factors.[93] Thus, while the report of cognitive decline by patients and their informants is important, objective cognitive assessment is crucial to accurately identify cognitive dysfunction particularly when anosognosia is present.

While there is no gold standard for cognitive screening post-stroke, several brief cognitive screening tests (30 minutes or less) have been used in the identification of post-stroke cognitive impairment. [94-98] The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) have been the most widely studied cognitive screening instruments,[94, 96, 97] with the MoCA generally being recommended over the MMSE,[94, 96, 99]particularly in subacute phases post-stroke,[98] as it has less of a ceiling effect and is more sensitive to mild cognitive impairment. Yet, several other cognitive screeners show initial evidence for their utility in identifying cognitive impairment post-stroke.[95-97, 100] The choice of the best screening tool to use for a given patient will vary based on the psychometric properties of the test, demographic (age, sex, educational attainment), cultural and language characteristics of the patient, circumstances of test administration (e.g., time, bedside/clinic/telehealth), and the presence of other stroke-related impairments.[101]

Unfortunately, most screening instruments were not developed to identify the heterogeneous presentation of post-stroke cognitive deficit and might miss subtle (yet impactful) post-stroke cognitive changes. Furthermore, stroke-related impairments, such as motor weakness, unilateral neglect and aphasia, as well as demographic factors such as education, language or culture, may render standard cognitive screening tools inadequate.[102] Tailored comprehensive neuropsychological evaluations, with use of appropriate normative data that considers demographic (educational attainment, age, and sex), cultural and linguistic factors, and accounts

for stroke-related deficits may improve diagnostic accuracy, provide a thorough characterization of the patient's cognitive strengths and weaknesses, and identify mild cognitive changes over time.

Early detection of cognitive impairment in the acute stroke unit is essential for informing interventions and for discharge planning, and the natural history of post-stroke cognitive impairment indicates that it is also important to assess for cognitive changes over time. However, the comparative effectiveness of different screening strategies--including whom to screen, when, and how often-- has not been evaluated in prospective clinical trials. There are potential downsides to screening including cost and the potential to falsely label patients as cognitive impaired based on low test scores from confounding factors such as cultural bias, education bias, test anxiety, or administration in a second language. False positive diagnoses can cause harm by inducing psychological distress or reducing patient autonomy, for example by leading to loss of the license to drive or to independently manage financial affairs. Notwithstanding these uncertainties, which should be addressed in future research, unquestionably it is necessary to screen whenever there is a cognitive complaint or a clinician concern over cognitive ability. Clinician concern should be triggered by unexplained patient difficulties with cognitive-related activities of daily living, following clinician instructions, or providing a reliable history. Stroke systems of care need to be resourced to provide cognitive screening and assessment in patients at risk, including sufficient time for cognitive screens, if indicated, and healthcare professionals to follow up with detailed assessments and plans for accommodation and rehabilitation.

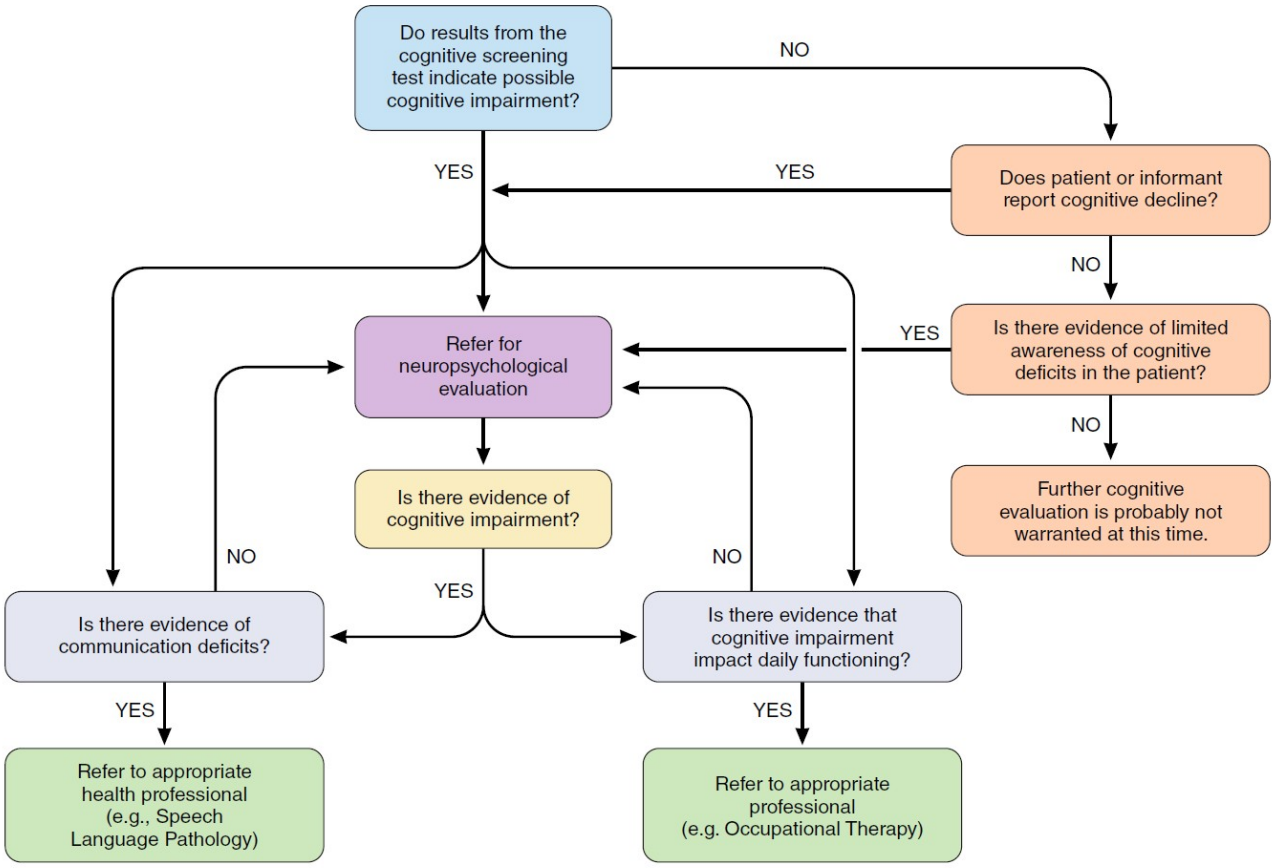
Management of post-stroke cognitive impairment

Interdisciplinary collaboration

Collaboration between physicians including neurologists, gerontologists and primary care physicians, speech language pathologists, occupational therapists, neuropsychologists, nursing and related health professionals is crucial throughout levels of post-stroke care for the optimal identification and management of cognitive problems post-stroke. A tailored neuropsychological evaluation is best suited to thoroughly characterize cognitive strengths and weaknesses, which is important for optimal management of PSCI. This also will aid in individualizing care tailored to the patient's needs, such that involvement of all disciplines is not needed for all patients.

For example, speech-language pathologists can identify and treat cognitive and communication deficits post-stroke (as well as dysphagia). Occupational therapists can further evaluate and manage the functional impact of cognitive problems in patients' daily activity contexts. A streamlined, interdisciplinary model of care beyond the acute and subacute phases post-stroke is needed for optimal monitoring and, management of cognitive deficits. Telehealth services might be a useful tool to implement such a model, provided barriers to these services are addressed. [103] While referral patterns differ depending on local resources and expertise, **Figure 3** provides a decision tree to help guide collaborations between relevant healthcare services, particularly in the process of screening and diagnosis of PSCI in post-acute care settings, as comprehensive and evidence-based post-acute care models are developed. The team composition should be tailored to the symptoms and needs of the individual patient.

Figure 3. Considerations for assessment and multidisciplinary evaluation of PSCI



Cognitive rehabilitation

In general, cognitive rehabilitation (including restorative cognitive training and functional cognitive rehabilitation) after stroke results in small improvements of cognitive functioning compared to control conditions (treatment-as-usual or "active" sham intervention).[104] Small gains, both immediate and sustained, occur in several cognitive areas (attention, memory, executive function) and visuospatial neglect. Specifically, memory gains occur with strategy training,[105-107] but attention training does not produce consistent benefits.[108, 109] Benefits of computerized cognitive training such as engaging and gamified cognitive exercises accessed from the patients' own computers or mobile devices over standard cognitive rehabilitation are inconsistent but tend to be better with clinician-directed programs.[110-113] Emerging evidence,

albeit from small or lower-quality studies [114] suggest potential cognitive benefits of virtual reality tools and,[115-117] training and education for family and patients.[118-120]

Physical activity

Physical activity may have a positive impact on cognitive function after stroke, with a possible advantage of aerobic compared to non-aerobic exercise. [121-123] Small studies suggest cognitive benefits of specific forms of physical activity, such as Tai Chi, [124] boxing[125], and resistance exercises.[126] Evidence regarding the added benefit of using virtual reality with physical activity is inconclusive.[127, 128]

Medical and pharmacological treatments

Because the risk of PSCI increases with stroke recurrence, secondary stroke prevention including antihypertensive therapy, statins, diabetes control, and anticoagulation for atrial fibrillation is an important approach to prevent the risk or worsening of PSCI.[129] Treatments for hypertension and lifestyle programs to reach target blood pressure after stroke have so far failed to show positive impacts on cognitive function.[130, 131] Current evidence is insufficient to prove whether some antihypertensive drug classes are better than others at preserving cognition. Nonetheless, hypertension treatment reduces the risk of incident and recurrent strokes which are risk factors for PSCI. In the general population, blood pressure lowering with antihypertensive agents compared with control is associated with a reduced risk of cognitive impairment and incident dementia.[132,133] More research is needed to close the gaps in the disparities in hypertension control that extend beyond lifestyle factors and the effect of this on the incidence and progression of PSCI.

There are knowledge gaps in the effect of interventions for smoking, obesity, diabetes, hyperlipidemia and obstructive sleep apnea for reducing the risk of PSCI, although they are generally considered to be additional important modifiable risk factors for preventing cognitive decline.[134] Simultaneous treatment of multiple vascular risk factors as compared to only one or few were associated with a slower cognitive decline in a cohort of patients with AD and could improve or maintain cognitive functioning in at-risk elderly people from the general population. [135, 136] Similar studies of multiple simultaneous interventions are needed in patients with PSCI.

Systematic reviews of dopamine agonists[137] and selective serotonin reuptake inhibitors[138-140] show no consistent beneficial effects on cognition following stroke. Individual small clinical trials have reported a variety of pharmaceutical agents that may have a potential benefit on global cognition: neurotrophics (cortexin),[141] peptides such as cerebrolysin [142] and relaxin,[143] citicoline (cytidine-5′-diphosphocholine),[144] and nitrates (glyceryl trinitrate).[145] Specific pharmaceuticals may impact defined aspects of cognition, including effects of dopamine agonists on hemi-inattention [146] and selegiline on attention and executive function.[147]

Cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine), and memantine, a N-methyl D-aspartate (NMDA) receptor antagonist, are sometimes prescribed for patients with dementia after stroke, although more work is needed to define the safety and efficacy of these drugs in this population.[148, 149] Randomized trials provide moderate quality evidence for small improvements in cognition, of uncertain clinical relevance, with donepezil, rivastigmine, galantamine, or memantine; however, they are complicated by adverse events (including dizziness and diarrhea) and patient discontinuation.[150]

Emerging, complementary, and integrative treatments

Small studies have shown the benefits of remote ischemic conditioning for visuospatial, attention, and executive functions [151] and long-term (over 6 months) global cognition.[152] Further confirmatory studies with larger samples are warranted.[153] Several studies suggest potential benefit from transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). [154, 155] In a meta-analysis of 15 studies (N=820 participants) of tDCS, compared with sham tDCS or control, anodal tDCS was associated with a small improvement in the general cognitive and attention performance but not with memory.[154] Most of these studies however were of lower methodological quality, lacked sham tDCS and lacked safety data.[154] Well-designed studies are needed to determine the potential benefits of neuromodulation in the treatment of post-stroke cognitive deficits and to establish the optimal treatment protocols.[154] Acupuncture treatments may also have a positive effect on global cognition. [156-158] However, a meta-analysis suggests that the majority of these studies were of low quality.[158] The combination of acupuncture with other therapies (e.g., cognitive or physical rehabilitation) may enhance the benefits of either alone.[159, 160]

Preliminary and exploratory studies suggest potential cognitive benefits from a variety of herbal treatments and vitamins including Huperzine A,[161] depsides salts from Salvia Miltiorrhiza[162], ginkgo biloba[163], pomegranate polyphenols [164] and Cerebralcare Granule,[165] but no benefits from mailuoning[166], folic acid and B-vitamins.[167] None of these are approved by the US Food and Drug Administration for use in post-stroke cognitive impairment. Finally, there is a paucity of randomized studies of the potential effects of 'heart healthy' diets [e.g., Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean diet, Mediterranean-DASH Intervention for Neurodegenerative Delay diet (MIND) diet] on cognition after stroke.

Anticipatory guidance for patients and their caregivers

Actionable Considerations for the Clinician When Cognitive Impairment is Detected on Screening

Stroke survivors with dementia are at higher risk of mortality, disability and institutionalization.[168] When cognitive impairment is detected on screening, comprehensive cognitive evaluation, such as a battery of standardized neuropsychological assessments, can further help characterize impaired cognitive domains.[169] In addition to the management of post-stroke cognitive deficits described above, other considerations include assessing for safety issues regarding home environment, return to work (if applicable), and driving as well as assessing for caregiver fatigue and connecting patients and caregivers with available community resources when possible. Advance care planning including personal medical directives and identifying an enduring power of attorney should also be considered.

Home Safety

Recommendations for home safety post-stroke are predominantly related to the ability to perform daily activities of living due to limitations in mobility and cognition. The most common issues in the home environment for stroke survivors are using the bathroom and limited mobility and communication.[170] Examples of recommendations for these issues include providing appropriate equipment for mobility, installing grab bars or raising toilet seats in the bathroom, and establishing a personal emergency system for simplified access to immediate help.[170] Impaired cognition is also associated with falls, and the majority of falls occur at home.[171] To ensure home safety, health care providers need to assess the home environment, identify home safety issues, and provide appropriate recommendations to stroke survivors and their caregivers. Transitional

care processes, especially those that are more intensive, may increase home safety and reduce hospital readmission rates.[172]

Return to Work

Evidence for a relationship between cognitive function and return to work after a stroke is primarily from prospective observational studies. Deficits in global cognitive function[173] and specifically executive function[174] are negatively related to return to work. The risk of cognitive decline at 1 year post-stroke is higher for people who were not employed before the stroke and for those who did not return to mentally stimulating jobs after a stroke.[175] Qualitative studies consistently indicate that lack of knowledge of, or support for, "invisible" deficits such as cognitive impairments, are deterrents to return to work or maintaining a job after returning to work.[176-178] Return to work may be facilitated by cognitive or vocational rehabilitation.[179]

Driving

In many cultures, driving is a sign of independence, has a strong impact on quality of life, and may be necessary for work or for socializing. After a stroke, approximately one third of patients require some type of training or rehabilitation to return to driving.[180] Cognitive abilities have been linked to success on driving tests. However, a systematic review of 53 studies did not find strong evidence to recommend any one cognitive assessment tool over another.[181] Although inconsistencies in these studies' methodologies and results prevent strong conclusions, better attention and executive function are most often related to a return to driving.[182, 183] A variety of training programs exist, although many do not encompass all of the components that impact successful driving (e.g., cognitive function, sensory perception, mobility, motivation).[180] A systematic review of four randomized controlled trials with 245 participants reported no improvements in on-road performance or any cognitive function following a driving intervention, although driving simulations may be more effective than other training programs.[184]

Conclusions and future directions

PSCI is common and contributes to the poorer health status of stroke survivors. It often occurs in the presence of a variety of stroke-related deficits and other comorbid conditions such as depression, adding complexity to both its diagnosis and treatment. Management requires a multi-pronged approach that includes evaluation and management of co-morbid conditions,

anticipatory guidance for matters such as home safety and driving, implementation of secondary stroke prevention strategies to minimize progression of cognitive impairment, and importantly, administration of treatments to optimize functioning and improve cognition (Figure 4). Thus, the comprehensive management of patients with PSCI should involve an interdisciplinary collaboration of the patient and their caregivers with health professionals including neurologists, occupational therapists, speech therapists, nurses, neuropsychologists, gerontologists, and primary care physicians. Given the prevalence of PSCI and its association with poor health-related outcomes, the implementation of protocols to systematically evaluate and treat PSCI based on locally available resources is warranted.

As outlined in Table 1, there are multiple unanswered questions regarding the pathophysiology, diagnosis and treatment of PSCI. More studies are needed on the exact mechanisms of PSCI and the effects of specific stroke subtypes and the interaction between the pre-existing brain pathology, socio-cultural factors, and the acute stroke event. The DISCOVERY study (Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on Recovery), is an ongoing prospective, multicenter, observational, nested-cohort study of 8,000 ischemic and hemorrhagic stroke patients, without history of dementia, enrolled at the time of index stroke from thirty clinical sites across the US and followed for a minimum of 2 years, with serial cognitive evaluations and assessments of functional outcome, with subsets undergoing research magnetic resonance imaging and positron emission tomography and comprehensive genetic/genomic and fluid biomarker testing. The overall scientific objective of this study is to elucidate mechanisms of brain resilience and susceptibility to PSCI in diverse US populations. [14] Future research might inform best practices for cognitive screening post-stroke. Perhaps the most pressing need, however, is the development of effective and culturally-relevant treatments for PSCI, through the conduct of adequately powered clinical trials of cognitive rehabilitative techniques, pharmaceutical agents, and lifestyle modifications in diverse groups of patients. Along with this, studies are required to evaluate if multidisciplinary clinics or other models of care improve outcomes for patients with PSCI. Given the significant contribution of PSCI to the growing burden of dementia, focusing on these unanswered questions should be considered a priority.

Figure 4. Summary of contributing factors, differential and considerations for management of Post-stroke cognitive impairment

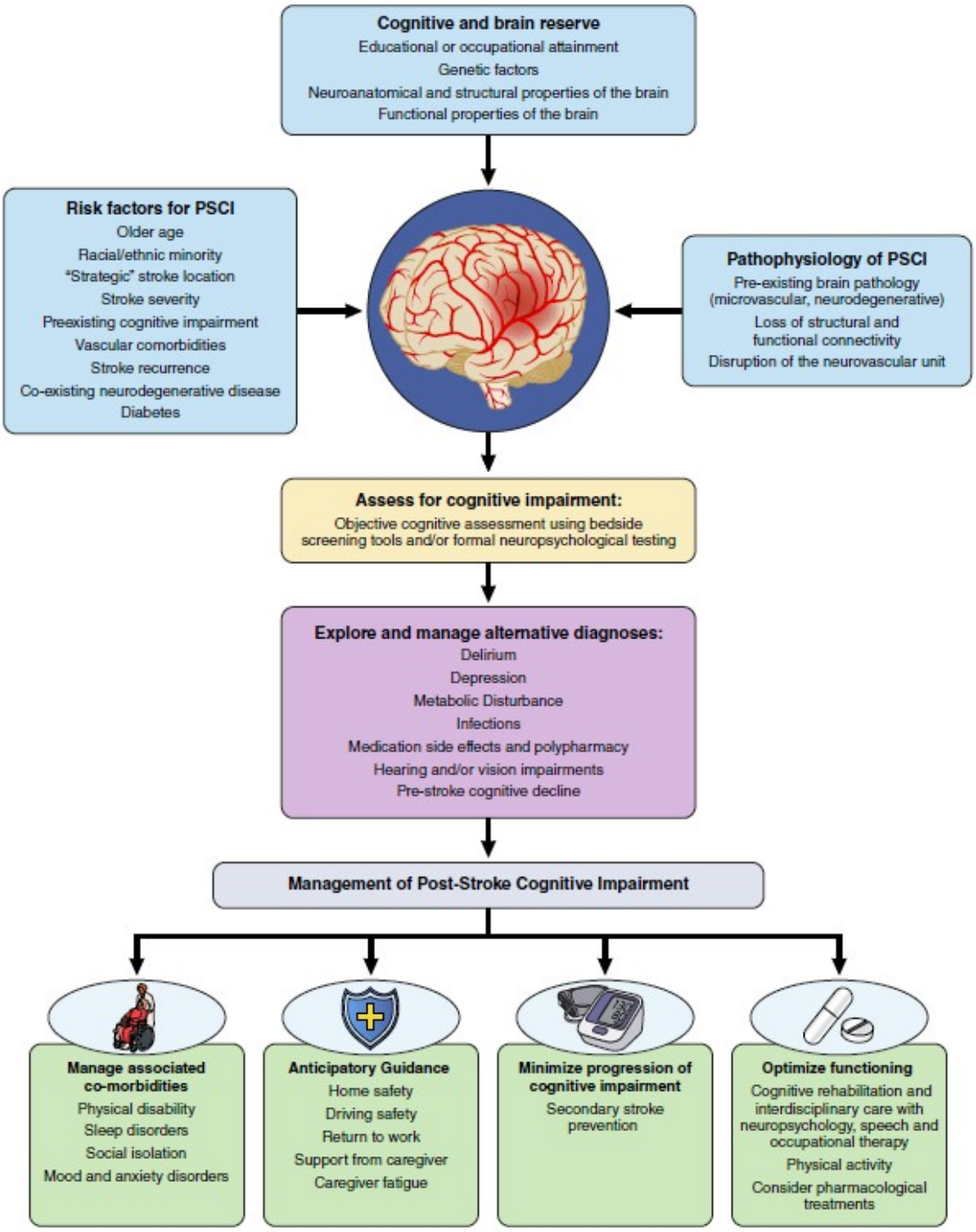


Table 1. Considerations for clinical practice and gaps needing additional studies according to section

Section	Suggestions for clinical practice	Gaps
Prevalence and incidence	The prevalence of PSCI differs by timing of assessment, diagnostic criteria, demographics and case-mix, resulting in substantial heterogeneity in reported estimates. PSCI is most common in the first year after stroke with the rate of mild cognitive impairment (22-80%) being more common than dementia (7-34%).	Estimates of incidence adjusted for competing risk of death, overall and in specific subgroups including minority populations and women are needed to better ascertain actual public health burden.
Natural history	PSCI tends to improve over time with most recovery occurring within the first 3 to 6 months.	More research is needed on the individual post-stroke cognitive trajectories.
Delayed onset cognitive impairment following stroke	Late post-stroke dementia defined as new dementia with onset more than three to six months after the stroke is estimated to occur in about 1.7% of stroke survivors per year.	Further studies are needed to characterize the types of late post-stroke dementia. Studies evaluating late post-stroke cognitive impairment should exclude those with impairment before 3-to -6 months from the stroke and thus not report on the cumulative incidence of cognitive impairment which combines early and delayed onset.
Differential diagnosis	PSCI can be exacerbated by other complications or comorbidities, such as metabolic abnormalities, medication side effects, infections, delirium, sleep disorders, hearing and vision impairments and depression. The impact of pre-stroke cognitive decline and coexisting age-related neuropathologies such as Alzheimer's disease should be considered.	More research is needed to determine if fluid (blood/CSF) and imaging biomarkers can be used to assist with the diagnosis of PSCI.
Symptoms and cognitive domains affected	Cognitive deficits post-stroke can be limited to specific domains, or may be global, depending on the size and location of a given stroke.	More research is needed to understand how stroke location and size interact with cognitive reserve to cause PSCI with different severity and cognitive profiles.

Pathophysiology	Stroke-related injury to the neurovascular unit, secondary neurodegeneration and loss of structural and functional connectivity may lead to PSCI	More research is needed on the exact mechanisms of PSCI and the effects of specific stroke subtypes (i.e., acute ischemia, ICH, or aneurysmal subarachnoid hemorrhage) as well as stroke severity, lesion location, and the complex interaction between the pre-existing brain pathology and the acute stroke event.
Risk factors	The risk of cognitive decline after stroke is determined by cerebral vulnerability/reserve together with the impact of the stroke lesion. Key risk factors include older age, pre-stroke cognitive decline, pre-existing white matter disease or neurodegeneration, diabetes, stroke severity, prior/recurrent stroke, stroke location and acute cognitive status.	Further studies are required to determine the independent predictors of post-stroke cognitive decline, the role of non-cerebral factors including infection, frailty and social factors and the added value of blood, CSF and brain imaging biomarkers.
Association with other post stroke outcomes	PSCI is associated with other adverse outcomes, including physical disability, sleep disorders, behavioral and personality changes, depression, and other neuropsychological changes all leading to lower quality of life.	More studies are needed to evaluate the association and frequency of co-occurrence of PSCI with other post-stroke outcomes including anxiety, apathy, and fatigue and the effect of sleep interventions and treatment of comorbid depression and anxiety on post-stroke cognitive outcomes.
Screening and diagnostic modalities in the clinic	Tailored neuropsychological evaluations improve diagnostic accuracy for cognitive impairment post-stroke, provide a thorough characterization of the patient's cognitive strengths and weaknesses, and best identify subtle cognitive changes over time post-stroke.	More studies are needed to elucidate the optimal timing for screening for PSCI, the best screening tools and whether screening affects patient outcomes More research is needed on the optimal testing for the additional impact of stroke on cognitive impairment in individuals who already have a history of dementia as well as the development of cognitive assessments that can be practically used by busy

		clinicians and that would capture the heterogeneous nature of PSCI including in patients with impaired language function.
Management	Interdisciplinary collaboration is essential for the optimal identification, and management of PSCI. Clinician-directed behavioral cognitive rehabilitation and physical activity are likely beneficial for post-stroke cognition. While individual small studies show the benefits of some pharmaceutical treatments for specific cognitive abilities, there are no consistently positive effects of pharmaceutical agents for post-stroke cognition.	Additional studies are needed to examine the impact of heart-healthy diets and treatments for underlying risk factors (e.g., smoking, obesity, and obstructive sleep apnea) on post-stroke cognitive function. Appropriately powered randomized controlled studies are needed for pharmacological as well as non-pharmacological treatments such as ischemic conditioning, neuromodulation, and acupuncture for post-stroke cognitive function.
Anticipatory guidance	Comprehensive cognitive evaluation with considerations for pharmacological and non-pharmacological treatments, management of stroke risk factors to prevent stroke recurrence, targeting of high risk populations, evaluation for comorbid complications and assessing for home safety, driving and return to work (if applicable) are warranted.	High-quality studies are needed to evaluate the benefit of multidisciplinary clinics for individuals with stroke and cognitive impairment on the quality of life, cognitive function, caregiver burden and functional outcome.

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