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NEUROPROTECTION

REVIEW

Unravelling the nexus of stroke and dementia: Deciphering the role of secondary neurodegeneration in orchestrating cognitive decline

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Abstract

Stroke is the leading cause of acquired disability. The development of acute ischemic stroke treatments, such as mechanical thrombectomy and tissue plasminogen activator, has resulted in more patients surviving the initial insult. However, long-term complications, such as post-stroke cognitive impairment (PSCI) and dementia (PSD), are at an all-time high. Notably, 80% of stroke survivors suffer from cognitive impairment, and a history of stroke doubles a patient's lifetime risk of developing dementia. A combination of greater life expectancy, an increase in the number of strokes in young individuals, and improved survival have inherently increased the number of years patients are living post-stroke, highlighting the critical need to understand the long-term effects of stroke, including how pathological changes in the brain might give rise to functional and behavioral changes in stroke survivors. Even with this increased risk of PSCI and PSD in stroke survivors, understanding of how the stroke itself develops into these conditions remains incomplete. Recently, secondary neurodegeneration (SND) following stroke has been linked with PSCI and PSD. SND is the degeneration of brain regions outside the original stroke site. Degeneration in these sites is thought to arise due to functional diaschisis with the infarct core; however, observation of SND pathology in multiple regions without direct connectivity to the stroke infarct suggests that the degeneration in these regions is likely more complex. Moreover, pathological hallmarks of dementia, such as a deposition of neurodegenerative proteins and iron, cell death, inflammation and blood–brain barrier alterations, have all been found in regions such as the thalamus, hippocampus, basal ganglia, amygdala and prefrontal cortex following stroke. Hence, in this review, we present the current understanding of PSCI and PSD in the context of SND and outline how remote anatomical and molecular changes may drive the development of these conditions.

KEYWORDS

cognitive impairment, dementia, diaschisis, ischemic stroke, secondary neurodegeneration

Highlights

- Due to advances in acute stroke treatment and care, the number of people surviving stroke has increased. However, this has led to an increase in the number of patients experiencing post-stroke cognitive impairment (PSCI) and dementia (PSD).

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- Atrophy in regions distal from the stroke site, termed secondary neurodegeneration (SND), has commonly been linked to PSCI and PSD in both clinical and experimental studies.
- Regions affected by SND are highly correlated with the location of the infarct. In fact, SND is thought to develop due to the degeneration of connecting fibers both within the infarct itself and between degenerating regions.
- Various molecular changes are associated with sites of SND, such as excitotoxicity, oxidative stress, neuroinflammation, blood–brain barrier breakdown, microcirculatory changes, iron and neurodegenerative protein deposition, thus highlighting potential molecular targets to halt/prevent SND and its association with PSCI.

1 | INTRODUCTION

Stroke poses a massive global health burden, with one in four people suffering from a stroke in their lifetime and over 12.2 million new strokes each year.[1] Incidentally, with improvements in acute stroke treatments, such as mechanical thrombectomy and tissue plasminogen activator, the number of people dying from strokes has reduced.[2–4] However, globally, the number of people living with the effects of stroke has markedly increased, with over 101 million people currently living with some degree of post-stroke complications.[5] Alarmingly, the incidence of strokes in young people of working age (15–49 years old) has also increased over time, with over 20% of the reported strokes being within this age demographic.[6] This is particularly detrimental when we consider that patients who survive the initial stroke insult are at a significantly increased risk of several neurological complications. While impairment of motor functions is common and is the central focus in stroke rehabilitation, stroke also affects cognition. Indeed, cognitive impairments following stroke can persist for years following the initial stroke insult, significantly worsening the quality of life and survival of stroke patients.[7] Given this, an enhanced understanding of the brain mechanisms that drive post-stoke cognitive impairment is crucial for early detection and development of treatments.

Stroke is a highly heterogeneous neurological condition caused by a disturbance of the cerebral circulation and manifests various outcomes, including sensorimotor, visual, speech, mood, and cognitive impairments. Hemorrhagic stroke is caused by the rupture of a cerebral artery, followed by bleeding in/around the brain tissue. In contrast, ischemic stroke is caused by an occlusion of an artery, which reduces cerebral blood flow to the tissue within that arterial territory. Ischemic stroke accounts for approximately 62% of all stroke cases and, therefore, will be the focus of this review.[5] The type of deficit that results from stroke is primarily determined by the functions of the specific brain regions affected by the disruption of cerebral circulation and the severity of tissue damage. For instance, over 50% of ischemic strokes occur in the middle cerebral artery (MCA) and its associated cerebral branches.[8] The MCA supplies most of the outer brain surface, nearly all the basal ganglia, the internal capsule, and part of the frontal lobe and temporal gyrus. Specifically, the cortical branches of the MCA supply blood to the primary motor and somatosensory cortical areas, which supply the face and upper limbs. Therefore, the most common neurological consequence of MCA stroke is impairment of sensorimotor skills, which manifests as weakness in the muscles, paralysis, loss of sensation, and hemiparesis. However, it is important to note that impairments seen post-stroke can extend beyond sensorimotor function alone. Indeed, branches of the MCA supply blood to parts of the frontal, temporal, and parietal lobes of the brain, as well as deeper structures, including the caudate, internal capsule, and thalamus, which are involved in various executive functions and cognitive processes. In line with this, several studies have reported that patients with MCA infarction may show cognitive impairment in various cognitive domains, such as global cognition, memory, language, attention, executive and visuospatial function.[9,10]

The prevalence of cognitive impairment in stroke patients can range from 30% to 70%, depending on the diagnostic criteria used in the assessment.[11,12] The definition of post-stroke cognitive impairment (PSCI), adopted by this review, is "a new cognitive deficit that develops in the first three months following stroke and persists for a minimum of six months, which is not explained by any other condition or disease."[13] Whereas 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."[12] Indeed, PSD can manifest as vascular dementia (VaD), degenerative dementia (such as Alzheimer's disease [AD]) and mixed dementia (coexistence of vascular and neurodegenerative lesions).[14] Of these, VaD appears to be the most common subtype of dementia.[15,16]

The trajectory of PSCI and PSD may be influenced by multiple factors, including stroke type (ischemic vs. hemorrhagic), stroke severity, location of cerebrovascular insult, pre-existing comorbidities (e.g., previous stroke, hypertension, diabetes, etc.) and demographics (e.g., age and socioeconomic status). For instance, studies have found that patients with a history of stroke have double the risk of developing dementia compared to aged-matched controls.[15,17] However, rates of PSD are at least twice as high after recurrent stroke as they are after the first-ever stroke.[18] Moreover, diabetes,

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previous cognitive decline, atrial fibrillation, and low educational attainment are all considered predictors of PSCI and PSD.[19–21] Age is also a major risk factor for the development of PSCI and PSD, with the incidence of dementia increasing as the age at stroke time increases.[22] Notably, however, a nationwide population-based cohort study using data from Danish medical databases found a higher relative risk of dementia in younger survivors of stroke than older survivors when they were compared to their age-matched controls.[22] Highlighting that even without the impact of age-related co-morbidities, stroke is an independent risk factor for dementia.

The same study,[22] as well as the Oxford Vascular study,[23] have also both identified that the risk of PSD was higher following hemorrhagic stroke as compared to ischemic stroke. This is thought to be due to more severe brain injury following hemorrhagic stroke compared to ischemic, as well as the paucity of effective therapies for hemorrhagic stroke.[24] Notably, the Oxford Vascular study demonstrated that this increased risk of PSD after hemorrhagic stroke was less pronounced after adjustment for stroke severity.[23] This suggests that the significant difference between ischemic and hemorrhagic stroke, accounting for the increased risk of PSD, is likely due to the level of brain injury and, hence, stroke severity.

Critically, in the context of stroke severity, the Oxford Vascular study reported that approximately 34% of patients with severe stroke develop PSD, compared to approximately 8% in those with minor stroke and approximately 5% in those with transient ischemic attack.[23] In terms of the location of cerebrovascular insult, a study by Nys et al.,[25] investigating several cognitive domains in 190 patients within 3 weeks after a first stroke, demonstrated that 74% of cortical stroke patients developed cognitive impairment, compared to 46% of patients with sub-cortical and 43% of patients with infratentorial (e.g., cerebellum, brain stem) stroke. Of the cognitive domains affected, executive function was the most commonly effected domain following cortical and subcortical stroke, while visual perception was the most effected domain following infratentorial stroke.[25] Interestingly, Shimmyo and Obayashi investigated cognitive dysfunction after pontine stroke and found that the severity of cognitive decline was likely attributable to fronto-ponto-cerebellar diaschisis, highlighting that while the location of the stroke is significant in determining the risk of PSCI, this significance may be the result of secondary changes post-stroke.[26]

Indeed, in addition to causing damage at the initial infarct site, ischemic stroke can also induce neurodegenerative changes in remote brain regions, a process known as secondary neurodegeneration (SND).[27,28] SND involves the progressive death of neurons in brain regions outside the initial infarction site. SND develops over a longer time scale than the initial infarction process. Indeed, it has been observed within 1 month after stroke and can persist for years.[29] Sites of SND primarily include the ipsilateral thalamus, hippocampus, and basal ganglia, some of which are regions critical for cognition.[28,30] The mechanisms underlying post-stroke SND share some overlapping hallmarks with VaD and involve neuronal loss, degeneration of the corticospinal tract, neuroinflammation, accumulation of neurotoxic proteins, blood–brain barrier breakdown and microcirculatory dysfunction.[28,29,31–34] Several lines of evidence suggest that SND plays a vital role in the formation of cognitive impairment after stroke. For instance, Diao et al.[35] demonstrated with T1-weighted magnetic resonance imaging (MRI) examinations that verbal short-term memory impairment in 97 patients with subcortical ischemic stroke was not associated with the initial infarct site but rather with sites of SND, particularly the cingulate gyrus and the frontal gyri. Using diffusion tensor imaging (DTI), Fernández-Andújar et al.[32] similarly demonstrated that verbal fluency performance was associated with remote thalamic diffusion abnormalities in 17 patients at 3 months following ischemic stroke.

Given the fact that both PSCI and PSD, as well as SND, do not necessarily manifest immediately after stroke but rather often slowly develop over time, it raises the question of whether targeting SND processes can help improve the quality of life of PSCI and PSD patients. In this narrative review, we aim to present the current understanding of PSCI and PSD in the context of SND. We summarize the relationship between remote anatomical changes of the brain and functional outcomes after stroke, the molecular basis of SND and potential therapeutic targets.

2 | REGIONS OF SND AND CLINICAL FUNCTIONAL OUTCOME

Occurrence of SND and links with PSCI or PSD, has been described in regions such as the thalamus, hippocampus, basal ganglia, amygdala and pre-frontal cortex (PFC).[36–42] Other areas such as the corticospinal tract, contralateral brain regions, the cerebellum and the spinal cord have also shown evidence of SND, but in-depth discussion into these regions is beyond the scope of this review.[30,43–45] Damage within these regions can occur in concert or in a temporal fashion.[46–48] However, it is essential to note that while there is evidence that SND occurs in multiple regions simultaneously, the majority of SND studies typically examine individual brain regions at a specific time. As such, in this review, we will similarly investigate each selected region separately, with the understanding that there is likely a critical interplay between regions,[46,47] driving not only degeneration but also the development of functional decline and PSCI. By the end of this review, we will highlight the complex nature of SND and its links with PSCI and PSD, anticipating that future research will consider this secondary damage as a spatiotemporal phenomenon, investigating the breadth of cortical and subcortical sites and their association with cognitive changes.

2.1 | Thalamus

For decades, the understanding of the thalamus lay in its role as the primary relay center of the brain,

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primarily functioning to pass information to the cerebral cortex through vast connections with the peripheral and central nervous systems.[49,50] However, this view has now been expanded to recognize its role as a central integrator of inputs from other cortical systems, with the thalamus now considered critical for human behaviors such as cognition, mood, sensory processing, and motor function.[51] The multi-faceted role of the thalamus and its widespread connections with the cortex is likely why it is one of the most readily investigated areas of SND. Indeed, thalamic atrophy is most commonly seen within patients in the first 1–2 weeks following stroke but has been observed as early as 8 days post-stroke, with volume loss still apparent out to 3.5 years post-stroke.[32,33,36,52] In experimental studies, thalamic SND is most commonly reported within the first-week post-stroke,[53,54] with one study showing neuronal loss as early as Day 1 following permanent MCA occlusion (pMCAo) in mice[55] and another showing evidence of neuronal loss out to 7 months following pMCAo in rats.[56]

The current literature investigating correlations between secondary thalamic atrophy and PSCI have shown inconsistent results. While some patient studies failed to find any association between post-stroke thalamic atrophy and episodic memory specifically,[31] other studies have demonstrated clear correlations between thalamic atrophy and several cognitive domains.[35,52,57] Stebbins et al.[57] demonstrated through structural MRI analysis that patients with PSCI in multiple domains have significant volume loss within the bilateral thalamus compared to post-stroke patients with no cognitive impairments, demonstrating that thalamic atrophy predicts global cognitive dysfunction. This is interesting as other patient studies have shown that thalamic atrophy instead affects specific cognitive domains. For example, left thalamic atrophy is correlated with post-stroke verbal memory impairment[58] and right thalamic atrophy is correlated with lower verbal fluency performance.[32] However, it is important to note that both studies investigated a single time point of 3 months post-stroke. In contrast, Stebbins et al.[57] recruited patients from 3 to 6 months post-stroke, suggesting that initial damage within the thalamus is likely contained, thus only affecting a single cognitive domain; however, as time goes on, the damage worsens and affects multiple cognitive domains, furthering the idea that SND is a spatiotemporal phenomenon.

Conversely, when investigating the levels of thalamic atrophy with structural MRI and the association to memory performance 10 years after stroke in younger individuals, Schaapsmeerders et al.[31] showed no association between the two but instead saw an association with hippocampal atrophy. The reason for this conflicting result is unknown but may involve the specific cognitive tools used, with these perhaps better suited for detecting hippocampal-dependent change. Indeed, it is important to note that some of the variability seen in PSCI studies is likely due to the specific test used, as neuropsychological assessments are known to assess different aspects of cognitive change, and there is no clear consensus amongst studies. Highlighting the need to develop a specific pipeline of cognitive testing for all stages of PSCI development (acute, sub-acute and chronic).[59,60]

Alternatively, it could be due to the 10-year follow-up time, suggesting that thalamic atrophy and its association with PSCI might be transient. It could also reflect differences in the age of the stroke patients, as the lack of association was noted in young (<50 years, mean of 39 years) stroke survivors, whereas other studies looked at older patients (on average >50 years). Lastly, it is important to note that most studies only investigated the thalamus and did not investigate other SND regions. As studies show concomitant contributions from various brain regions to PSCI, such as the thalamus, hippocampus, amygdala, and PFC,[46] it is important to recognize that the thalamus is likely not single-handedly driving PSCI. Particularly, 3–6 months following stroke in patients, relationships were found with thalamic volume loss and multiple cognitive domains with known frontal and temporal lobe function, thus suggesting that post-stroke thalamic damage may act on connected regions of the brain to worsen the cognitive deficit.[57] Notably, various experimental studies have shown links between multiple regions of SND and cognitive impairment and suggested that PSCI is likely contributable to damage in thalamic circuits with memory-dependent regions, such as the hippocampus and PFC.[47,61]

Although previous studies have shown associations between specific thalamic nuclei and specific cognitive domains,[62] there appears to be a lack of literature surrounding these associations post-stroke. Of the studies investigated, Stebbins et al.[57] noted atrophy specifically in the left medial dorsal nucleus, ventral lateral nucleus, ventral anterior nucleus, and pulvinar nucleus in the cognitive impairment group compared with the noncognitive-impaired group. However, they did not investigate if these changes were associated with specific cognitive domains and whether this atrophy was associated with cognitive changes alone or if it was a combination of the nuclei. Studies investigating post-stroke anxiety and depression have similarly found distinct correlations between specific thalamic nuclei and different functional outcomes.[32,52,63] Specifically, Kuchcinski et al.[52] demonstrated degeneration of specific thalamic nuclei at 1 year following ischemic stroke and suggested that different functional outcomes could be expected depending on the location of the thalamic lesion. For example, SND of the pulvinar nucleus is involved in post-stroke anxiety, likely due to its projections with the amygdala, a critical region involved in anxiety disorders.[52] Conversely, post-stroke depression was associated with SND of the mediodorsal nuclei, likely due to its connection with the orbitofrontal circuit, which modulates empathy and socially acceptable behavior, as well as the cingulate circuit, which is involved in motivation.[52]

These findings indicate that specific thalamic nuclei likely affect specific cognitive domains following stroke. Given that distinct nuclei of the thalamus interact with distinct cortical areas and hence are affected differently depending on the stroke location, it would be of great interest to examine if atrophy of specific thalamic nuclei

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was associated with specific cognitive domains following stroke. Indeed, the early changes observed in the thalamus and the association between thalamic degeneration and cognitive impairment suggest that, even early on post-stroke, thalamic SND is a good predictor of PSCI and, thus, warrants further investigation as it holds potential as a diagnostic or prognostic indicator of SND and long-term cognitive dysfunction.

2.2 | Hippocampus

The hippocampus is a structure known for its role in memory and episodic learning and has been associated with various cognitive domains, such as processing speed, working memory, spatial navigation, and abstract reasoning.[64] Indeed, hippocampal atrophy is strongly associated with memory impairment and the inherent risk of dementia, making it a strong predictor of dementia even in asymptomatic individuals.[65,66] Likely because of this, the hippocampus is also one of the most readily investigated regions of post-stroke SND, with studies noting hippocampal atrophy in stroke patients as early as 3 months post-stroke and out to at least 10 years post-stroke.[28,31,34,66–68] Experimental studies have shown similar evidence of SND with hippocampal atrophy seen as early as 3 days following transient MCA occlusion (tMCAo) in rats[69] and out to at least 12 months following pMCAo in cynomolgus monkeys.[69]

The current literature investigating secondary hippocampal atrophy following stroke and its association with PSCI has shown some inconsistencies. While the majority of studies have reported positive correlations between post-stroke hippocampal SND and cognitive decline in patients,[31,37,70,71] some studies have shown conflicting results.[72] Correlations between decreased hippocampal volume and cognitive function have been noted as early as 10–14 days post-stroke and as late as 10 years post-stroke.[31,46] Conversely, Sachdev et al.[72] found no evidence of hippocampal atrophy, or an association between hippocampal atrophy and PSCI, 3–6 months following stroke in patients. They suggested that this is likely explained by the time post-stroke, proposing that their time point was still in the early stages of cognitive impairment development.

In keeping with this, in young stroke patients, a decrease in hippocampal volume was associated with worsened memory performance and delayed processing of visuospatial information at a mean follow-up time of 10 years.[31] Notably, the decreased hippocampal volume correlated with follow-up duration after stroke,[31] suggesting that hippocampal SND worsens over time, specifically from decade to decade. As such, this highlights that the timepoint of 3–6 months post-stroke in the Sachdev et al.[72] study may have been too early to pick up on hippocampal atrophy. This is further supported by Jia et al.,[46] who saw correlations between hippocampal atrophy and cognition in their "baseline" measurements of 10–14 days post-stroke, but not when the exact measurements were conducted at 3 months post-stroke. Indeed, as no such changes were seen in hippocampal atrophy between "baseline" and 3 months, and that at 3 months all domains of cognitive functioning were improved, it is possible that early on following stroke, cognitive changes are more reflective of the initial stroke itself, as opposed to secondary changes. In contrast, beyond 6 months, an increase in hippocampal atrophy has been observed, which correlates with PSCI.[70,73]

Similar discrepancies in findings have also been seen in experimental studies. While some studies have shown correlations between hippocampal atrophy and cognitive changes in rodents,[74,75] another rodent study saw no such association at 1 month following tMCAo.[76] Although the reason for these contrasting results was not explained, it is possible that it is the result of limitations of the neuropsychological assessments used. Indeed, all three studies assessed cognition with a different testing paradigm, affecting the interpretation of the differences. Similarly, to human studies there is an inherent need to develop a distinct pipeline for assessing cognition in animal studies.[77,78] This will be aided by the future development of more translationally relevant tasks, such as the touchscreen operant chambers, which are a rodent analogue of the human Cambridge Neuropsychological Test Automated Battery (CANTAB).[79]

It is possible, however, that the discrepancies seen in rodent studies could also be due to the fact that SND is proposed to be driven by functional connections[28] with the infarct core and other damaged regions, and hence, differing stroke methodologies may result in different levels of damage in different regions at various time points. Furthering this understanding, one research group investigated multiple time points and regions following pMCAo in cynomolgus monkeys. Interestingly, they found that, at 12 weeks, the ipsilateral dorsolateral PFC and the thalamus had significant neuronal loss, whereas no such change was observed in the hippocampus.[47] Conversely, when they investigated this at 12 months following stroke, they discovered that neuronal loss similarly affected the hippocampus.[80] They suggested that this is likely due to the rate of SND in the hippocampus being much slower than that of the thalamus. This further highlights the idea of SND being a spatiotemporal phenomenon.

Of importance, the studies discussed above looked at the hippocampus as a whole, rather than individual hippocampal subfields. Specifically, the hippocampus can be divided into the cornu ammonis (CA1, CA2–3), dentate gyrus, the presubiculum, and the subiculum, with each subfield suggested to have a specialized function.[81] Indeed, when investigated 3 months following a stroke in patients, the presubiculum and the subiculum were the only regions shown to be significantly smaller than controls and correlated with cognitive function.[71] Notably, atrophy of the presubiculum and the subiculum have been shown to be the earliest hippocampal anatomical marker of AD,[82] suggesting that investigating hippocampal subfields as opposed to the hippocampus as a whole may provide a better understanding of the spatiotemporal dynamics of hippocampal damage and how it correlates with PSCI and PSD.

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2.3 | Basal ganglia

The basal ganglia are a group of subcortical nuclei, primarily responsible for motor control, but which also play a key role in a variety of other functions, including action selection, decision making, and emotion.[83] The basal ganglia comprise the striatum (caudate nucleus and putamen), the globus pallidus (GP), the substantia nigra (SN) and the subthalamic nucleus.[83] Likely because the striatum is commonly a part of the infarct following MCA strokes, there is little evidence of SND within the caudate, putamen, and GP. However, a few studies have shown atrophy in these regions in patients around 3–6 months following stroke and out to approximately 6 years.[38,39,84–87] Within experimental studies, the striatum showed evidence of SND as early as Day 7 following strokes restricted to the motor cortex in rats.[88] Conversely, likely due to its connections with the striatum, the SN, another key basal ganglia nucleus and the source of dopamine input to the striatum, is a frequently reported area of post-stroke secondary atrophy in patients, with studies showing volume loss within the first few weeks following stroke.[89–92] In experimental studies, evidence of degeneration was first evident at Day 2 in the SN following pMCAo in rats[93] and Day 3 following tMCAo,[94] with atrophy most commonly seen within the first week following stroke in rodents.[95,96]

Although various studies have found increased PSCI when the basal ganglia are directly involved in the initial infarct,[97,98] studies examining secondary damage and how it links with PSCI are sparse. Nevertheless, such studies are beginning to emerge. For example, Lopes et al.[39] demonstrated atrophy of the putamen in both post-stroke no-dementia (PSND) and PSD patients, and, in both groups, the number of lacunes within the putamen correlated with worse memory performance, suggesting that, independent of dementia, the putamen is involved in PSCI. Interestingly, they also observed atrophy within the caudate nucleus of the PSND group, which was not seen in the PSD group. However, no correlations with cognitive measures were noted, suggesting that while the basal ganglia as a whole might influence the development of PSCI and PSD, not all subregions may be equally involved. Indeed, evidence indicates that cognitive impairment is sensitive to the connectivity of the basal ganglia in that the strength of the connection from the contralateral ventral anterior thalamus to the ipsilateral caudate nucleus positively correlated with cognitive performance in patients with PSCI.[99] Such evidence further supports the idea that PSCI is likely conducive to damage in the thalamus, altering its connectivity with other subcortical regions, and as such, may not be directly correlated with secondary atrophy within the basal ganglia. It is important to note, however, that a limitation of both studies is that they did not ensure that the basal ganglia was not involved in the initial infarct, and, as such, it is not possible to clearly delineate if this association is a secondary process involving the basal ganglia or, again, highlights thalamic axonal degeneration and SND as driving factors in PSCI development. As such, there needs to be further investigation to fully understand SND in the basal ganglia and how it may contribute to PSCI and PSD.

2.4 | Amygdala

The amygdala is the region of the brain primarily associated with emotional processing, but it also plays a key role in memory processing and learning.[100] Indeed, studies have demonstrated that atrophy within the amygdala or specific amygdala circuits results in deficits in social cognition (i.e., social processing and modulation of behavioral responses),[101] suggesting that atrophy within the amygdala or its circuits may play a role in PSCI. However, very few studies have examined secondary atrophy within the amygdala following stroke, and only a few have looked at the association with PSCI. Specifically, within stroke patients, evidence of atrophy within the amygdala is first noted within 10–14 days post-stroke,[46] and seen up to 12 months post-stroke.[102] However, within experimental studies, little to no research has investigated secondary changes within the amygdala following stroke. This is interesting given that, in stroke patients, SND within the amygdala has been linked to PSCI.[41,46]

Indeed, patients 3–6 months following stroke onset had significantly smaller amygdalae than aged-matched controls, which correlated with measures of PSCI. The authors argued that the mechanism of atrophy within the amygdala was possibly due to white matter lesions causing the denervation of connecting neurons.[41] This was further supported by the observation of atrophy within the amygdala as early as 10–14 days post-stroke in patients with basal ganglia infarcts. This atrophy persisted out to 3 months post-stroke and was shown to be associated with PSCI, with diaschisis of connecting neurons proposed as the underlying cause.[46] Indeed, a loss in functional connectivity between the atrophic cortical regions (amygdala and thalamus) and the PFC was also described and shown to be associated with poorer cognitive performance. Thus, disruption in key circuits important for cognitive function, including connections with the PFC, are likely to play a role in driving PSCI.

2.5 | PFC

The PFC supports cognitive functioning and working memory,[103] including executive control, attention, and working memory. It also has a ventromedial portion that regulates emotions and motivation.[104] Likely due to its connectivity with brain regions that degenerate early on, the PFC has been identified as a cortical area particularly susceptible to neuronal degeneration associated with dementia,[105] including the deposition of amyloid-β (Aβ) and hyperphosphorylated tau (p-tau).[106,107] However, studies investigating SND within the PFC remain sparse. Experimental studies have demonstrated neuronal loss within the dorsal lateral PFC at 12 weeks following pMCAo in cynomolgus monkeys.[47] Likewise,

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within stroke patients, atrophy within the PFC is noted at 3 months post-stroke and seen up to 15 months post-stroke.[108]

In terms of the links with PSCI and PSD, significant pyramidal neuron atrophy was observed within the dorsal lateral PFC of PSD patients at least 3 months post-stroke at post-mortem, compared to post-stroke patients without dementia.[42] Particularly, they demonstrated selective atrophy of cortical layers III and V, in which they found significant correlations with cognitive domains, demonstrating that the PFC atrophy seen in PSD patients was significantly associated with PSCI. Furthermore, they suggested that the observation of selective atrophy of the PFC is reflective of diaschisis within the frontal-subcortical circuits.[42] Importantly, this aligns with the observation that functional connectivity between the atrophic thalamus and amygdala and the PFC was disrupted in PSCI patients, suggesting that the mechanism of PSCI due to SND may involve PFC dysfunction.[46] This was further supported in an experimental study which showed an association of significant neuronal loss and inflammation within the dorsal lateral PFC and thalamus at 12 weeks following pMCAo in cynomolgus monkeys, with increased PSCI.[47] Although the functional connectivity between the two regions was not investigated, it was proposed that dysfunction in the dorsal lateral PFC-thalamus circuit was most likely the contributing factor to the observed PSCI.

3 | ANATOMICAL BASIS FOR SND

Sites of SND have generally been considered to result from axonal degeneration of regions anatomically connected to the infarct site.[28] However, further research into these regions suggests they may be more complex, especially when multiple regions are considered.[109] Studies have shown that SND may not always be due to direct connections with the cortex and may instead result from dysfunction in connections with other regions of SND.[109] Although the mechanism driving the degeneration of these connections is still unclear and likely region-specific,[109,110] it is important to highlight that SND and its association with PSCI is likely driven by connections with the infarct and/or other SND regions. Indeed, in this section of the review, we will highlight the possible mechanisms driving axonal degeneration in each region and discuss the connections of each of these regions, toward an improved understanding of the driving factors of SND in distal brain regions.

3.1 | Thalamus

The primary mechanism responsible for secondary thalamic degeneration post-stroke is retrograde degeneration of the thalamocortical fibers which connect the thalamus with the ischemic cortex.[111] Numerous clinical neuroimaging studies have noted the degeneration of specific thalamic nuclei post-stroke, dependent on their connection with the infarct core, in strokes where the thalamus is initially spared[33,52,63] (Figure 1). As such, Kuchcinski et al.[52] demonstrated high R2* values, indicative of iron accumulation (extracellular accumulation of iron is an indicator of neurodegeneration[133]) within the ipsilateral mediodorsal and pulvinar nuclei 1 year following stroke. Following previous studies on thalamocortical connectivity,[50,134] iron accumulation was observed in the medio-dorsal nucleus with more anterior infarcts (i.e., frontal and anterior temporal cortices), while iron accumulation within the pulvinar nucleus was observed with more posterior infarcts (i.e., parietal, temporal and occipital cortices). This suggests that the initial infarct location strongly determines the specific thalamic nuclei affected,[52] a pattern also observed in pre-clinical stroke studies.[133,135]

Interestingly, an endothelin-1-induced prefrontal infarct rat model study to visualize the anatomical connectivity between the infarct lesion and distal brain areas found that the cortices that suffered ischemia were connected to the medial and lateral parts of the dorsomedial thalamic nuclei where secondary damage processes, such as microglial recruitment, were ongoing at 28 days post-stroke.[135] However, Dihné et al.,[109] using both the MCAo and photothrombotic stroke models, demonstrated that the thalamic nuclei affected by SND may not always be a result of retrograde degeneration of thalamocortical connections as, in their MCAo model, the reticular thalamic nucleus (RTN) showed clear signs of SND. Still, it was devoid of efferent projections to the ischemic cortex.[109] As such, they suggested that this SND pathology may result from alternative, rather than direct, thalamic connections, such as the connection between the RTN and the GP. Given that such connections were affected by the initial stroke, this may have reduced the inhibitory GABAergic input from the GP to the RTN, in turn creating an imbalance between excitatory and inhibitory input that could result in neuronal death.[109] Indeed, the lack of SND in the RTN following photothrombotic stroke further supports this theory, as the infarct was confined to the cortex with no GP involvement.[109] As such, secondary thalamic degeneration may result from retrograde degeneration of the specific thalamocortical fibers or connections with other cortical structures.

3.2 | Hippocampus

Unlike the thalamus, the anatomical basis for secondary hippocampal degeneration is less clear, although as hippocampal damage has been noted to be more delayed than the thalamus,[47] it may reflect the significant functional connectivity between the thalamus and the hippocampus[136] (Figure 1). The subiculum of the hippocampal formation projects both directly, via the fornix, and indirectly, via the mammillothalamic tract, to the anterior thalamic nuclei (namely, the anterior medial, anterior ventral, and anterior dorsal nuclei) (for review see Aggleton et al.[113]). This projection is known to be reciprocal, with the anterior thalamic nuclei also projecting directly to the hippocampus via the cingulum,[114] and indirectly via the retrosplenial cortex.[115]

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These connections between the hippocampus and anterior thalamic nuclei are known to be critical for episodic memory.[113,137] Notably, in the absence of direct hippocampal damage, cognitive deficits were detected in rats following tMCAo, due to degeneration in the thalamus of the labelled afferent hippocampal pathways. In keeping with this, a rise in Mn^{2+} signal, a marker used to indicate functional activity of neurons, was observed within the ipsi-lesional thalamic-hippocampal connections 28 days following stroke. This indicates that while connections from the hippocampus to the thalamus remain intact, connections from the thalamus to the hippocampus may malfunction after stroke, leading to memory impairment.[138] Thus, following a stroke, this disruption in functional connectivity from the thalamus to the hippocampus could lead to knock-on hippocampal degeneration and atrophy. Intriguingly, this study did not see any evidence of neuronal loss in either the thalamus or the hippocampus, suggesting that the degeneration of the connecting fibers was enough to contribute to PSCI.[138] It is important to note, however, that only a subset of the animals were used for neuronal analysis, and the contralateral hemisphere was used as the control; given that previous studies have seen evidence of SND within the contralateral hemisphere,[34] the degree of SND should be interpreted with caution.

Indeed, experimental studies have shown significant neuronal atrophy within both the thalamus and hippocampus at 28 days following experimental stroke.[139,140] Further, Holmberg et al.[48] demonstrated

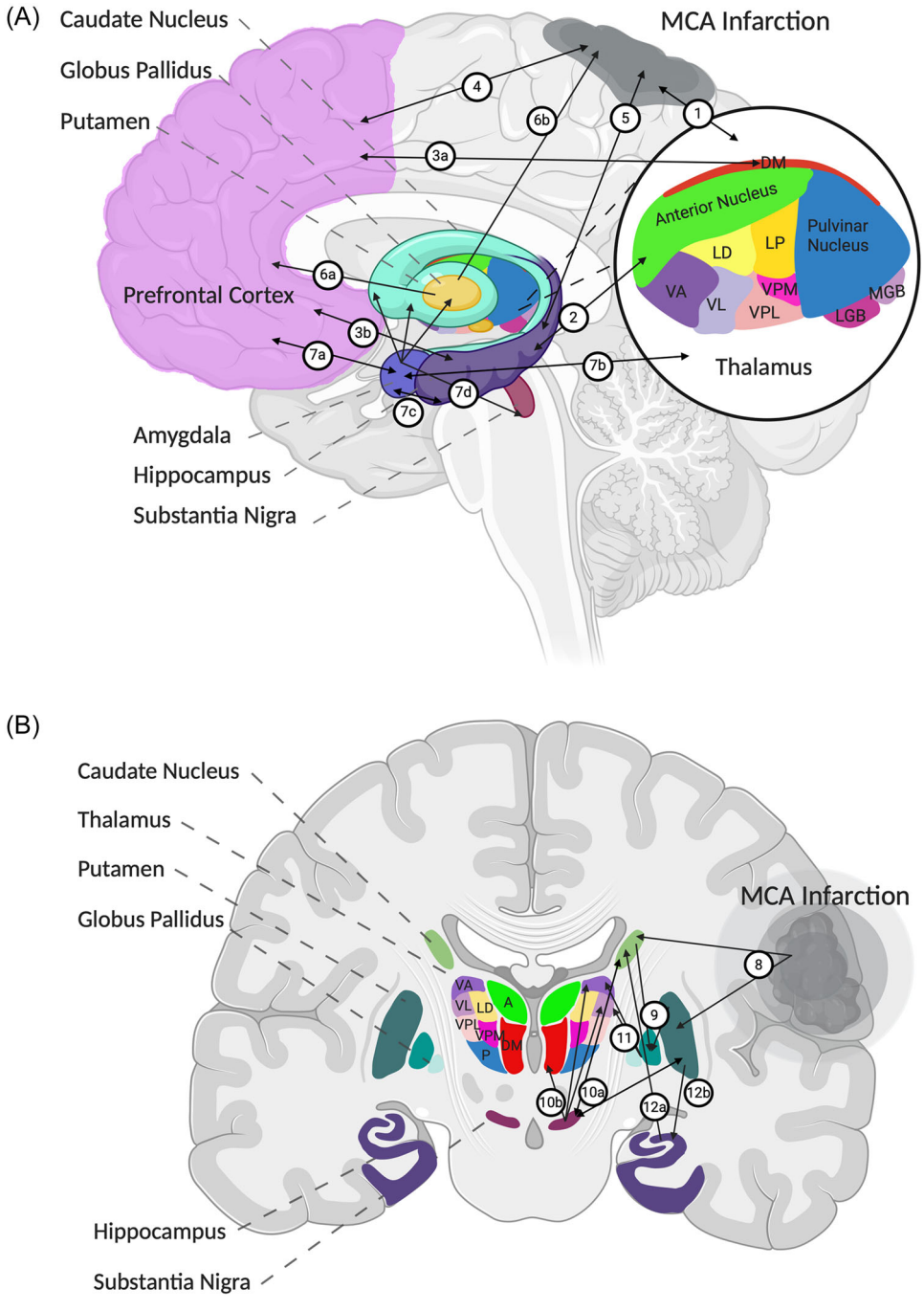

FIGURE 1 (See caption on next page).

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with an extradural compression model of focal ischemia in the somatosensory cortex that hippocampal atrophy is sometimes seen prior to thalamic atrophy. While thalamic neuronal degeneration was first apparent at Day 3 and maximal at Day 5, hippocampal neuronal degeneration was seen earlier at Day 1 and reached maximum at Day 3 post-stroke.[48] Differing connections with the primary cortical lesion were proposed, highlighting that in some cases, dependent on the site of infarction, hippocampal SND may arise in a similar fashion to thalamic SND, in that it is a result of degeneration of circuits between the hippocampus and the cortex. In support of this, the hippocampus is known to have widespread connections with the cerebral cortex. A recent study looking at the hippocampal connectome using super-resolution 1150-direction diffusion MRI provides important insights, reporting strong connectivity with the medial temporal lobe (42% of tracts), but also with regions of the occipital (15% of tracts), frontal (3% of tracts) and parietal lobes (1% of tracts).[120] Such cortico-hippocampal connections are known to be critical for the various aspects of episodic memory.[141] As such, it is fair to assume that hippocampal SND arises from degeneration of connecting fibers with either other subcortical regions undergoing damage or with the infarct site itself.

3.3 | Basal ganglia

Various SND imaging studies and experimental models include subjects with infarcts within the striatum itself, making it difficult to reliably analyze secondary basal ganglia atrophy.[33,38,86,138] To specifically evaluate SND of the striatum, a clinical neuroimaging study included patients with purely cortical stroke only. They reported atrophy of the caudate nucleus, putamen, GP and thalamus >3 weeks post-MCA stroke.[87] Infarct localization was shown to significantly influence the secondary changes seen within the basal ganglia and thalamus, with MCA strokes associated with atrophy of these structures, whereas anterior cerebral artery or posterior cerebral artery strokes were not.[87] Such findings suggest that degeneration in the striatum of the basal ganglia is likely due to the connection with the infarct site (Figure 1).

Indeed, sub-regions of the basal ganglia are known to have specific and widespread connectivity with the cerebral cortex. The striatum is classically known to be the main input area for cortical connections to the basal ganglia,[142] with the striatum divided into four clusters: a dorsomedial portion with highly convergent inputs, a lateral portion with dense innervation from sensorimotor areas, a ventral anterior portion with input from limbic areas and a ventral posterior portion, with input from both limbic and visual/auditory areas.[127] Anatomical tract-tracing studies have enhanced understanding of GP connectivity, revealing connections between the GP and cortical regions critical for the control of motivation (anteroventral GP to medial prefrontal and orbitofrontal cortices), cognition (anterodorsal GP to lateral prefrontal cortex) and action (posterior GP to frontal motor cortices).[143] Similarly, connections have been found between the GP externus and widespread sensorimotor, associative and limbic areas using probabilistic diffusion tractography.[144]

Evidence from both clinical and pre-clinical studies[40,89,145] suggest that the main component of the basal ganglia susceptible to SND is the SN likely due to its connections with the striatum, a common infarct location in both clinical and experimental stroke subjects. Indeed, degeneration in the SN 1 year after supratentorial stroke was strongly associated with the infarct location, most commonly seen in the setting of

FIGURE 1 Proposed secondary neurodegeneration seen after middle cerebral artery (MCA) occlusion. (A) Sagittal view. (B) Coronal view. (1) Ischemic insult causes retrograde degeneration in the thalamocortical fibers which connect the cortex to the thalamus, thus causing secondary neuronal damage.[111,112] (2) The anterior thalamic nuclei share both direct and indirect reciprocal connections with the hippocampus,[113–115] thus possibly causing knock-on neuronal damage in the hippocampus. (3) The pre-frontal cortex (PFC) has connections with the mediodorsal thalamic nuclei (3a)[49,116,117] and the ventral and dorsal hippocampus (3b),[118] thus, neuronal damage could spread to the PFC via these connections. (4) The PFC also shares widespread reciprocal connections with multiple areas of the cerebral cortex,[119] suggesting that secondary neurodegeneration (SND) may develop within the PFC via direct connections with the area of the infarct itself. (5) The hippocampus also shares widespread connections with the cortex itself;[120] therefore, neuronal damage in the hippocampus may result from anterograde degeneration of these connections with the infarct site. (6) The globus pallidus (GP) shares connections with the medial and lateral prefrontal cortex (6a), as well as the sensorimotor cortex (6b), suggesting that neuronal damage within the GP may be the result of retrograde degeneration of cortical fibers, and might cause knock-on damage in the PFC. (7) The amygdala shares widespread connections with the PFC (7a),[121,122] the thalamus (7b),[123] the hippocampus (7c)[124] and the basal ganglia (7d);[125,126] as atrophy in the amygdala is associated with degenerating connections,[46] neuronal damage in the amygdala is likely due to knock-on damage from other secondary neurodegeneration sites. (8) The striatum receives direct input from various cortical regions;[127] thus, neuronal damage in the striatum may be due to anterograde degeneration of the connections. (9) The striatum sends both direct and indirect projections to the GP;[128] thus, possibly causing knock-on neuronal damage in the GP. (10) The substantia nigra (SN) shares reciprocal connections with the striatum[129] (10a) and the SN directly projects to multiple thalamic nuclei, including the medio-dorsal, ventral anterior, and ventral lateral[130] (10b), thus neuronal damage in the SN may be the result of knock-on damage from the striatum or retrograde degeneration of the thalamic connections. (11) Similarly, the internal segment of the GP also projects to the ventral anterior and ventral lateral nuclei of the dorsal thalamus,[131] so neuronal damage in the GP could be the result of retrograde degeneration of these thalamic connections. (12) The striatum also shares connections with the posterior hippocampus, specifically the hippocampus sends input to the caudate nucleus (12a) and receives input from the putamen (12b);[132] thus, there may be an association between hippocampal and striatal neuronal damage. Created with BioRender© (https://biorender.com). A, anterior thalamic nucleus; DM, mediodorsal thalamic nucleus; LD, laterodorsal thalamic nucleus; LGB, lateral geniculate thalamic nucleus; LP, lateral posterior thalamic nucleus; MCA, middle cerebral artery; MGB, medial geniculate thalamic nucleus; P, pulvinar thalamic nucleus; p-Tau, hyperphosphorylated tau; VA, ventral anterior thalamic nucleus; VL, ventral lateral thalamic nucleus; VPL, ventral posterolateral thalamic nucleus; VPM, ventral posteromedial thalamic nucleus.

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ipsilateral striatum infarction.[40] This is most likely due to interruption of the nigrostriatal pathways, known anatomical connections between the SN and striatum.[146] Clinical investigations have supported such findings,[89,92] for example, Nakane et al.[89] investigated 18 patients with striatal infarctions and 6 with cortical infarctions and only reported SN degeneration in patients with striatal infarctions. Similarly, Ogawa et al.[92] investigated 10 patients with striatal infarction (with or without cortical involvement) and 15 patients with cortical infarction only, reporting that while degeneration was noted in the SN of the striatal group, no such changes were seen in the cortical group. Such findings suggest that striatal infarction contributes to SND within the SN, although a decrease in the inhibitory neurotransmitter GABA, which mediates the nigrostriatal pathway, has also been proposed. This hypothesis posits that, following striatal damage, GABA is decreased in the SN, resulting in a loss of inhibition to the SN, thus causing degeneration.[91] Indeed, this theory is supported by experimental studies showing GABA-mediated degeneration following MCAo in rats.[147,148]

3.4 | Amygdala

Similar to the above regions, SND within the amygdala is thought to develop due to the degeneration of connecting neurons.[41,46] In line with this, basal ganglia infarcts induced atrophy within the left amygdala at 3 months post-stroke in patients and coincided with decreased functional connectivity between the left amygdala and the right dorsolateral superior frontal gyrus.[46] This was further supported by Sachdev et al.,[41] who demonstrated that patients 3–6 months following stroke onset had significantly smaller amygdalae than aged-matched controls and argued that the mechanism of atrophy in the amygdala was possibly due to white matter lesions causing denervation of connecting neurons, suggesting that SND within the amygdala is specifically dependent on its connections to the infarct and/or other regions of SND.

In line with this, the amygdala is known to have complex connections with a large number of both cortical and subcortical regions, including the major known sites of SND (for review, see Meisner et al.[101]) (Figure 1). Cortically, the amygdala has widespread connections with multiple regions of the frontal, temporal, insular, and occipital cortices, in particular bidirectional projections with the medial and orbitofrontal PFC,[121,122] which play a key role in decision-making and affective processing[149,150] and goal-directed behaviors,[151] respectively. Widespread connectivity has also been reported with various thalamic nuclei. In line with this, diffusion-weighted imaging and probabilistic tractography in 50 healthy volunteers has shown that the amygdala has strong connections with the temporal thalamic parcellation (i.e., dorsal parts of the medial and inferior pulvinar, the superior portion of the mediodorsal nucleus and portions of the anterior nuclear complex). Intermediate-strength connections, in order of descending strength, were found with the frontal (mediodorsal nucleus, ventral anterior nucleus, ventrolateral nucleus and portions of the anterior complex), occipital (portions of the inferior pulvinar) and parietal (anterior pulvinar) thalamic groups. In contrast, only weak connectivity between the amygdala and either somatosensory or motor-related nuclei of the thalamus was observed.[123]

Beyond these cortical and thalamic connections, the amygdala also has connectivity with multiple subcortical structures. For example, the amygdala has direct reciprocal connections with the hippocampus, with studies in macaque monkeys showing that the accessory basal, medial basal and cortical nuclei of the amygdala send specific connections to the CA fields and subiculum of the hippocampus,[124] with the strongest innervation along the longitudinal axis of the anterior hippocampus.[152] These connections are thought to play a role in the encoding and consolidation of memories with emotional significance. Similarly, the amygdala shows connections with various aspects of the basal ganglia. Early tracing studies of amygdalostriatal projections showed a link between the amygdala, particularly the basolateral nucleus, and widespread regions of both the caudate/putamen and nucleus accumbens.[125,126] Subsequent studies have reported connections between the central nucleus of the amygdala and other nuclei of the basal ganglia, including the GP external, a pathway thought to be important for fear learning,[153] and the SN, a pathway thought to be important for reward prediction error during learning[154] and enhanced attention.[155] Similarly, the amygdala is the target of various projections from the basal ganglia, including, for example, recently outlined projections from the ventral tegmental area.[156,157] Of note, stimulating the subthalamic nucleus, another basal ganglia nucleus, leads to increased activity within the basolateral amygdala,[158] suggesting a potential connection between the two. To date, evidence of a direct connection between the two has not been demonstrated.

Recently, data from 200 individuals in the Human Connectome Project used probabilistic tractography and k-means clustering to parcellate the amygdala into three clusters: a medial cluster (centromedial and cortical nuclei), a basal cluster (basal nuclei) and a lateral cluster (lateral nuclei). The lateral cluster was strongly connected with sensory areas, as well as, via the uncinate fasciculus, with the PFC. While both the medial and basal clusters had connections with the hypothalamus, septal area and bed nucleus of stria terminalis, the basal cluster had connections with the PFC, hippocampus and cingulum, whereas the medial cluster had unique connections with the ventral tegmental area of the midbrain through the medial forebrain bundle.[159] This underscores the complex direct and indirect connectivity of the amygdala, making it potentially vulnerable to SND.

3.5 | PFC

Studies examining neuronal loss in the PFC, and links with functional connectivity, remain sparse, but several PSCI studies have investigated the functional

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connectivity of the PFC with the motor cortices, although results between studies are quite varied. For example, decreased functional connectivity of dorsolateral and medial PFC was reported in the PSCI group compared to healthy controls,[160] whereas increased functional connectivity was observed in the dorsomedial PFC of PSCI patients compared to controls.[161] Such increased connectivity was further corroborated by Kong et al.,[162] who looked at the association of cognitive assessments and functional connectivity and found that while the PSCI group demonstrated a decrease in the bilateral connectivity of the motor/sensory cortices, they showed increases in 26 other channels, mostly in the PFC. They argued that the increase in functional connectivity of the PFC was indicative of compensation for cognitive impairment, thus needing the activation of additional brain regions. Interestingly, none of these studies investigated the level of degeneration within the brain, meaning that it is difficult to determine whether such increased functional connectivity compensates for degeneration within the PFC. Particularly, given increased functional connectivity between the PFC and stroke site, and the involvement of other regions, it is important to understand whether the PFC itself is degenerating (like seen in experimental studies and PSD patient studies) and what is driving any degeneration.

Notably, when considering multiple regions, degeneration within the thalamus, hippocampus and amygdala, and degeneration of connections between these regions and the PFC was associated with poorer cognitive performance following ischemic stroke.[116,163] Such data certainly suggests that diaschisis between SND regions and the PFC (Figure 1) represents a PSCI mechanism rather than degeneration within the PFC per se. Indeed, the mediodorsal nucleus of the thalamus has been shown via both tracer[117,164] and neuroimaging studies[116,163] to be highly interconnected with the PFC,[49] with these connections known to be critical for the modulation of multiple cognitive processes.[165] Similarly, the PFC receives direct monosynaptic projections from the ventral hippocampus[118] and sends monosynaptic projections from the anterior cingulate portion of the medial PFC back to the dorsal hippocampus.[166] These connections are known to play a central role in multiple cognitive and behavioral processes (for review, see Sigurdsson and Duvarci[167]). Moreover, as mentioned above, the amygdala shares bidirectional projections with the medial and orbitofrontal PFC,[121,122] which are known to play a key role in decision-making, affective processing[149,150] and goal-directed behaviors,[151] respectively. Finally, the basal ganglia share five parallel circuits with selected cortical areas of the PFC, three of which are associated with cognitive and behavioral function. Particularly, the dorsolateral prefrontal circuit, key for executive function; the lateral orbitofrontal circuit, which is involved in integrating emotional information to appropriate behavioral responses; and the anterior cingulate/medial orbitofrontal circuit, which is involved in mechanisms surrounding motivation.[168]

These studies outlining the widespread connectivity of multiple SND regions and the associated degeneration of these connections highlight that SND and the associated PSCI and PSD are likely driven by axonal degeneration of connections with the infarct site and/or with other SND regions. As such, it is fair to assume that the timing, location and extent of SND in distal brain regions is highly dependent on the location of the initial infarct, such that future studies investigating SND, both clinically and pre-clinically, should determine the regions of interest based on the connectivity with the initial stroke site, and other degenerating regions.

4 | MOLECULAR BASIS OF SND

Despite the increasing number of studies documenting the presence of post-stroke SND and its negative effect on cognitive outcomes, the mechanisms that lead to this neurodegeneration remain poorly understood, and there are currently no interventions to treat or prevent this delayed neurodegeneration and its progression to dementia.[28] As such, recent studies have focussed on identifying the key molecular and cellular changes involved in SND (Figure 2), to develop targeted treatments that halt the degeneration process and improve long-term outcomes following stroke.[28,180,181]

4.1 | Excitotoxicity

Excitotoxicity is a key process in the acute ischemic cascade and was one of the first molecular mechanisms of ischemic damage to be readily investigated.[182] The excitotoxic process refers to the presence of excess glutamate that cannot be efficiently processed leading to overstimulation of the *N*-methyl-D-aspartate receptors (NMDAR), increases in intracellular calcium and unregulated intracellular signalling.[182] Excitotoxicity is a commonly reported acute ischemic injury process and has been linked with SND. In a study investigating the excitotoxic process of secondary thalamic degeneration, increased levels of glutamate decarboxylase were seen in the thalamus 2 days following a cortical ablation-induced stroke model and an intracortical injection of kainic acid in adult mice.[169] Indeed, chronically increased glutamate signalling via ionotropic receptors can be beneficial and stimulate neuronal plasticity mechanisms. However, as this study showed an increase in glutamate decarboxylase that preceded neuronal damage within the thalamus by at least 2 days following cortical ablation and by 7–10 days following intracortical kainic acid injection,[169] it is more likely suggestive of an increased inhibitory tonus, as shown previously following stroke.[183,184] This suggests that excitotoxic changes may predispose the tissue to neuronal damage, similar to what is commonly seen within the first week following stroke. These dual properties are likely the reason why acute interventions that block excitotoxicity have not proved effective clinically. Indeed, this highlights that the timing of drug administration[182] is vital in seeing benefits when targeting excitotoxicity

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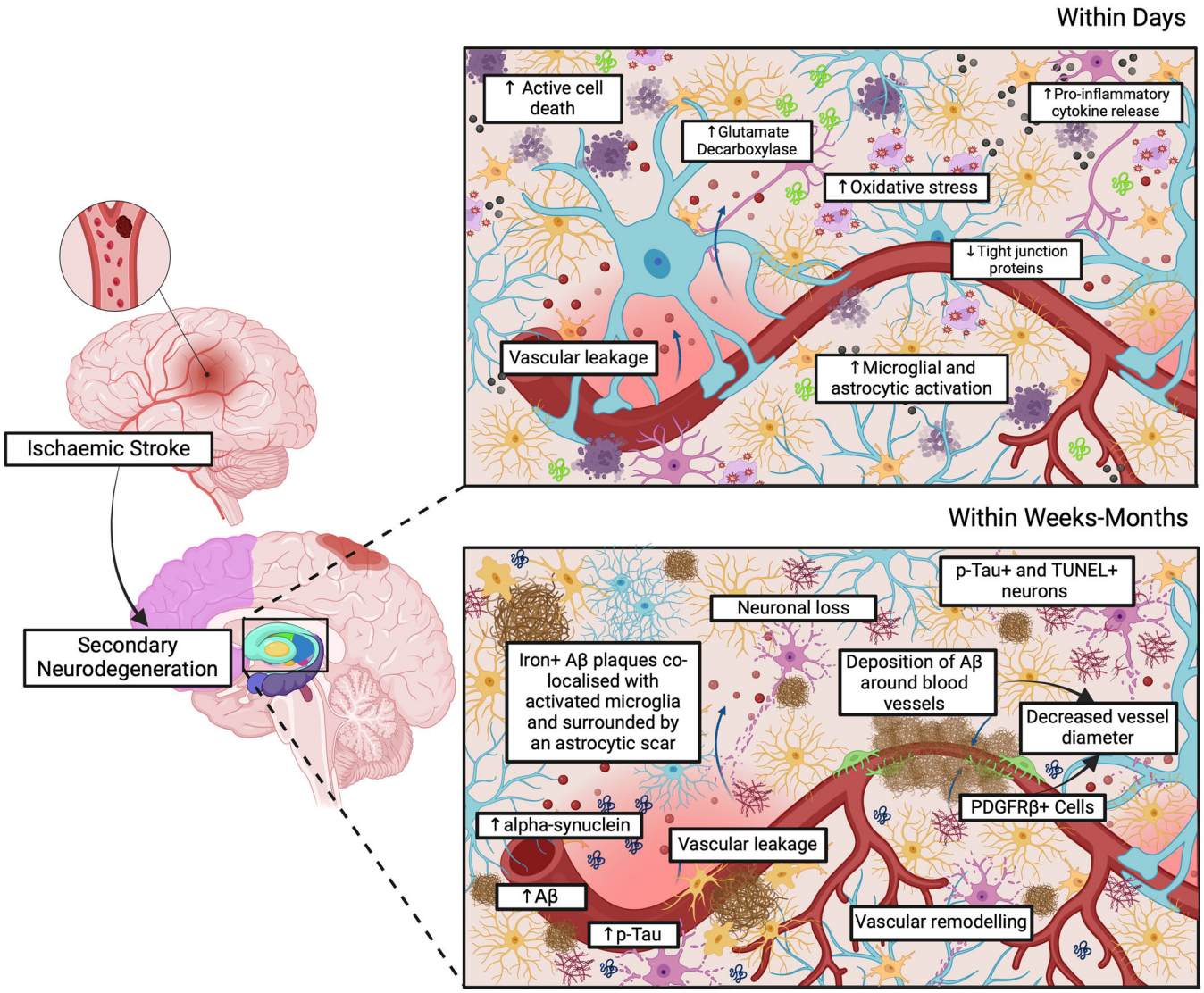

FIGURE 2 Molecular basis of secondary neurodegeneration. Within days, at sites of secondary neurodegeneration (SND), we begin to see an increase in glutamate decarboxylase,[169] increased release of pro-inflammatory cytokines,[170] increased microglial and astrocytic activation,[171,172] decreased tight junction proteins,[173] vascular leakage[174] and evidence of apoptosis[93] and necrosis.[175] Within weeks to months, at sites of SND, we see the accumulation of amyloid-beta (Aβ) with iron, activated microglia and an astrocytic scar,[56,176] vascular leakage and remodelling,[177] deposition of Aβ around blood vessels and evidence of pericyte constriction associated with decreased vessel diameter,[177] increased levels of Aβ,[176] hyperphosphorylated tau (p-tau)[178] and alpha-synuclein,[179] as well as p-tau and TUNEL+ neurons.[178] Adapted from a published figure (Hood et al.[177]) and created with BioRender© (https://biorender.com).

following stroke. As SND is a delayed phenomenon and thus has a prolonged therapeutic window, excitotoxic drugs targeting SND may be more clinically efficacious. Interestingly, this is supported by two treatment studies, one of which determined that interruption of the interactions between NMDAR and PSD95 after low oxygen post-conditioning treatment alleviated secondary damage in the thalamus following photothrombotic occlusion in mice,[185] while the other study determined that treatment with an anti-excitotoxic agent (MK-801) reduced the levels of secondary neuronal loss in the SN following MCAo in mice.[95] Although these findings suggest a mechanistic role of excitotoxicity in SND, it is important to recognize that these treatments may promote neuroprotection via a suite of mechanisms, meaning further work into the underlying effects of these drugs is required to determine if excitotoxicity does indeed play a mechanistic role in SND.

4.2 | Cell death

Focal ischemia in the cerebral cortex results not only in acute cell death in the ischemic cortex, but also in delayed cell death in distal regions such as the thalamus, SN and hippocampus.[61,93,186] The nature of cell death in these remote sites is currently under debate; however, several studies have reported evidence of apoptosis in these sites following experimental stroke.[93,175,178,187–189] Specifically, in a rat MCAo model, apoptotic-like cells were seen in the SN 2 days following ischemia,[93] with comparable findings of neuronal death within the SN 3–4 days following cerebral ischemia in a separate MR imaging study.[190] Moreover, when the pathophysiology of cell death in the SN was investigated by administrating a Nogo-A (a myelin-associated inhibitor of axon regeneration) antagonist it was discovered that cellular death in the

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SN post-stroke may be due apoptosis, as treatment inhibited apoptosis within the SN.[189]

In the context of secondary thalamic injury after stroke, several studies have reported apoptotic-like cell death up to 28 days following an MCAo.[178,187,188] Interestingly, various studies have also noted significant reductions in neuronal death within the thalamus with specific therapeutic interventions.[61,186,191–193] Indeed, inhibition of the autophagy pathway by Beclin-1 knockdown decreased secondary thalamic injury in rats between 7 and 14 days post-MCAo, as shown by fewer autophagic and apoptotic neurons as well as a decrease in neuronal loss and gliosis, further highlighting that cellular death within SND regions is likely driven by a multitude of factors.[193] This was supported by Wei et al.,[175] whom showed evidence of concurrent necrotic and apoptotic cell death in individual cells (possible evidence of necroptosis) within the thalamus <10 days following cerebral ischemia. Interestingly, this research group also investigated the morphological changes in cells within the infarct core and surrounding penumbra and determined that the TUNEL-positive cells in the core differed from the thalamus and the penumbra in that they only showed necrotic changes, suggesting different mechanisms of cellular death in SND compared to the primary injury.[175]

Conversely, Rupalla et al.,[194] reported that even though significant neuronal death was noted within the thalamus from 6 to 90 days post-MCAo in mice, very few apoptotic cells were discovered at any survival timepoint, indicating that degeneration of thalamic neurons may not always be associated with apoptosis. As we know that stroke lesions caused by different experimental models can result in differences in the SND regions affected, it is probable that we see similar changes in the cellular mechanisms associated. Indeed, although no apoptotic cells were noted in the thalamus of this study, this study showed a marked increase in microglial activation,[194] a process known to be associated with the cellular death mode, pyroptosis.[195]

It is important to also acknowledge that there are a vast number of other modes of cellular death such as ferroptosis, necroptosis, pyroptosis, and parthanatos, that may be playing a role in driving neuronal loss within these SND regions.[196] Although these sub-types have not been investigated chronically within SND regions, all of them have been implicated in driving neuronal loss acutely following stroke.[197–200] As important, these sub-types have been linked with other key features of SND regions, such as neuroinflammation, iron deposition, and accumulation of neurotoxic proteins,[200–203] as discussed in the sections below. Thus, it is important for future literature to delve deeper into the specific cellular death mechanisms at play in these distal sites to really understand what might be driving this delayed degeneration seen following stroke.

4.3 | Neuroinflammation

Neuroinflammation is one of the more readily investigated molecular mechanisms of SND, encompassing increased resident microglia[56,135,171,204] and astrocytes)[111,169,205,206] and infiltrating inflammatory cells,[207] with our comprehensive review covering this at length (for review, see Stuckey et al.[29]). Clinical and pre-clinical studies consistently highlight inflammatory spikes in remote brain regions preceding neuronal damage. For instance, in rats post-MCAo, TNF levels rose by Day 1 in the ipsilateral thalamus, with microglial and astrocytic activation by Day 3, and neuronal degeneration by Day 14.[170] This was further supported by the observation of microglial activation in the thalamus was seen at 7 days following transient MCAo (rat), which was sustained out to 112 days post-stroke, with delayed neuronal loss only evident at Day 14.[140] Interestingly, the same study also showed attenuation of neuronal loss strictly within the thalamus and behavioral recovery with the anti-inflammatory properties of (+)-naloxone, a drug used clinically to treat opioid overdose and a known reducer of microglial activation. This suggests that targeting inflammation in SND may mitigate not only secondary neuronal damage, but also functional deficits. Indeed, other non-specific neuroinflammatory treatments, such as Edaravone, a novel scavenger of free radicals, Osteopontin, a cytokine-like glycoprotein, and FTY720, a known sphingosine-1-phosphate receptor agonist, have also shown promise in ameliorating SND and associated functional decline.[139,208,209] This not only highlights that inflammation is likely a key driver of SND but also that targeting SND specifically shows promise for ameliorating post-stroke functional decline, such as PSCI and PSD.

Notably, SND studies consistently link inflammation, particularly microglia, with amyloid deposition. Following permanent MCAo in rats, activated microglia and macrophages in the thalamus were associated with neuronal loss and co-localized with amyloid deposition at 7 months post-stroke.[56] Early accumulation of Aβ and phosphorylated tau, alongside increased inflammatory cells, has been noted within the thalamus and hippocampus as early as 1–2 weeks post-stroke in multiple rodent studies.[74,179,210] A time-course study further demonstrated that reactive microglia in the thalamus exhibit increased iron content suggestive of neurodegeneration, initially intracellularly at 3 weeks post-stroke, and by 6 months, resembling Aβ plaques around thalamic structures.[133] These findings underscore inflammation as a likely key driver of SND neurodegeneration. Yet gaps remain in understanding long-term inflammatory processes beyond 6 months and their species-specific variations. While microglial modulators show pre-clinical promise, their clinical efficacy remains inconsistent,[211–213] highlighting the need for refined therapeutic strategies. Bridging the gap between experimental models and patient outcomes is imperative, requiring diverse models encompassing age, gender, and comorbidities to align pre-clinical findings with clinical trials effectively.

4.4 | BBB breakdown

The blood–brain barrier (BBB) is a largely impermeable, homeostatic interface comprised of structural components, including endothelial cells, tight junctions,

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pericytes, neurons, astrocytic end feet and the extracellular mnaatrix.[214] The vital role of the BBB is to maintain the homeostasis of the CNS by regulating the trafficking of cells, fluids and solutes between the brain and the surrounding vasculature.[214] It is well-established that, following an ischemic stroke, BBB permeability increases, prior to neuronal damage in the ischemic core,[215,216] such that studies are now investigating whether alterations may also contribute to SND.[174,217] Indeed, an early study reported neuronal degeneration, extravasation of albumin and gliosis within the ipsilateral thalamus 7 days following MCAo in rats.[174] Similar results were seen by Ling et al.[217] with neuronal loss, activated microglia, and angiogenesis observed within the ipsilateral ventroposterior nucleus of the thalamus 14 days following MCAo in rats. To determine the reason behind this increase in BBB permeability, Li et al.[173] explored the integrity of the tight junctions in these areas following stroke, reporting a decrease in the number of tight junction proteins and an increase in albumin levels within the ipsilateral thalamus by 24-h post-MCAo.[173] Following on from this study, the group investigated whether the administration of Netrin-1, an axonal guidance molecule, for 7 days post-MCAo in rats, would protect against BBB-associated secondary injury.[218] Notably, they discovered improvements in neurological function, up-regulation of tight junction proteins and decreased levels of extravasated albumin within the ipsilateral thalamus 14 days following ischemia.[218] These studies suggest that, early on following a stroke, BBB breakdown does affect brain regions distal from the infarct site.

A study by Hood et al.[177] explored longer-term BBB permeability and showed evidence of sustained IgG presence (indicative of BBB leakage) out to 84 days post-photothrombotic stroke in the CA1 region of the hippocampus. Importantly, at this time point, mice also showed evidence of cognitive impairment; while correlation does not equal causation, this result is of particular interest, given the fact that BBB permeability is known to increase neuroinflammation and neuronal damage within the brain,[214] which was also observed in these animals at the same time points. As such, future SND studies need to investigate the temporal dynamics of BBB breakdown and how it relates to other pathological changes in the tissue, such as neuroinflammation, to determine whether it is a mechanism worth exploiting for targeted treatments.

4.5 | Microcirculatory dysfunction

Normal cerebral microcirculation is essential for brain function, as it fuels the brain tissues' high and continuously changing metabolic demand with the optimized supply of oxygen and nutrition. The reduction of cerebral blood flow in ischemic stroke causes neuronal damage or death and microvascular injury, including BBB leakage (as discussed in Section 4.4), endothelial activation, and both leukocyte and platelet adhesion.[219] In the acute phase of stroke, structural and functional changes in the microcirculation during the ischemia-reperfusion process can lead to reperfusion failure even after successful recanalization, a concept known as the 'no-reflow' phenomenon.[220] Changes in microvascular density have previously been reported in regions outside the initial infarct, including the ipsilateral thalamus, SN and hippocampus.[221] While restoration and/or increased microvascular density following stroke can be beneficial for promoting cerebral blood flow, it should be noted that aberrant angiogenesis and vascular remodelling may lead to detrimental effects such as BBB leakage, edema formation and hemorrhagic transformation.[222]

Hood et al.[177] recently demonstrated that cortical photothrombosis causes persistent remote hippocampal cerebrovascular dysregulation out to 84 days post-stroke. They showed an association between cerebral capillary narrowing, Aβ deposition, and PDGFRβ+ cells (suggestive of pericyte constriction) in the peri-infarct areas and hippocampal CA1 at 84 days post-stroke. It is not unreasonable to speculate that reductions in capillary diameter may have implications for cerebral blood flow.[223] However, this was not included in the study scope. Interestingly, they also showed a sustained increase in vessel density, potentially suggestive of angiogenesis/vasculogenesis,[177] which was not accompanied by a sustained increase in PDGFRβ staining. Given that pericytes are positive for PDGFRβ, the authors speculated that the vessels may be immature and may have contributed to the observed vascular leakage in the same regions. These changes may be suggestive of mechanisms contributing to secondary neurodegenerative processes. However, conversely, there is evidence suggesting that the microvascular changes may contribute to the restoration of blood flow in distal regions and are associated with functional recovery. Indeed, Hayward et al.[224] showed that while at Day 2 after tMCAo in rats, cerebral blood flow was reduced in the bilateral thalamus and IgG extravasation was observed, recovery was apparent at Day 7 with chronic hyperperfusion at Day 30 and 3-month post-stroke. In fact, angiogenesis was also observed within the ipsilateral thalamus at the end of the 3-month follow-up. It is unclear as to why these differences were observed between the two studies.[177,224] Still, seeing as we are considering two different species (rats vs. mice), two different MCA models (intraluminal filament vs. photothrombotic) and two different SND regions (thalamus vs. hippocampus), more research is needed to comprehensively understand the extent of cerebrovascular changes outside the ischemic core, to understand if they are beneficial or harmful to disease progression.

4.6 | Oxidative stress

Oxidative stress is a process of cellular degradation brought on by an imbalance in reactive oxygen species (ROS) and endogenous antioxidant defences in the brain. It is well known to contribute to tissue injury and infarct expansion in the acute phase post-stroke.[216] Notably, several studies have identified signs of

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oxidative stress within the thalamus and hippocampus following experimental stroke, highlighting its potential mechanistic role in SND. Specifically, studies have noted spikes in manganese superoxide dismutase (MnSOD),[225,226] a critical enzyme for eliminating ROS, which suggests an increase in superoxide production in these areas, as well as 8-hydroxyl-2′-deoxyguanosine (8-ohdG)[181,227] and heme-oxygenase (HO-1),[133,228] both of which are biomarkers of oxidative stress. Numerous studies have reported attenuation of neuronal damage within the thalamus or hippocampus when oxidative stress was targeted.[227,229] Administration of the antioxidant ebselen to rats once per day for 14 days, starting at 24 h following MCAo, attenuated oxidative stress and autophagy activation within the ipsilateral thalamus, thus reducing the level of secondary damage.[225] Interestingly, the group determined the immunoreactivity of MnSOD was colocalized with Beclin-1 and LC3-positive cells (autophagic markers) and that ebselen not only reduced the level of MnSOD, but also prevented the elevation of LC3-II and Beclin-1, suggesting that oxidative stress may specifically be associated with autophagy activation in the ipsilateral thalamus following cerebral infarction.[225]

Moreover, Yang et al.[227] investigated the neuroprotective effect of risperidone-induced hypothermia and found that, at 5 days following transient ischemia in gerbils, CA1 pyramidal neurons of the hippocampus showed increased levels of 8-OhdG and 4-hydroxy-2-nonenal, a lipid peroxidation marker, and this elevation was decreased by risperidone treatment. Notably, previous studies have demonstrated that risperidone can elevate antioxidants and, as such, is used for therapy of oxidative stress.[230,231] Thus, these findings suggest that risperidone-induced hypothermia protects hippocampal neurons from damage by maintaining endogenous antioxidants.[227] Nevertheless, it remains unclear whether the protective effects of these antioxidant treatments are temporal and/or sustained. SND is known to continue over a longer post-stroke period, with additional studies needed to investigate whether these specific treatments are effective at later time points. Moreover, both groups also noted a reduction in the stroke-associated elevation in gliosis in these areas following treatment, suggesting that the reduction in oxidative stress may not be the only cause of the attenuation of secondary damage.[225,227]

4.7 | Accumulation of neurotoxic proteins

Accumulation of neurotoxic proteins, such as Aβ, phosphorylated tau and α-synuclein, are characteristic pathological features of various neurodegenerative diseases.[232–234] Interestingly, the accumulation of these proteins within the ischemic region and SND sites have been found in numerous clinical and experimental studies.[176,179,235–239] This accumulation may provide an obvious explanation for the prevalence of cognitive impairment and dementia following stroke.[70,240–243]

In experimental ischemic stroke studies, altered amyloid precursor protein (APP) processing and Aβ accumulation are particularly consistent pathological features of SND sites, and, as such, may be responsible for the disruption of cellular functions after stroke.[176,238] Aβ accumulation is increased in the hippocampus at 7, 28, and 84 days after photothrombotic stroke in mice, correlating with persistent impairment in cognitive function.[74] Furthermore, at 14 days post-stroke, α-synuclein was also observed in the hippocampus of mice with cognitive impairment, suggesting that deposition of both Aβ and α-synuclein in the hippocampus post-stroke may be associated with the persistent cognitive decline seen post-stroke.[179] Within the thalamus, APP and Aβ were diffuse acutely after the infarct (1 week), but accumulated, leading to dense plaque-like deposition, at 9 months following stroke.[176] Furthermore, accumulation of Aβ and APP within the thalamus has been linked with impaired calcium homeostasis.[237–239] Specifically, Hiltunen et al.[239] discovered that 7 and 30 days after MCAo, increased calcium levels and β-secretase (BACE) activity coincided with increased β-amyloidogenic processing of APP and imbalanced Aβ degrading enzyme levels in the thalamus, but not in the ischemic cortex. The coaccumulation of calcium and Aβ in the thalamus has also been noted up to 26 weeks after MCAo.[238] The non-selective calcium channel blocker bepridil, administered for 27 days post-MCAo, significantly decreased levels of Aβ and calcium within the ipsilateral thalamus, and further alleviated the alterations in APP processing.[237] Alternatively, thalamic Aβ deposition has also been shown to be associated with the accumulation of autophagosomes, via increased BACE1 levels following cerebral ischemia.[244] As such, it is possible that various molecular changes precipitate alterations in APP processing and Aβ deposition in the thalamus following stroke and thus, cannot be attributed to one mechanism or pathway.

Adding another level of complexity are the inconsistencies observed between small animal experimental findings and those from human and non-human primate studies.[80,235,236,245–247] Specifically, in cynomolgus monkeys, there was no evidence of Aβ accumulation within the thalamus 12 months following MCAo, despite neuronal loss being observed in the area. Interestingly, there were also no significant elevations in the level of Aβ peptides within the CSF or plasma noted.[80] Similar discrepancies have been described in marmosets, in which the thalamus was devoid of any sign of Aβ and calcium aggregation in MCAo animals.[245] Regarding clinical studies, a similar lack of Aβ in the thalamus was noted in post-mortem brains following stroke.[236] As such, it is possible that the accumulation of Aβ within the thalamus following stroke is a transient phenomenon or is associated with specific pathological changes or demographic factors, or even could be species specific. Consequently, further studies investigating thalamic Aβ deposition across species are warranted.

Although not as consistently as Aβ, hyperphosphorylation of tau has also been reported within SND sites.[178] Specifically, secondary neuronal loss and p-tau appeared in the ipsilateral thalamus from 3 to 28 days

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post-stroke in a rat MCAo model.[178] This correlated with the pattern and expression of Aβ deposition in the ipsilateral thalamus following MCAo noted in a previous study by the group, indicating that secondary thalamic damage is related to the Aβ deposits and p-tau.[178] Moreover, approximately 50% of p-tau-positive neurons were also TUNEL-positive, apoptotic-positive cells, indicating that p-tau plays a distinct role in SND via an apoptotic pathway.[178] Interestingly, when p-tau was investigated in the hippocampus following cerebral ischemia, researchers found that overactivation of NR2B-containing NMDARs through entorhinal–hippocampal connection initiates the accumulation of p-tau in the hippocampus.[248] These findings suggest that, in sites of SND, p-tau plays a key role in the degeneration of tissue. Although there have been certain advancements in the last couple of years, the involvement of tau phosphorylation in SND, specifically what initiates this hyperphosphorylation, remains largely unknown.

Similarly, the role of alpha-synuclein in SND remains unknown, likely due to a lack of investigation. A photothrombotic mouse study did see an increase in alpha-synuclein within both the thalamus and hippocampus at 14 days following stroke; however, no correlation with cognitive performance was seen.[179] As alpha-synuclein, has previously been shown to be associated with neuronal death and cognitive deficits in other neurodegenerative conditions, it is unclear as to why no association with PSCI was observed.[249] As this was the only study found to investigate alpha-synuclein in SND, future research is needed to fully understand how its aggregation in SND regions affects the pathology.

4.8 | Accumulation of iron

Iron accumulation in regions known to undergo SND (i.e., the ipsilateral thalamus and SN) is associated with worsened functional outcomes and neurodegeneration post-stroke[40,52]; however, it is unclear whether iron accumulation is a cause or consequence of SND. In both clinical and pre-clinical studies, extracellular iron accumulation is often used as a surrogate marker for neurodegeneration and can be assessed non-invasively through MRI techniques sensitive to magnetic susceptibility including T2W* and R2* mapping, susceptibility weighted imaging and quantitative susceptibility mapping.[250–252] Clinically, high R2* values, interpreted as iron accumulation, have been observed in the ipsilateral thalamus 1–12 months post-stroke.[27,52] Further, these changes were associated with poorer cognitive and functional outcomes, as well as post-stroke anxiety. Interestingly, van Etten et al.[253] showed, using T2W* imaging, that these changes might begin as early as 1-day post-stroke. Similar changes in the ipsilateral SN have been reported by Linck et al.[40] at 1-year post-striatal stroke, associated with worse motor outcomes. In pre-clinical studies, iron accumulation was observed in the thalamus of rats as early as 3–4 weeks post-stroke (MCAo and photothrombosis). Interestingly, at these early time points, iron deposition is colocalized with activated microglia and accompanied by gliosis.[133,254] Justicia et al.,[133] showed that, over time, the iron staining became more diffuse in the parenchyma (7 weeks) before seeming to cluster around areas of APP deposition resembling Aβ plaques (out to 24 weeks). These changes were accompanied by worse performance on the adhesive removal task, indicating sensory disturbances. Similar reports of iron clustering in the thalamus have been reported by Walberer et al.[56] at 7 months post-embolic stroke in rats. Interestingly, the authors observed co-localization with microglia and marked neuronal loss. Notably, at these late time points, the thalamus displays marked neuronal loss in the regions where iron accumulates and amyloid deposits. These studies suggest that iron deposition is a factor in SND, and may enhance neuronal loss in these regions and, hence, contribute to functional decline. It is important to note that neuroinflammation, in the form of activated microglia, may be a key driver in iron deposition in these regions.

5 | FUTURE PERSPECTIVES

Due to advances in acute stroke treatment and care, the number of people surviving stroke has increased. However, this has been matched by an increase in the number of patients experiencing PSCI and dementia. The long-term heterogeneity in stroke outcomes may be explained by a number of factors, including stroke site and severity, acute complications and chronic factors such as SND. There is an increasing body of evidence showing links between the location and severity of SND and the specific functional presentation. However, despite the obvious links with functional decline, the field's understanding of the driving factors of SND is still emerging. Nevertheless, it is clear that SND, and the specific regions affected by this phenomenon, are associated with a decrease in functional connectivity, whether that is within the infarct site itself or between the distal regions affected. Moreover, there is a clear molecular basis to these SND sites, highlighting multiple potential targets for treatment development. Consequently, modulating degeneration in these distal sites following stroke is likely to reduce the risk of PSCI and dementia.

AUTHOR CONTRIBUTIONS

Shannon M. Stuckey: Writing—original draft (lead); writing—review and editing (lead). **Rebecca J. Hood**: Supervision (equal); writing—original draft (supporting); writing—review and editing (supporting). **Lin Kooi Ong**: Writing—original draft (supporting); writing—review and editing (supporting). **Isabella M. Bilecki**: Writing—review and editing (supporting). **Lyndsey E. Collins-Praino**: Supervision (equal); writing—original draft (supporting); writing—review and editing (supporting). **Renée J. Turner**: Supervision (equal); writing—review and editing (supporting).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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