Post-stroke Cognitive Impairment

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2.1 Introduction

Post-stroke cognitive impairment (PSCI) is one of the most representative syndromes of vascular cognitive impairment (VCI). The current research on both the pathophysiology and the biomarkers of VCI is based on PSCI. However, cognitive decline is less interesting for those neurologists investigating stroke when compared to other stroke-related symptoms and signs, including hemiplegia and language disturbance. Conversely, memory clinic doctors exploring dementia are not greatly familiar with the differential diagnosis underlying cognitive impairment following stroke.

Post-stroke cognitive impairment is known to have a major impact on recovery after stroke. In contrast to Alzheimer's disease, a significant part of the disease is anticipated to be prevented by controlling vascular risk factors from the middle age. Indeed, a recent study that reported a reduction in the prevalence of dementia also suggested it to be a result of the decrease in vascular dementia [1].

Despite this implication for therapeutic and preventive effects, the mechanism behind the occurrence of PSCI, the sensitivity of its identification, and the ways it can be prevented and treated are still to be fully determined. Additional research is needed in many areas, such as in understanding its pathogenesis, developing appropriate biomarkers, and attempting the detection of successful treatments.

This chapter will summarize the knowledge about PSCI gathered to date and discuss the direction that researchers should strive to.

2.2 Epidemiology

2.2.1 Ischemic Stroke and PSCI

With regard to the epidemiology of PSCI, Pendlebury et al. summarized its prevalence and incidence rates at each hospital and community-based clinical setting, distinguishing between patients with a first-ever stroke and recurrent strokes [2]. In brief, about 10% of patients with a first-ever stroke and 30% of those with recurrent strokes also presented PSCI, which differed depending on whether they were included in hospital or community-based studies.

Furthermore, the time at which the cognitive function was assessed is crucial, considering that the post-stroke cognitive function changes dynamically and greatly varies depending on the time intervals between cognitive assessment and stroke onset. Most of the previous studies evaluated the baseline cognitive function at

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3–6 months following stroke onset, given the delirium and acute confusional state which immediately follow acute stroke [3–5]. However, such studies were conducted at very different time intervals; therefore, care must be taken when interpreting their results.

Additionally, PSCI prevalence may differ depending on the area of the cognitive domain assessed. Previous studies reported the impairment of memory and frontal function to be characteristic of PSCI [6]. In contrast, although the visuospatial function and language are believed to be relatively preserved, this is again dependent on the location of the stroke lesions and the eligibility criteria of the corresponding studies.

2.2.2 Hemorrhagic Stroke and PSCI

Important data related to intracerebral hemorrhage were recently obtained with the effort of the PITCH (Prognosis of Intracerebral Hemorrhage) cohort [7]. This study included a total of 218 non-demented patients with spontaneous intracerebral hemorrhage and reached a median follow-up duration of 6 years. The cumulative incidence rates of new-onset dementia in patients without any history of either stroke or transient ischemic attack were 14.6% and 21.8% at 1-year and 4 years post-intracerebral hemorrhage, respectively. In contrast, they were higher in patients with both previous strokes and lobar intracerebral hemorrhage. Multiple microbleeds (>5 in number), disseminated superficial siderosis, and higher cortical atrophy scores were identified as risk factors for PSCI following intracerebral hemorrhage. This provides information on the high-risk groups which require surveillance.

2.3 Classification

The existing classification of PSCI, for example, multi-infarct dementia and strategic infarct dementia, is based on both the location and the number of ischemic lesions observed in the brain imaging. In addition, its classification is linked to the time of cognitive impairment occurrence in relation to the time of stroke onset. Recent research revealed the causes of cognitive impairment to differ according to early- and late-onset PSCI [8]. For example, early-onset PSCI, which is usually defined when occurring within 6 months from the stroke, is mainly affected by stroke itself, including its lesion location and burden. However, delayed-onset PSCI, which arises past the 6 months following stroke, is associated with severe small vessel diseases [5]. Furthermore, although the amyloid pathology also affects delayed cognitive impairment, it has a greater impact on pre-stroke cognitive impairment. From a therapeutic point of view, a classification method reflecting the pathophysiology, rather than simply classifying by imaging findings, is needed.

For example, in the Alzheimer's disease field, the A/T/N classification system, which reflects the pathophysiology of the disease, is sought to identify patients at an early stage [9]. I propose to classify PSCI into mild vs. major (based on the neuropsychological finding) and early onset vs. delayed onset (based on the intervals between the onsets of cognitive impairment and stroke) and to describe the accompanying main pathology. For example, it can be classified as "delayed-onset major post-stroke neurocognitive disorder with superimposed amyloid pathology," "delayed-onset major post-stroke neurocognitive disorder with superimposed severe small vessel disease," or "early-onset major post-stroke neurocognitive disorders with strategic lesion." This method will help to recruit a relatively homogeneous group of patients in future clinical trials, enabling the identification of both the causes and the mechanisms underlying PSCI.

2.4 Clinical Characteristics

The clinical features of patients with PSCI are variable depending on both the location and the size of their lesion. Generally, decreased processing speed, dysexecutive symptoms, and memory impairment are well-known characteristics of PSCI [6]. However, when the lesion is too large,

the cognitive impairment may be overlooked due to other neurological deficits.

PSCI patients often also present gait disturbances, voiding difficulties, and behavioral symptoms, such as aggression, agitation, anxiety, and depression, during the early stage of the disease. However, further research concerning the reason behind the presence of these problems from the beginning of the disease are still required. Please note that gait disturbances, including frontal gait disorders, will be discussed in more detail in other chapters.

Furthermore, these symptoms are not fixed and greatly vary over time given the brain neuroplasticity after injury. In previous cohort studies, approximately 7.8% of the patients reported better cognitive function than the baseline, 14% had worse, whereas the rest remained at the same level [10]. In addition, Levine et al. suggested the changes in cognitive function prior to and following stroke to be also domain specific, enabling a better understanding of the dynamic changes in cognitive function due to stroke [11]. Specifically, a sudden drop and subsequent accelerated rate of decline in global cognition, but only a sudden drop in new learning and an acceleration in fluency rate of decline, were observed.

Considering that the PSCI encompasses a wide range of patients, determining both the selection criteria and the evaluation methods of the patients included in each study is fundamental for a better understanding of its clinical features.

2.5 Neuropsychological Evaluations

2.5.1 Brief Screening Tests

As mentioned earlier, considering the distinct clinical characteristics of PSCI from Alzheimer's disease, specific neurophysiological assessment tools are needed. Memory decline is one of its most prominent features, similar to other neurodegenerative dementia, while frontal-executive/attention deficit and decline of speed processing are also among the earliest features in PSCI patients [6]. Therefore, a tool able to sensitively detect cognitive decline in these domains is needed [12].

The most appropriate screening tool for evaluating PSCI is yet to be determined. To date, the consensus is known to be relatively favorable to Montreal Cognitive Assessment (MoCA), given that Mini-Mental State Examination (MMSE) is insufficient to evaluate the frontal function. In fact, previous studies showed that 32% of patients who did not report any abnormality in their MMSE scores had abnormal MoCA scores [6]. In addition, contrary to MMSE, the MoCA domain subtest score helped the differentiation between PSCI groups based on the abnormalities observed in both the executive function and attention domain [6]. Furthermore, another study indicated the cognitive decline with a baseline MOCA score lower than 26 to be associated with subsequent cognitive impairment (defined as clinical dementia rating ≥ 0.5), functional impairment (defined as modified Rankin scale >2), and death after 3 years of follow-up [13]. Additionally, the Addenbrooke's Cognitive Examination-Revised (ACE-R) was found to be more useful than the MMSE, considering its ceiling effect in discriminating between the mild cognitive impairment and normal groups [12].

The 5-min MoCA and the 5-min National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) vascular cognitive impairment harmonization standards neuropsychological protocol (VCIHS-NP), consisting of subtests of the MoCA, are designed to be tested verbally without the use of hands and may be useful in acute stroke patients with dominant hand paralysis or as a screening test through the telephone [14, 15].

Considering not only the type of the screening test but also the timing of the assessment is necessary. To confirm the diagnosis, the neuropsychological assessments should be performed at least 3 months following the stroke onset to rule out the effects of delirium or confusion in its acute phase. However, to identify the high-risk group for PSCI requiring early treatment, conducting an appropriate screening test within 1–2 weeks from the onset [6, 14] may be beneficial. Furthermore, follow-up

of the cognitive function through yearly screening or detailed examinations is also essential to confirm the occurrence of delayed cognitive impairment. Finally, the main risk factors known to date include older age, female sex, lower education levels, previous stroke history, severe white matter hyperintensities (WMHs), and multiple microbleeds [2, 7]. Patients at risk of developing future cognitive impairment should be informed and followed up regularly.

2.5.2 Detailed Neuropsychological Tests

A statement from the American Heart Association/American Stroke Association proposed that the vascular dementia diagnosis should be based on those neuropsychological test which assesses a minimum of four cognitive domains, including executive/attention, memory, language, and visuospatial function [16]. Furthermore, the diagnostic and statistical manual of mental disorders (DSM-5) recommends evaluating the following domains: complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition [17]. Additionally, an International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) statement suggests the following cognitive domains need to be assessed in vascular cognitive disorders: attention and speed processing, frontal-executive function, learning and memory, language, visuoconstructional-perceptual ability, praxis-gnosis-body schema, and social cognition [18].

The NINDS-CSN proposed the VCIHS-NP as the standardized tests to evaluate cognitive function [19] in PSCI patients. It consists of a 5-, 30-, and 60-min protocol, with the 5-min protocol representing a constellation of MoCA subtests, as mentioned earlier. Given that the VCIHS-NP was indicated as a reliable evaluation tool for multinational and multicenter trials and to comprise sensitive and specific tests for patients with VCI, many countries published local norms and validation data. In addition, the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), which are usually used in patients with degenerative dementia, were used for the cognitive evaluation of VCI. Furthermore, the VDAS-Cog, a modified version of the ADAS-Cog, Cambridge cognition examination (CAMCOG), and several computerized cognitive evaluation tools are also employed.

2.5.3 Interpretation of Neuropsychological Tests

While determining the identification of cognitive impairment, most of the diagnostic criteria are presented in comparison with norms for age, gender, and education levels. In the case of mild neurocognitive disorders, a decrease between −1 and −2 standard deviations from the age-, sex-, education-adjusted mean of the normal distribution is observed, whereas major neurocognitive disorders are defined as a decrease of −2 standard deviations or more [17].

Attention should be paid not only to the type of tests but also to both the appropriate performance of such tests and the correct interpretation of the results. In addition to cognitive function, the presence of any physical barrier that may affect the test results should also be carefully examined. For instance, hearing loss and visual acuity abnormalities can have a significant impact on the test results. Either hemiplegia or visual field defect caused by stroke can influence the trail making test results, for example. Therefore, inspecting these conditions thoroughly before the neuropsychological evaluations and recording the situation in detail in each case is of fundamental importance for examiners.

Furthermore, the use of appropriate statistical methods when analyzing the change in cognitive function over time and when handling longitudinal data is necessary [20]. Each cognitive domain is not independent and affects each

other. In addition, the test results at a given point are affected by previous test results. Therefore, suitable analytical methods which consider such effects are needed [20]. Moreover, patients with severe neurological deficits or cognitive decline are more likely to be excluded from analysis during the follow-up, which may lead to attrition bias in clinical trials. Therefore, efforts should be made to prevent these patients from being overlooked, for example, by conducting either telephone-based cognitive testing or home visits [21].

2.6 Pathophysiology and Imaging Studies

Recent developments in the imaging technology enabled a better understanding of the complex pathophysiology of PSCI (Fig. 2.1).

2.6.1 Large International Multicenter Cohort for Lesion-Symptom Mapping: Identifying the High-Risk Location

In addition to the already well-known strategic locations, we recently opened a new chapter in lesion-symptom mapping through large collaborative studies, such as the meta-analyses on strategic lesion locations for vascular cognitive impairment using lesion-symptom mapping (META VCI MAP) (https://metavcimap.org). Collaborators are collecting large lesion-function datasets from all around world and creating a functional map of the brain, without neglecting any part of the brain. Future researchers will not only understand the cognitive map of the brain through this work but also help the selection of high-risk groups, vulnerable to cognitive decline.

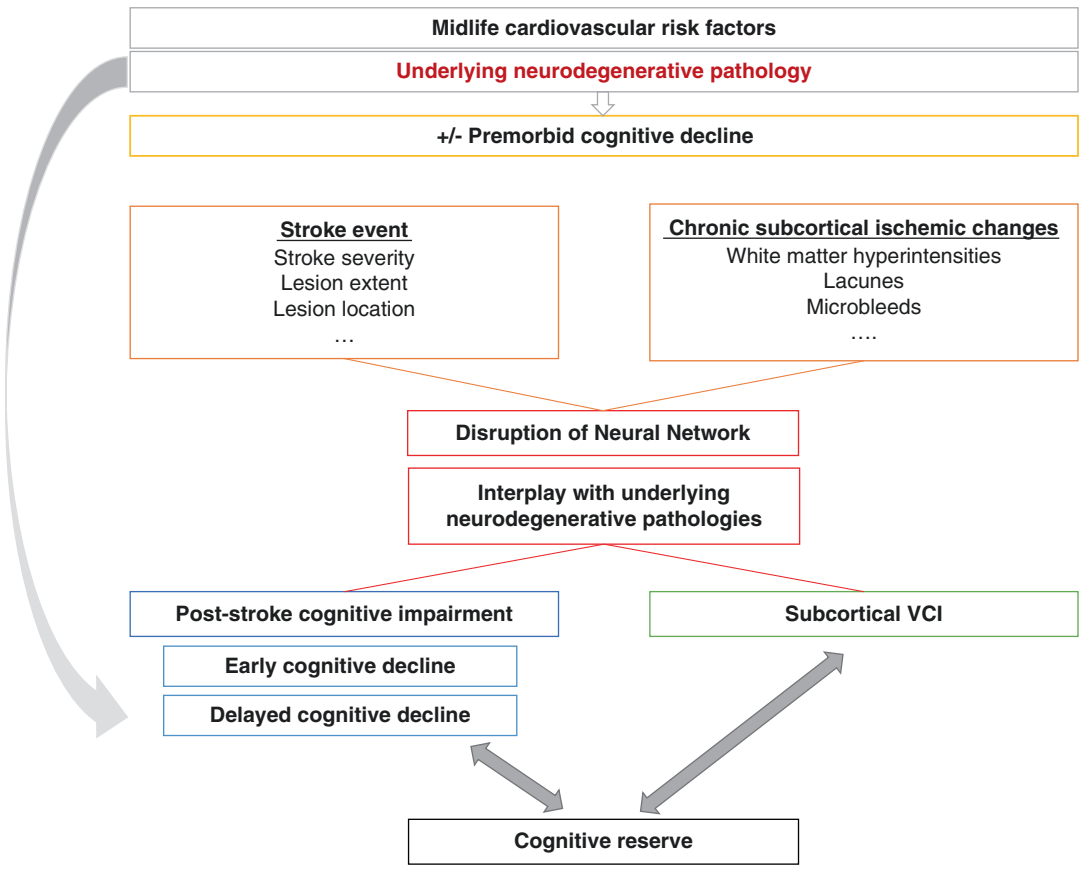

Fig. 2.1 A schematic diagram of post-stroke cognitive impairment pathophysiology

However, various obstacles exist, including the fact that lesion-symptom mapping studies are based on the accurate registration of patients' stroke lesions from a common template [22]. In fact, it was statistically tested that certain areas are related to cognitive disability. However, some points to consider are the following: (1) errors in the registration of lesions from the common template, (2) mapping errors due to the reconstruction of the functional circuit following stroke, and (3) the presence of few stroke lesions in certain areas, which may lead to their exclusion from the analysis.

2.6.2 Connectivity Analysis: Identifying a More Distributed Effect by Focal Lesions

In addition to the lesion-symptom mapping mentioned above, Duering et al. provided excellent insights into the mechanism by which stroke lesions lead to remote brain structural changes and cognitive impairment [23]. In fact, they revealed through diffusion tensor imaging techniques that a lacunar infarction located in the anterior thalamic radiation caused corresponding frontal cortical thinning and decreased frontal domain function.

The concept that a lesion of the same size has a significant effect on its cognitive ability when located in an important region, such as a hub [24, 25], is traditionally known as strategic infarction. Some lesions, including the anterior thalamus, caudate head, and medial temporal lobe, are recognized to cause a cognitive impairment after stroke. In addition to these observations, recent advances in the imaging techniques helped in understanding the reason behind such detrimental consequences of lesions in the whole brain (Fig. 2.2). After various connectivity analysis, it was shown that the brain network attributes, including network efficiency and characteristic path lengths, are worsened by focal lesions. These metrics provide us with an intuitive understanding of information processing efficiency in the brain.

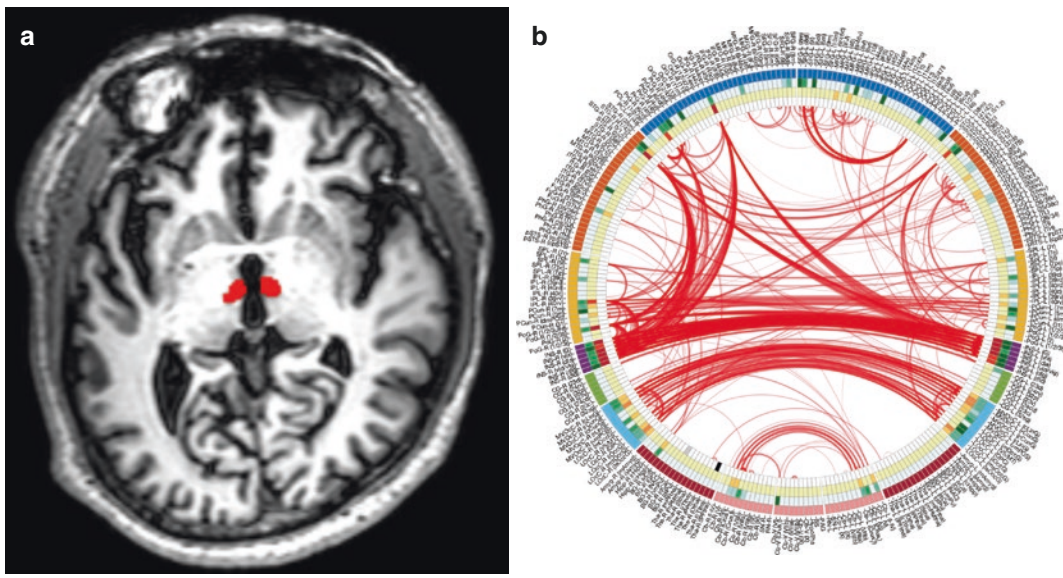

Fig. 2.2 Representative neuroimaging findings on post-stroke cognitive impairment. In the past, post-stroke cognitive impairment was classified and defined through both the location and the size of the lesion (**a**, red-colored lesion masks). Following the advancements in the neuroimaging techniques, the visualization of the effects of such strategic lesions on the whole brain connectivity is today possible (**b**). Magnetic resonance imaging (T1) of the bilateral paramedian thalamic infarction (artery of the Percheron territory). Whole brain connectome of the same patient identified using the resting-state functional MRI

Furthermore, the Corbetta group is actively studying the changes in functional neural network composition using the resting-state functional magnetic resonance imaging (MRI) [26]. The conceptual changes in the neural network structure, such as the reduction of network efficiency and modularity, are currently researched via well-designed studies, which showed that interhemispheric integration and intrahemispheric segregation are important for several behavioral impairments following stroke [26]. In addition, modularity was another useful indicator of post-stroke cognitive recovery [27].

The remaining challenges are to both facilitate the understanding of such discoveries by clinicians and to improve the effectiveness of diffusion tensor imaging and resting-state functional MRI for their application in the clinical field. Finally, the development of new imaging techniques, which can be intuitively understood, is also of crucial importance.

2.6.3 Superimposed Amyloid Pathology: Finding an Accomplice

Mok et al. conducted a study on stroke patients with amyloid positron emission tomography (PET) positivity and found them to have a steeper decline in cognitive function, as assessed by both MMSE and MoCA, compared with patients with amyloid PET negativity [3]. The amyloid pathology not only damages neurons but also affects cerebral blood vessels, given that amyloid deposits in blood vessels interfere with amyloid clearance through the disruption of the glymphatic system and consequently contribute to brain degeneration [28]. However, recent studies delivered conflicting results, as amyloid PET did not indicate any increase either inside or surrounding infarcted lesions [29], while tau depositions were observed nearby the ischemic lesions following stroke [30]. This superimposed amyloid pathology is thought to influence pre- and post-stroke cognitive function through several mechanisms.

2.7 Treatment

While research on biomarkers is actively being conducted, clinical trials on potential treatments are yet to show successful results, as determined by a valuable review published in *Nature Reviews Disease Primers* [31].

Briefly, the prevention of recurrent strokes and chronic ischemic changes is theoretically a reasonable therapeutic goal to consider. However, in the case of antiplatelet drugs, major clinical trials, including the PRoFESS (aspirin plus extended-release dipyridamole vs. clopidogrel) and the SPS3 (aspirin plus clopidogrel vs. aspirin plus placebo), failed to provide significant results [32, 33]. In fact, a critical appraisal of the study results indicated the absence of evident cognitive decline in the control group. In addition, the PRoFESS used the MMSE as its primary outcome variable, through which the sensitive detection of cognitive impairment is difficult [32]. Similarly, although patients with subcortical infarction were included in the SPS3, more than half of them had none or only mild WMHs, while little cognitive decline was observed in the control group, as described above [33].

Therefore, conducting further research by appropriately selecting a high-risk group able to show the therapeutic effect is fundamental. A recent PICASSO trial is awaiting for its results [34, 35], which are expected to be of great interest and value. This study was conducted on patients with multiple cerebral microbleeds and prior intracerebral hemorrhage, with a large number of the participants presenting moderate to severe WMHs. While this is known to distinguish the population at risk of cognitive decline following stroke, the effect of the trial drug cilostazol is expected to be clearly identified. Cilostazol has preclinical and clinical evidence for its protective effects on WMH progression [36], by decreasing amyloid beta accumulation and increasing regional cerebral blood flow, as well as the effect of preventing recurrent strokes [34, 37, 38].

Furthermore, although the results are not consistent for anticoagulants, recent studies in patients with atrial fibrillation indicated that

the use of anticoagulants may prevent dementia, suggesting that prevention of ischemic lesions may be effective to prevent cognitive decline [39].

In addition, the protective effects of other drugs, including statins, peroxisome proliferator-activated receptor (PPAR)-gamma agonists, and angiotensin-receptor blockers, on PSCI are currently under investigation.

Similarly, a non-pharmacological approach using multifaceted interventions, such as dietary modification, physical activities, and cognitive interventions, is actively researched. Although each individual intervention does not bring the desired effects, several interventions applied at the same time may prove effective, such as the FINGER trial [40].

Accordingly, the American Heart Association offers the "life's simple 7," promoting a healthy lifestyle for the middle age population [http://www.heart.org/en/professional/workplace-health/lifes-simple-7]. Specifically, it consists of the following suggestions, stop smoking, eat better, get active, lose weight, manage blood pressure, control cholesterol, and reduce blood sugar, and provides detailed advice on how to achieve each goal. Furthermore, the concept of optimal brain health, recently published in the *Stroke* journal as a presidential advisory from the American Heart Association/American Stroke Association, also addresses the direction in which such preventive strategies should be pursued [41] and offers advice on how to define, monitor, and protect optimal brain health.

2.8 Future Directions and Collaborations

As mentioned earlier, several research topics are yet to be solved. Large multicenter cohort studies, including the STROKOG and METACOHORTS, are being conducted to answer burning questions, such as the determination of the cognitive burden in stroke patients and the mechanisms by which cognitive functions change over time [42, 43]. In addition, studies like the META VCI MAP will reveal important cognitive maps, which were not previously known. By identifying the genetic predisposition to PSCI, important data on precision medicine are needed to develop some treatments tailored to the individual patient [44]. Furthermore, the DEMDAS cohort will provide longitudinal data covering various serum and neuroimaging biomarkers, including diffusion tensor imaging, resting-state functional MRI, and amyloid PET [4]. Finally, besides such well-known large cohorts, basic experiments using animal models and computational modeling will ensure the discovery of the pathophysiological mechanisms underlying PSCI. We hope that both the efforts of various research groups investigating the cognitive dysfunction following stroke and the knowledge gained will extend to the therapeutic trials.

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