

Review

Electroacupuncture in Post-Stroke Cognitive Impairment: A Review From the Perspective of Programmed Cell Death

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Abstract

Stroke remains a leading cause of mortality and long-term disability worldwide, and post-stroke cognitive impairment (PSCI) is among its most prevalent and debilitating sequelae. Accumulating evidence suggests that electroacupuncture (EA) modulates dysregulated programmed cell death (PCD) after stroke, including apoptosis, autophagy, ferroptosis, and pyroptosis, which play central roles in neuronal loss, synaptic disruption, and cognitive decline. Specifically, EA may suppress excessive neuronal apoptosis and ferroptosis, modulate autophagic activity, and attenuate pyroptosis-associated neuroinflammation. However, the mechanisms underlying the effects of EA in PSCI remain fragmented, and the lack of standardized treatment protocols limits its clinical translation. In this review we integrate clinical findings with molecular and cellular evidence to propose a unified mechanistic framework in which EA may improve cognitive function and may act through modulation of multiple PCD pathways. We further highlight EA as a potential multi-target and network-oriented intervention with therapeutic potential in stroke rehabilitation, providing a mechanistic basis for future studies and standardized clinical application.

Keywords: post-stroke cognitive impairment; electroacupuncture; programmed cell death; apoptosis; autophagy; ferroptosis; pyroptosis

1. Introduction

Stroke is a cerebrovascular event caused by acute focal injury to the central nervous system, typically characterized by neurological deficits, and has become the second leading cause of death and disability worldwide after ischemic heart disease [1]. Post-stroke cognitive impairment (PSCI) is a common neurological complication following stroke, with severity ranging from mild deficits to dementia. PSCI generally refers to all cognitive impairments occurring after stroke, emphasizing the temporal relationship between cognitive decline and the stroke event. In contrast, post-stroke dementia (PSD) refers to immediate and/or delayed persistent cognitive decline after stroke that meets the diagnostic criteria for dementia. PSD is generally regarded as part of the vascular dementia (VaD) spectrum, whereas VaD also encompasses multiple subtypes beyond PSD, including multi-infarct dementia and subcortical small-vessel dementia, which may occur in patients without a definite history of stroke [2,3].

Within the first year after a stroke, up to 60% of survivors may experience cognitive impairment, representing an incidence nearly 50 times higher than that of the general population. Even minor strokes can negatively im-

pact activities of daily living, cognitive function, and quality of life [4,5]. Most patients do not regain their pre-stroke cognitive abilities, and approximately one-third develop dementia within five years [2]. The risk of cognitive impairment persists even a decade after the stroke [6]. However, currently, there is no clearly effective treatment for PSCI. Preventive strategies primarily focus on managing risk factors such as smoking, obesity, diabetes, hyperlipidemia, and obstructive sleep apnea, yet substantial evidence gaps remain [7]. Early intravenous thrombolysis or mechanical thrombectomy represents the most critical interventions during the acute phase of stroke. However, these endovascular treatments are highly time-dependent, and previous studies have primarily reported overall functional outcomes, with limited evidence regarding their independent effects on cognitive function [8,9]. Current pharmacological interventions primarily include cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine), the NMDA receptor antagonist memantine, and nootropic agents, often combined with medications targeting vascular risk factors [2,10]. However, these drugs have limited efficacy in improving global cognition and daily functioning, show limited long-term efficacy, and are often associ-



ated with adverse events (e.g., dizziness, diarrhea) as well as poor patient adherence [11,12]. Non-pharmacological interventions, including cognitive rehabilitation, behavioral therapy, psychological support, and caregiver education, are also widely used in PSCI management [13,14,15]. Still, most lack robust evidence, and even when effective, improvements in cognition are modest and not sustained [13,14,16]. Given these limitations, exploring safe and effective adjunctive therapies, such as acupuncture, remains clinically important for improving cognitive symptoms associated with PSCI.

Electroacupuncture (EA) combines traditional acupuncture with modern electrical stimulation, delivering electrical stimulation of defined frequency and intensity through acupuncture needles at selected acupoints [17]. It enhances conventional cognitive training and is widely used in post-stroke rehabilitation [18]. A growing body of clinical and preclinical evidence suggests that EA may improve post-stroke cognitive function [19,20]. Many of these studies focus on programmed cell death (PCD)-related pathways, especially apoptosis, autophagy, ferroptosis, and pyroptosis, which are considered central mechanisms underlying the neuroprotective and cognition-enhancing effects of EA [21]. However, current clinical studies are limited by inconsistent evidence regarding efficacy and lack of standardized treatment protocols. Mechanistic studies, although reporting numerous signaling pathways, remain fragmented and lack systematic integration, leaving the overall framework of EA-mediated regulation of PCD after stroke unclear. This review aims to systematically assess the therapeutic strategies and efficacy of EA in PSCI from both clinical and preclinical perspectives, with a particular focus on its regulation of multiple PCD types, thereby providing insights for future translational research and individualized therapeutic strategies.

2. Application of EA in PSCI: Clinical Evidence and Evaluation

2.1 Diagnostic Criteria and Outcome Measures

PSCI is a highly heterogeneous syndrome involving multiple cognitive domains, including memory, attention, executive function, language, and visuospatial ability. Current diagnosis of PSCI primarily relies on neuropsychological assessment combined with stroke history, neuroimaging findings, and activities of daily living. The Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) are the most widely used screening tools [2]. MoCA is more sensitive to mild cognitive impairment and executive dysfunction, whereas MMSE is more suitable for assessing global cognitive status and dementia severity. In clinical studies, MMSE scores <24 and MoCA scores <26 are commonly used cutoff values for cognitive impairment [22,23]. Existing randomized controlled trials (RCTs) have shown that EA demonstrates superior efficacy over control interventions in both cognitive scale scores and certain neu-

roimaging outcomes (**Supplementary Table 1**). A meta-analysis of 37 RCTs involving 2869 participants showed that 2–8 weeks of EA significantly improved both MMSE (MD = 2.88, 95% CI: 2.09–3.66) and MoCA scores (MD = 2.66, 95% CI: 1.95–3.37) [20].

Nevertheless, current outcome assessment in PSCI remains limited. As summarized in **Supplementary Table 1**, existing clinical studies have predominantly focused on global cognitive outcomes assessed using the MoCA or MMSE, whereas domain-specific cognitive outcomes have been reported less frequently, and information on lesion location has been even more limited. In addition, baseline cognitive severity varied considerably across studies. In some trials, baseline MoCA scores were close to 24, suggesting relatively mild impairment, whereas in others, baseline scores ranged from 15 to 18, indicating more pronounced cognitive decline (**Supplementary Table 1**). Such variability complicates cross-study comparisons and may contribute to inconsistent estimates of EA efficacy across different disease severities. In addition, different cognitive scales show variable sensitivity across cognitive domains. MoCA places greater emphasis on executive function, attention, and visuospatial ability, whereas MMSE has limited sensitivity for early mild cognitive impairment and frontal executive dysfunction [22,23]. Both scales are also influenced by age, educational level, and cultural background, further complicating interpretation. Many studies currently use total MoCA or MMSE scores as primary outcomes, while stratified analyses of specific cognitive domains such as memory, executive function, and attention are less commonly reported (**Supplementary Table 1**). This limits understanding of the domain-specific cognitive effects of EA [2].

Recent advances in neuroimaging have provided more objective measures for evaluating PSCI outcomes [24]. Functional magnetic resonance imaging (fMRI) studies have shown that EA enhances functional connectivity within the default mode network (DMN) in patients with vascular cognitive impairment [25]. EA also improved local network metrics, including clustering coefficient (Cp) and local efficiency (Eloc). Notably, Eloc enhancement correlated positively with MoCA scores, and several cognition-related brain regions exhibited significant differences in nodal properties, suggesting improved brain network integration following EA intervention [26]. Pre-clinical studies have primarily focused on the hippocampus and its subregions, particularly the CA1 region and dentate gyrus. These findings suggest that EA-mediated improvement in memory-related cognition may be closely associated with hippocampal protection and neuroplastic regulation (**Supplementary Table 2**). Other regions examined include the prefrontal cortex, cingulate cortex, retrosplenial cortex (RSC), thalamus, and striatum, which are involved in executive function, attention, and cognitive control. Notably, most existing studies are primarily mecha-

nistic in nature, and brain region selection is therefore partially determined by experimental design. Consequently, evidence supporting specific “EA–brain region–cognitive domain” relationships remains limited.

2.2 Methodological Challenges

Despite encouraging clinical findings, several methodological limitations remain in current EA studies on PSCI. Differences in EA control design may substantially influence efficacy comparisons. Sham EA is commonly used as a control intervention in EA studies. Its primary aim is to mimic the procedural characteristics of real EA while minimizing specific acupoint stimulation and therapeutic effects. Common approaches include stimulation at non-acupoints or sham locations (e.g., tail-root stimulation or non-acupoint electrical stimulation on the trunk), minimal acupuncture stimulation (MAS), and flat-head sham needles combined with simulated electrostimulation [19,27,28,29,30]. Nevertheless, sham EA remains methodologically controversial. On the one hand, non-acupoint stimulation, superficial needling, or low-intensity electrical stimulation may still activate peripheral nerves, spinal sensory pathways, and brain network activity; therefore, these procedures may not be physiologically inert and could underestimate the true efficacy of EA. On the other hand, studies lacking rigorous sham controls and using only sham surgery or routine care as comparators may inadequately control for placebo effects, nonspecific effects, and procedural stimulation, potentially overestimating EA efficacy. Furthermore, substantial variability exists across studies regarding the definition, stimulation methods, and parameter settings of sham EA, which further limits inter-study comparability [31]. Therefore, establishing a standardized sham EA system that balances blinding validity with physiological inertness remains a major methodological challenge in current EA research.

In addition, most existing studies primarily report the direction of change in outcome measures or statistical significance, while providing limited information on standardized effect sizes, such as Cohen’s *d* and the standardized mean difference (SMD), and on the minimal clinically important difference (MCID), which are essential for interpreting effect magnitude and clinical relevance. As shown in **Supplementary Table 1**, only a small number of studies reported explicit effect-size estimates or efficacy evaluation criteria, whereas most original studies did not provide sufficient data for standardized effect-size estimation or clinically meaningful interpretation. Even among the available reports, the robustness and interpretability of some effect estimates warrant cautious consideration. For example, Han et al. [32] reported Cohen’s *d* values of 4.44 and –2.00 for improvements in MoCA and National Institutes of Health Stroke Scale (NIHSS), respectively, following EA combined with conventional treatment, and re-

ported that 95% of patients achieved the NIHSS MCID. Such unusually large effects may have been influenced by sample size, baseline imbalance, or assessment methods. Moreover, definitions of “effective” and “markedly effective” outcomes remain inconsistent across studies. Some studies define marked efficacy as a $\geq 20\%$ improvement in MoCA scores, whereas others use thresholds $\geq 70\%$, further increasing heterogeneity among findings [33,34]. These study-specific efficacy criteria should not be considered equivalent to validated MCID thresholds and further limit cross-study comparisons and interpretation of the clinical relevance of treatment effects. Therefore, future studies of EA for PSCI require more standardized methodological frameworks and outcome evaluation criteria.

2.3 Intervention Strategies of EA

The therapeutic effects of EA are influenced not only by the timing of intervention, but also by acupoint selection and stimulation parameters. Although certain patterns in EA intervention strategies for PSCI have gradually emerged, considerable heterogeneity still exists among studies.

2.3.1 Timing of Intervention

Post-stroke cognitive function changes dynamically and may be influenced by multiple factors, including neural repair, secondary neurodegeneration, and recurrent cerebrovascular events. Notably, most existing studies assess cognitive outcomes at only a single post-stroke time point. Even in studies with follow-up designs, evaluations are commonly divided into 3-, 6-, or 12-month intervals, while standardized criteria distinguishing acute, subacute, and chronic stages of PSCI remain lacking. Current evidence demonstrates substantial differences in intervention timing between preclinical and clinical studies. Animal experiments are predominantly focused on the hyperacute phase within minutes to 24 h after stroke, and some studies even adopt EA pretreatment paradigms. In contrast, clinical studies are more commonly conducted during the rehabilitation or chronic stages, ranging from weeks to months after stroke (Table 1, Ref. [25,26,32,33,34,35,36,37,38,39,40]; Table 2, Ref. [19,27,28,29,30,31,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61]). This discrepancy may partly be attributable to current clinical practice patterns, in which EA is more frequently regarded as a rehabilitation intervention rather than an acute-phase therapy. Nevertheless, preclinical studies suggest that EA may exert neuroprotective effects across multiple stages, including hyperacute intervention, recovery-phase treatment, and preconditioning paradigms prior to stroke onset [62].

The optimal timing for post-stroke EA intervention remains controversial. Some investigators have suggested that EA should be initiated only after completion of acute medical management or during the rehabilitation phase [63]. However, other studies have proposed that 24–48 h

Table 1. Clinical characteristics and electroacupuncture intervention protocols in studies of post-stroke cognitive impairment.

Ref.	Sample size	Clinical diagnosis	Acupoint(s)	EA parameters	Course	Post-stroke timing
[26]	34	Mixed (IS/HS) Control: 5/12; EA: 7/10	GV20, GV24	Sparse-dense wave; 10/50 Hz; 0.5–5.0 mA; 30 min/day	5 days/ week 12 weeks	≤1 year
[35]	91	Mixed (IS/HS)	GV20, EX-HN3, EX-HN1, GB15, GB8, EX-HN5, ST8, HT7, LI4, LI11, CV4, ST36, ST40, SP6, GV26	Continuous wave; 2 Hz; 30 min/day	3 days/ week 8 weeks	29.4 ± 60.0 months
[25]	140	VCIND	GV20, GV24	30 min/day	5 days/ week 8 weeks	≥6 months
[36]	72	IS	EX-HN1	Continuous wave; 2 Hz; 2–3 W tolerated intensity; 20 min/day	5 days/ week 3 weeks	3–12 months
[37]	63	Mixed (IS/HS)	GV20, GV24, EX-HN3, EX-HN1, HT7, PC6, ST36, ST40, GB39, KI3	Sparse-dense wave; 10–50 Hz; 30 min/day	6 days/ week 4 weeks	≤6 months
[38]	90	VD	EX-HN1, GV20, GV24, GB20	Continuous wave; 300–500 pulses/min; tolerated intensity; 30 min/day	5 days/ week 6 weeks	>6 months
[39]	54	Mixed (IS/HS)	LI4, LI11, ST36, GB34, ST40, GV20, EX28:2, EX36:1	Low-frequency EA; 2 Hz; visible muscle contraction intensity; 30 min/day	2 days/ week 10 weeks	5–10 days
[32]	120	IS	EX-HN1	Continuous wave; 2 Hz; 1–2 mA; 20 min/day	Every other day for 28 days	2 weeks–1 year
[34]	106	IS	GV20, GV24, EX-HN1, GB20, EX-HN3, LI1	Low-frequency electromagnetic pulse EA; 120 pulses/min; tolerated intensity; 30 min/day	5 days/ week 4 weeks	4.3 ± 1.2 months
[33]	126	Mixed (IS/HS)	GV20, GV24, EX-HN1, GV17, CV12, LI11, HT7, ST36, SP6	Continuous wave; 8–10 Hz; 5–10 mA; 30–40 min/day	6 days/ week 8 weeks	Rehabilitation phase
[40]	120	Mixed (IS/HS)	GV20, GV24	Sparse-dense wave; low frequency; intensity NR; 30 min/day	6 days/ week 4 weeks	5.42 ± 1.87 months

IS, ischemic stroke; HS, hemorrhagic stroke; VD, vascular dementia; VCIND, vascular cognitive impairment no dementia; EA, electroacupuncture; GV20, Baihui; GV24, Shenting; EX-HN1, Sishencong; EX-HN3, Yintang; EX-HN5, Taiyang; GB15, Toulinqi; GB8, Shuaigu; ST8, Touwei; HT7, Shenmen; LI4, Hegu; LI11, Quchi; LI1, Shangyang; CV4, Guanyuan; CV12, Zhongwan; ST36, Zusanli; ST40, Fenglong; SP6, Sanyinjiao; PC6, Neiguan; GB39, Xuanzhong; KI3, Taixi; GB20, Fengchi; GV17, Naohu; EX28:2, mobility point; EX36:1, mobility point; Hz, hertz; mA, milliampere; W, watt; NR, not reported. Sparse-dense wave refers to alternating sparse and dense electrical stimulation. Continuous wave refers to continuous electrical stimulation. Post-stroke timing indicates the interval between stroke onset and study enrollment/intervention initiation.

after stroke, once vital signs and neurological status become stable, may represent an important therapeutic window for rehabilitation interventions [64,65], whereas a rat study suggested benefits gradually decline after 14 d post-stroke [66]. Meta-analyses of randomized controlled trials further indicate that acupuncture initiated within 48 h after stroke yields the greatest therapeutic benefit, with therapeutic

efficacy generally declining across the 2–15 d, 16–30 d, and 1–6 month stages, although outcomes remain superior to those of control groups overall [67]. Collectively, these findings suggest that EA may exert therapeutic effects across multiple stages of PSCI, with the first 48 h after stroke potentially representing an important intervention window.

Table 2. Characteristics of experimental electroacupuncture protocols in PSCI animal studies.

Ref.	Animal model	Acupoint(s)	Stroke phase of study	EA parameters	Course of acupuncture
[31]	MCAO rat	GV20, GV24	24 h after surgery	density wave, 1–20 Hz, 2 mA, 30 min/day	14 days
[41]	MCAO/R rat	GV20, GV24	24 h after surgery	dense–sparse wave, 2/100 Hz, 1 mA, 30 min/day	14 days
[42]	MCAO/R rat	GV20, GV24	24 h after surgery	dense–sparse wave, 1–20 Hz, 1–3 mA, 30 min/day	14 days
[43]	MCAO/R rat	GV20, GV24	2 h after surgery	dense–sparse wave, 1–20 Hz, 2 mA, 30 min/day	8 days
[28]	MCAO/R rat	GB20, GV16, GV14	10 days after surgery	continuous wave, 20 Hz, 1 mA, 30 min/day	14 days
[44]	MCAO rat	GB20, GV16, GV14	2 h after surgery	expanding wave, 1–20 Hz, 2 mA, 6 V, 30 min/day	8 days
[45]	MCAO/R mouse	GV20	2 h before surgery	2/15 Hz, 1 mA, 30 min	1 time
[46]	MCAO/R rat	GV20, GV24	2 h after surgery	1/20 Hz, 1–3 mA, 30 min/day	7 days
[47]	MCAO/R rat	GV20, GV24	24 h after surgery	dense–sparse wave, 2/20 Hz, 0.2–1 mA, 30 min/day	7 days
[48]	MCAO/R rat	GV20, PC6, KI1	1 h after surgery	dense–sparse wave, 1–20 Hz, 2 mA, 30 min/day	7 days
[29]	MCAO/R rat	GV20, GV24	24 h after surgery	dense–sparse wave, 1–20 Hz, 30 min/day	14 days
[30]	MCAO rat	GV20, PC6	Immediately	dense–sparse wave, 20 Hz, 1–2 mA, 20 min	Twice daily, 6 days/week, 3 weeks
[49]	MCAO/R rat	GB20	2 h after surgery	disperse wave, 1/20 Hz, 0.5–1 mA, 30 min/day	7 days
[19]	MCAO/R rat	GV20, GV24	2 h after surgery	disperse wave, 0.05 Hz, 0.5–1 mA, 30 min/day	7 days
[50]	MCAO/R rat	GV20, GV24	24 h after surgery	dense–sparse wave, 4/20 Hz, 2 V, 0.5 mA, 30 min/day	7 days
[27]	MCAO/R rat	GV20, GV24	5 min and 6 h after surgery	dense–sparse wave, 4/20 Hz, 0.5–1 mA, 30 min	2 times
[51]	MCAO/R rat	GV20, EX–HN3	24 h after surgery	continuous wave, 2 Hz, 1 mA, 10 min/day	14 days
[52]	BCCAO mouse	GV20	7 days after surgery	2/15 Hz, 1 mA, 30 min/day	14 days
[53]	MCAO/R rat	GV20, GV26	28 days after surgery	dense–sparse wave, 2/100 Hz, 3 mA, 40 min/day	10 days
[54]	MCAO/R rat	GV20, GV24	Immediately	disperse wave, 1/20 Hz, 0.2 mA, 30 min/day	14 days
[55]	MCAO mouse	GV20	Immediately	2/15 Hz, 1 mA, 20 min/day	14 days
[56]	MCAO/R rat	GV20, GV24	24 h after surgery	dense–sparse wave, 1–20 Hz, 0.2 mA, 30 min/day	14 days
[57]	MCAO/R rat	GV20, GV24	24 h after surgery	dense–sparse wave, 1–20 Hz, 0.2 mA, 30 min/day	14 days
[58]	MCAO/R rat	GV20, GV24	24 h after surgery	dense–sparse wave, 1–20 Hz, 0.2 mA, 30 min/day	14 days
[59]	MCAO/R rat	GV20, GV24	2 h after surgery	disperse wave, 1/20 Hz, 30 min/day	7 days
[60]	MCAO/R rat	GV20, GV24	4 h after surgery	disperse wave, 1/20 Hz, 30 min/day	7 days
[61]	MCAO/R rat	GV20, GV24	24 h after surgery	disperse wave, 1–20 Hz, 6 mA, 30 min/day	14 days

MCAO, middle cerebral artery occlusion; MCAO/R, middle cerebral artery occlusion/reperfusion; BCCAO, bilateral common carotid artery occlusion; GV20, Baihui; GV24, Shenting; GV26, Shuigou; GV14, Dazhui; GV16, Fengfu; GB20, Fengchi; PC6, Neiguan; KI1, Yongquan; EX–HN3, Yintang; Hz, hertz; mA, milliamper; V, volt; h, hour; min, minute. “Immediately” indicates EA intervention initiated immediately after surgery. “Stroke phase of study” refers to the initiation time of EA intervention after stroke modeling.

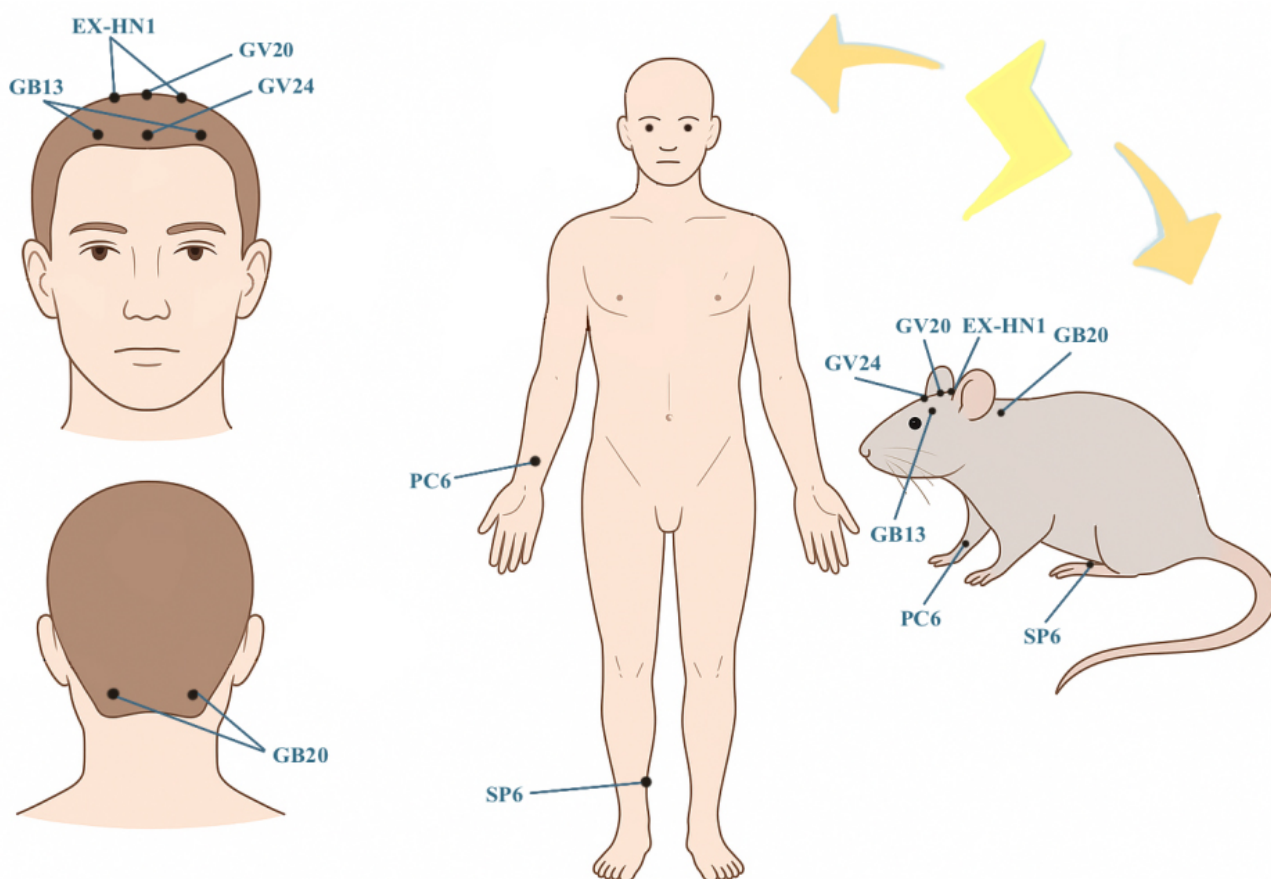


Fig. 1. Illustration of frequently applied acupoints in preclinical and clinical electroacupuncture (EA) research. EX-HN1, Sishencong; GB13, Benshen. Created with Procreate.

2.3.2 Acupoint Selection

Although a fully standardized acupoint prescription for PSCI has not yet been established, current EA treatment strategies demonstrate a relatively consistent pattern overall. Acupoint selection in preclinical studies is relatively simplified, mainly focusing on Baihui (GV20), Shenting (GV24), and several Governor Vessel-related occipital and cervical acupoints, including Fengchi (GB20), Fengfu (GV16), and Dazhui (GV14) (Fig. 1). This suggests that animal experiments tend to adopt fixed and standardized scalp acupuncture paradigms to improve the reproducibility of mechanistic studies (Table 2). Studies have suggested that stimulation of GV20 and GV24 may be associated with cerebral blood flow regulation, suppression of neuroinflammation, and modulation of hippocampal neuroplasticity [56,68,69,70]. A meta-analysis including 2044 patients demonstrated that acupuncture treatment centered on the Governor Vessel significantly improved cognitive function after stroke (OR = 3.00, 95% CI = 2.37–3.79, I^2 = 0%) [71].

In contrast, clinical studies generally retain GV20 and GV24 as core acupoints while further incorporating Sishencong (EX-HN1), Yintang (EX-HN3), Shenmen (HT7), Neiguan (PC6), Zusanli (ST36), and Sanyinjiao (SP6), re-

flecting a more individualized acupoint selection pattern (Table 1). Data mining analyses of 87 clinical and preclinical studies identified GV20, GV24, EX-HN1, GB20, and GB13 as the five most frequently used acupoints [20]. Further complex network analysis suggested that the combination “GV20-EX-HN1-PC6-SP6-GV24” may represent a core acupoint network for acupuncture treatment of PSCI [72]. In addition, a meta-analysis involving 659 experimental animals indicated that therapeutic efficacy varied among different acupoint combinations, with GV20 combined with GV14 potentially showing the greatest effect [73]. Overall, current EA protocols for PSCI are predominantly centered on Governor Vessel scalp acupoints. Nevertheless, acupoint selection may partly rely on clinical experience, and the relationships among specific acupoints, brain networks, and cognitive domains remain insufficiently understood. Frequently used acupoints in preclinical and clinical EA studies are illustrated in Fig. 1.

2.3.3 Stimulation Parameters

EA stimulation parameters are also important determinants of therapeutic efficacy. Although considerable heterogeneity exists among studies, both preclinical and clinical investigations have demonstrated relatively consistent

parameter patterns overall. Regarding waveform selection, dense–sparse wave stimulation is the most commonly used pattern in preclinical studies (Tables 1,2). Previous studies have suggested that dense–sparse wave stimulation may reduce tissue adaptation to stimulation and promote local metabolic activity and inflammatory clearance [74]. Animal experiments have further shown that dense–sparse wave EA produces superior effects on cognitive performance in rodents compared with other waveform patterns [75].

With respect to stimulation frequency, most studies employ low-frequency or alternating low–high frequency paradigms (Tables 1,2). Previous evidence suggests that 2 Hz low-frequency EA and alternating 2/100 Hz stimulation may exert greater therapeutic effects than 100 Hz high-frequency EA [76]. Mechanistic studies further indicate that low-frequency EA may more effectively regulate genes and proteins associated with neurogenesis, synaptic plasticity, and hippocampus-related memory function [36], suggesting that low-frequency stimulation may represent a core parameter pattern in current PSCI interventions.

Regarding stimulation intensity, animal studies generally employ fixed currents ranging from 0.2–6 mA to improve experimental reproducibility, whereas clinical studies more commonly adjust stimulation intensity according to patient tolerance or visible muscle contraction, reflecting greater emphasis on individualized stimulation and elicitation of “Deqi” sensation in clinical practice. In addition, 30 min/day is the most commonly used treatment duration in both preclinical and clinical studies, while only a few studies employ stimulation durations ranging from 10–40 min/day. This suggests that 30 min/day may have gradually emerged as an empirical standard duration for EA treatment in PSCI (Tables 1,2). Overall, current EA protocols are predominantly characterized by low-frequency stimulation, dense/sparse waveforms, moderate stimulation intensity, and 30 min/day treatment duration. However, substantial inconsistencies still exist across studies regarding frequency range, waveform definition, intensity expression, and parameter reporting methods, thereby limiting cross-study comparisons and protocol standardization.

3. Post-Stroke PCD Increases the Risk of PSCI

PCD is a tightly regulated form of cell death involved in various pathological processes [77]. Following stroke, ischemia-reperfusion or hemorrhagic injury induces neuronal damage through mechanisms including excitotoxicity, oxidative stress, inflammation, mitochondrial dysfunction, and energy metabolism impairment, collectively triggering multiple forms of PCD [78]. Excessive neuronal loss disrupts neural network integrity, synaptic connectivity, and neuroplasticity, thereby contributing to post-stroke cognitive decline [79]. Previous studies have shown that post-stroke brain injury involves multiple PCD path-

ways, including apoptosis, autophagy, ferroptosis, pyroptosis, necroptosis, phagoptosis, and parthanatos [78]. Based on this rationale, the following sections summarize the mechanisms underlying the major forms of PCD following stroke.

3.1 Post-Stroke Apoptosis

Apoptosis is a classical form of PCD primarily mediated through intrinsic mitochondrial and extrinsic death receptor pathways [80]. In stroke-injured neurons, typical apoptotic features include cell shrinkage, cytoplasmic condensation, nuclear fragmentation, and apoptotic body formation [81,82]. Excessive neuronal apoptosis is considered a major pathological contributor to PSCI [83]. Sustained neuronal apoptosis leads to neuronal and dendritic spine loss, disrupting hippocampal and cortical synaptic networks and ultimately impairing learning, memory, and executive function [60].

Following stroke, neuronal injury induces excessive glutamate (Glu) release [60], leading to prolonged activation of glutamate receptors [84]. The two major subtypes of ionotropic Glu receptors are N-methyl-D-aspartate receptors (NMDAR) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) [85]. Excessive Glu stimulation results in abnormal Ca^{2+} influx, intracellular Ca^{2+} overload, and subsequent calpain activation, ultimately triggering the intrinsic apoptotic pathway [85]. Extrinsic apoptosis is mediated by plasma membrane death receptors, including TNFR1, apoptosis antigen 1 (APO1/FAS/CD95), and TRAIL-R [86]. Following stroke, these receptors interact with FADD to form the death-inducing signaling complex, leading to pro-caspase-8 activation [87]. Activated calpains or caspase-8 further cleave the BH3-interacting domain death agonist (BID) into its truncated active form (tBID) [88]. tBID subsequently interacts with BAX on the mitochondrial membrane, promoting mitochondrial permeability transition pore (mPTP) formation and the release of pro-apoptotic factors, including cytochrome c (Cyt c) and apoptosis-inducing factor (AIF) [89]. Released Cyt c then associates with APAF1 and caspase-9 to form the apoptosome, ultimately activating caspase-3 and inducing apoptosis (Fig. 2).

3.2 Post-Stroke Autophagy

Autophagy is characterized by the sequestration of damaged organelles and cytoplasmic components into double-membrane autophagosomes, which subsequently fuse with lysosomes for cargo degradation and recycling [90]. Following stroke, cerebral ischemia and hypoxia reduce insulin and amino acid availability, thereby suppressing activation of the major autophagy inhibitor, mammalian target of rapamycin complex 1 (mTORC1). Under physiological conditions, mTORC1 suppresses autophagy through inhibition of the mammalian Atg1/Unc-51-like kinase (ULK) complex [91]. In contrast, post-stroke sup-

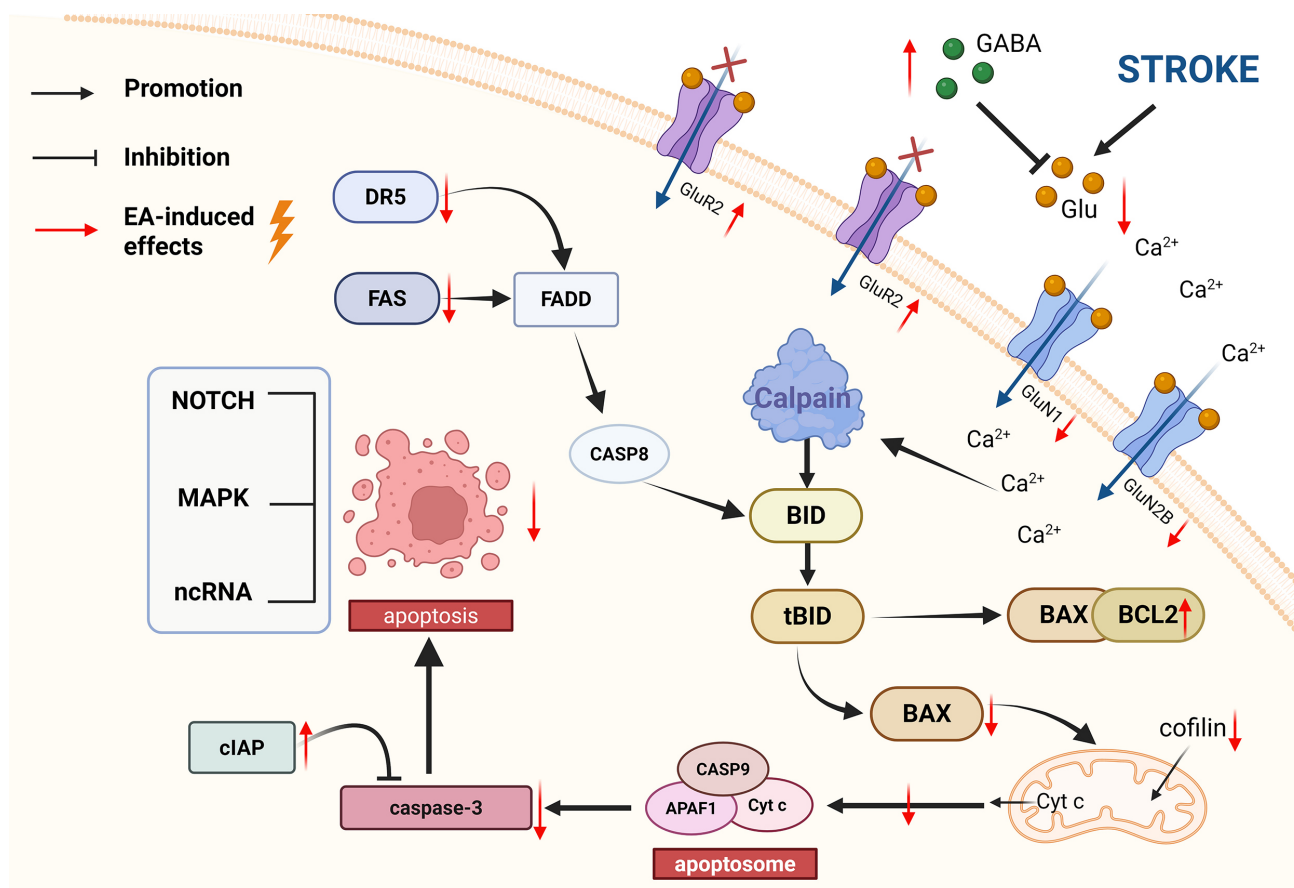


Fig. 2. EA regulates post-stroke apoptosis through modulation of excitotoxicity, mitochondrial dysfunction, and death receptor signaling pathways, thereby suppressing neuronal apoptosis. Additional regulatory mechanisms involve NOTCH, mitogen-activated protein kinase (MAPK), and non-coding RNAs. Created with BioRender with permission to publish. DR5, death receptor 5; FADD, FAS-associated protein with death domain; CASP8, caspase-8; BAX, BCL2-associated X protein; BCL2, B-cell lymphoma 2; cIAP, cellular inhibitor of apoptosis protein; CASP9, caspase-9; APAF1, apoptotic protease-activating factor 1; GABA, γ -aminobutyric acid; GluR2, glutamate receptor 2; GluN1, glutamate ionotropic receptor NMDA type subunit 1; GluN2B, glutamate ionotropic receptor NMDA type subunit 2B; ncRNA, non-coding RNA.

pression of mTORC1 permits ULK activation, initiating autophagosome formation and activation of autophagy-related proteins such as Beclin1 and LC3. During this process, LC3-I is converted to LC3-II, ultimately promoting autophagy [92,93].

In addition, mitochondrial dysfunction, endoplasmic reticulum stress (ERS), and intracellular Ca^{2+} accumulation following stroke further exacerbate neuronal autophagy [78]. Stroke-induced nutrient deprivation and disruption of Ca^{2+} homeostasis trigger ERS, which is characterized by ER dysfunction and accumulation of unfolded or misfolded proteins within the ER lumen [94,95]. This process activates autophagy through the unfolded protein response (UPR) while promoting cytosolic Ca^{2+} release, thereby contributing to neuronal injury [96]. Hypoxia-inducible factor-1 (HIF-1), which consists of oxygen-regulated HIF-1 α and constitutively expressed HIF-1 β subunits, is activated under post-stroke hypoxic conditions [97,98]. Activated HIF-1 α further induces post-ischemic autophagy through p53

upregulation [99]. Mitophagy, a selective and protective form of autophagy, removes damaged mitochondria [100], thereby limiting reactive oxygen species (ROS) accumulation and maintaining cellular homeostasis. Conversely, impaired mitophagy results in mitochondrial and ROS accumulation, which may activate the NLRP3 inflammasome [101], ultimately promoting neuroinflammation and pyroptosis (Fig. 3).

Autophagy exerts dual effects following stroke. Moderate autophagy supplies energy and nutrients to ischemic tissue [102]; for example, microglial autophagy facilitates clearance of apoptotic debris, limiting neuronal injury and inflammation [103]. However, excessive or sustained autophagy beyond a critical threshold may promote cell death [104]. In the context of PSCI, studies indicate that both upregulation and downregulation of autophagy-related factors can improve cognitive outcomes [28,50,105]. Preclinical evidence therefore suggests that precise modulation of autophagy may attenuate post-stroke neuronal structural

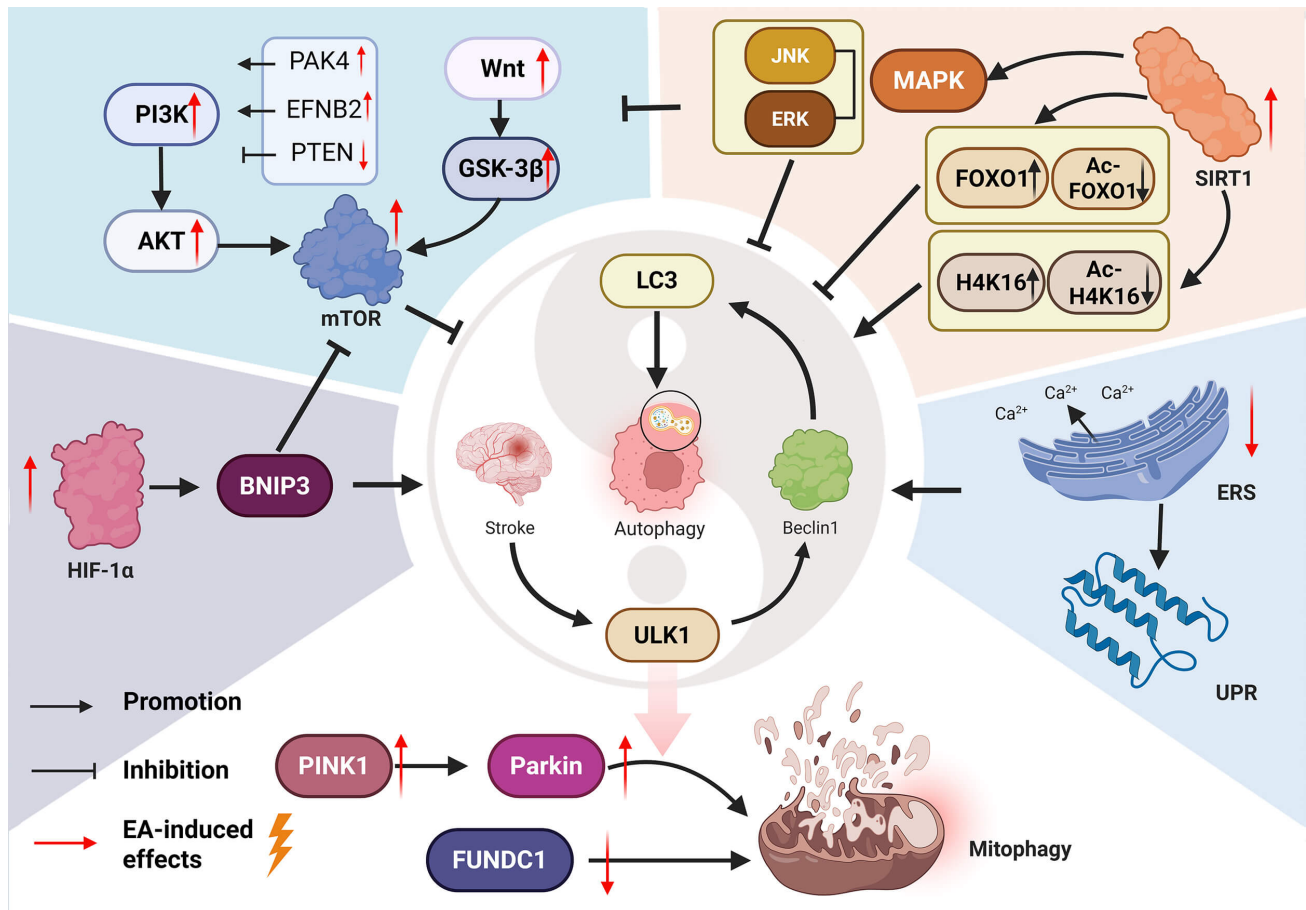


Fig. 3. EA regulates post-stroke autophagy and mitophagy through multiple signaling pathways, including PI3K/AKT/mTOR, Wnt/GSK-3 β , Silent information regulator 1 (SIRT1)-related pathways, Hypoxia-inducible factor-1 α (HIF-1 α), and endoplasmic reticulum stress (ERS) pathways, as well as PINK1/Parkin- and FUNDC1-mediated mitophagy. These effects contribute to the modulation of autophagic activity and neuronal protection after stroke. Created with BioRender with permission to publish. PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; Wnt, wingless-type MMTV integration site family; PAK4, p21-activated kinase 4; PTEN, phosphatase and tensin homolog; GSK-3 β , glycogen synthase kinase 3 beta; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; FOXO1, forkhead box O1; Ac-FOXO1, acetylated FOXO1; H4K16, histone H4 lysine 16; Ac-H4K16, acetylated histone H4 lysine 16; LC3, microtubule-associated protein 1 light chain 3; BNIP3, BCL2 interacting protein 3; ULK1, Unc-51-like kinase 1; PINK1, PTEN-induced kinase 1; FUNDC1, FUN14 domain-containing protein 1.

and functional damage, representing a potential therapeutic strategy for PSCI [43].

3.3 Post-Stroke Pyroptosis and Inflammation

Pyroptosis, also known as inflammatory cell death, is a form of PCD characterized by cell swelling, plasma membrane rupture, intracellular content release, and robust inflammatory responses [106]. Post-stroke ischemia, hypoxia, and metabolic disturbances damage neurons and glial cells, leading to the release of damage-associated molecular patterns (DAMPs). These DAMPs activate Toll-like receptor 4 (TLR4), which is highly expressed on microglia, thereby promoting microglial activation and inflammatory responses [107]. NF- κ B subsequently translocates to the nucleus, upregulating inflammation-related genes and cytokine production in astrocytes, thereby am-

plifying local inflammation. Subsequently, the NLRP3 inflammasome assembles and recruits ASC and caspase-1 to form a mature inflammasome complex [108]. Activated caspase-1 promotes the maturation and release of IL-1 β and IL-18 while cleaving Gasdermin D to form membrane pores, ultimately triggering pyroptotic cell death [109]. During pyroptosis, rupture of neuronal and glial cell membranes leads to the release of large amounts of proinflammatory cytokines, further exacerbating local inflammation and creating a vicious cycle [106] (Fig. 4).

Moreover, the phenotypic balance of microglia plays a critical role in regulating neuroinflammation and influences synaptic plasticity, brain network function, and cognitive performance [110,111]. The M1 phenotype is proinflammatory and releases TNF- α , IL-1, IL-6, and ROS, thereby exacerbating neuronal injury. In contrast, the M2 pheno-

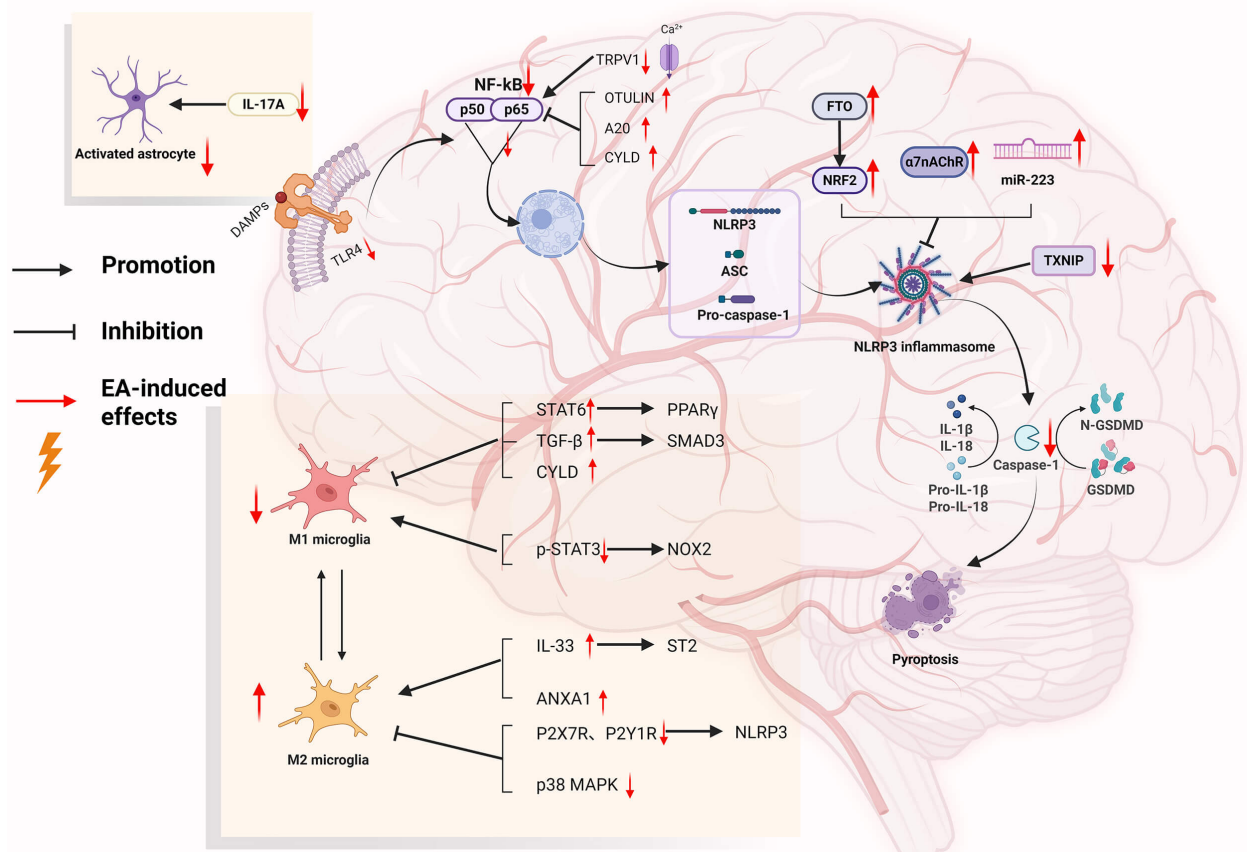


Fig. 4. EA modulates post-stroke pyroptosis and neuroinflammation by regulating microglial polarization, astrocyte activation, NLRP3 inflammasome assembly, and pro-inflammatory cytokine release. EA also influences multiple signaling pathways, including NF-κB, MAPK, STAT family proteins, and P2X7 receptors, thereby attenuating neuronal pyroptosis after stroke. Created with BioRender with permission to publish. NF-κB, nuclear factor kappa B; p50, NF-κB1 p50 subunit; p65, RelA/p65 subunit; IL-17A, interleukin-17A; TRPV1, transient receptor potential vanilloid 1; OTULIN, OTU deubiquitinase with linear linkage specificity; A20, tumor necrosis factor alpha-induced protein 3; CYLD, CYLD lysine 63 deubiquitinase; FTO, fat mass and obesity-associated protein; NRF2, nuclear factor erythroid 2-related factor 2; α7nAChR, alpha-7 nicotinic acetylcholine receptor; miR-223, microRNA-223; NLRP3, NOD-like receptor family pyrin domain-containing 3; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; TXNIP, thioredoxin-interacting protein; IL-1β, interleukin-1 beta; IL-18, interleukin-18; GSDMD, gasdermin D; N-GSDMD, N-terminal fragment of gasdermin D; STAT6, signal transducer and activator of transcription 6; PPARγ, peroxisome proliferator-activated receptor gamma; TGF-β, transforming growth factor beta; STAT3, signal transducer and activator of transcription 3; p-STAT3, phosphorylated STAT3; NOX2, NADPH oxidase 2; IL-33, interleukin-33; ST2, suppression of tumorigenicity 2; ANXA1, annexin A1; P2X7R, P2X purinoceptor 7; P2Y1R, P2Y purinoceptor 1; M1, pro-inflammatory M1 microglial phenotype; M2, anti-inflammatory M2 microglial phenotype.

type is anti-inflammatory and secretes insulin-like growth factor and neurotrophic factors that promote neural repair and regeneration [112]. Following stroke, microglia predominantly exhibit the M2 phenotype during the first 7 days and subsequently shift toward the M1 phenotype between days 7 and 14, further intensifying inflammation and tissue damage [113]. Astrocytes also exhibit phenotypic heterogeneity, with A1 astrocytes displaying neurotoxic properties and A2 astrocytes exerting neuroprotective effects [114]. During the acute phase after stroke, astrocytes tend to adopt the A1 phenotype, characterized by upregulation of complement component C3 and increased expression of

proinflammatory cytokines [115]. These changes further amplify local inflammation, resulting in widespread neuronal death and impairment of synaptic structure and function [116]. Following stroke, neuroinflammation and pyroptosis synergistically exacerbate neuronal injury, directly impairing cognitive domains such as learning, memory, and reasoning [117]. Animal studies suggest that inhibition of pyroptosis alleviates brain injury and improves post-stroke cognitive function [118,119]. Therefore, targeting neuroinflammation and pyroptosis may represent a promising therapeutic strategy for PSCI.

3.4 Post-Stroke Ferroptosis

Ferroptosis is an iron-dependent form of regulated cell death characterized by lipid peroxidation [120]. It is characterized by intracellular free iron accumulation, which catalyzes hydroxyl radical production through the Fenton reaction and subsequently drives lipid peroxidation within cellular membranes [121]. As the organ with the highest oxygen consumption and lipid content, the brain possesses a highly fragile redox balance that is readily disrupted by hemorrhagic or ischemic injury [122].

Post-stroke ferroptosis primarily involves three mutually reinforcing processes: (1) iron overload and dysregulated iron metabolism, (2) lipid peroxidation-induced damage, and (3) imbalance of antioxidant systems [120]. Regarding iron metabolism, uptake of transferrin (TF)- Fe^{3+} complexes through transferrin receptor 1 (TFR1) is markedly enhanced following stroke, increasing intracellular iron import and accelerating the reduction of Fe^{3+} to Fe^{2+} , thereby promoting an iron-overloaded environment. Meanwhile, ferritin, which is responsible for iron storage and detoxification, is often downregulated or undergoes enhanced autophagic degradation after ischemia/reperfusion or hemorrhage, further reducing the cellular capacity to buffer free Fe^{2+} . As a result, the labile iron pool expands, increasing susceptibility to ferroptosis [78]. Fe^{2+} serves as a substrate for the Fenton reaction, continuously generating hydroxyl radicals that drive non-enzymatic lipid peroxidation chain reactions. Once polyunsaturated fatty acids (PUFAs) are incorporated into membrane phospholipids (PUFA-PLs), lipid hydroperoxides (PUFA-OOH) progressively accumulate [123]. Moreover, stroke is associated with reduced glutathione (GSH) levels and decreased glutathione peroxidase 4 (GPX4) activity, thereby impairing the cellular capacity to eliminate lipid peroxides [124]. The resulting oxidative stress and lipid peroxidation ultimately lead to irreversible cellular damage and death (Fig. 5).

Ferroptosis has emerged as a critical mechanism contributing to neuronal injury following stroke [125]. Current preclinical studies suggest that modulation of iron homeostasis, enhancement of GPX4 activity, or inhibition of lipid peroxidation can improve post-stroke neurological outcomes [126]. These findings suggest that ferroptosis represents not only a key mechanism underlying stroke pathology but also a potential therapeutic target for PSCI intervention.

4. EA-Mediated Amelioration of PSCI: a Focus on PCD

As a neuromodulatory intervention characterized by multi-target and multi-pathway regulation, EA has demonstrated potential for improving post-stroke cognitive function in both clinical and preclinical studies. EA can modulate multiple PCD-related signaling pathways to suppress excessive or aberrant cell death, thereby preserving the structural and functional integrity of key cognitive brain

regions, such as the hippocampus and cortex (Tables 1,2). Building on these effects, the following sections systematically examine the potential mechanisms by which EA ameliorates PSCI by regulating distinct forms of PCD.

4.1 Apoptosis

Neuronal apoptosis in the ischemic penumbra is partially reversible, making intervention in apoptotic pathways a critical therapeutic strategy to reduce post-stroke cell death. Increasing evidence suggests that EA may improve cognitive function after stroke by attenuating neuronal apoptosis, and the underlying mechanisms have been extensively investigated.

4.1.1 Inhibition of Apoptotic Initiation Signals

EA may simultaneously suppress the initiation of both intrinsic and extrinsic apoptotic pathways. Regulation of intrinsic apoptosis primarily involves attenuation of excitotoxicity. EA may modulate glutamate (Glu) receptor activity to limit Ca^{2+} influx, thereby interfering with the early initiation of apoptotic signaling. AMPAR is a heteromeric complex composed of GluR1–GluR4 subunits, among which the GluR2 subunit is impermeable to Ca^{2+} . Stroke-induced downregulation of GluR2 increases AMPAR-mediated Ca^{2+} permeability, thereby aggravating neuronal calcium overload and increasing apoptotic susceptibility [127]. Studies have shown that EA treatment suppresses Glu release and increases GluR2 expression, which may contribute to reduced postsynaptic Ca^{2+} permeability [128,129].

NMDAR is a hetero-oligomeric receptor composed of GluN1, GluN2 (2A–2D), and GluN3 subunits. EA treatment has been shown to reduce GluN2B expression and is accompanied by decreased activation of downstream pro-apoptotic mediators, including calpain and phosphorylated p38 mitogen-activated protein kinase (MAPK) [130]. In addition, EA may activate the PI3K signaling pathway, suppress GluN1 expression, reduce overall NMDAR activity, and attenuate Ca^{2+} overload-induced neurotoxicity by limiting Ca^{2+} influx [131]. Furthermore, EA promotes dissociation of the NMDAR-PSD95-nNOS complex and reduces NMDAR-mediated nitric oxide (NO) production and related neurotoxic signaling, thereby alleviating mitochondrial dysfunction and neuronal apoptosis [132]. Notably, EA has also been reported to increase γ -aminobutyric acid (GABA) levels, enhance inhibitory neurotransmission, counteract Glu-mediated excitotoxicity, and restore excitatory–inhibitory balance, collectively contributing to synergistic neuroprotective effects [132,133]. Collectively, these findings suggest that EA may suppress Glu-mediated excitotoxicity and apoptotic initiation through modulation of glutamatergic signaling and enhancement of inhibitory neurotransmission.

EA may also exert neuroprotective effects against extrinsic apoptosis through regulation of key death receptors,

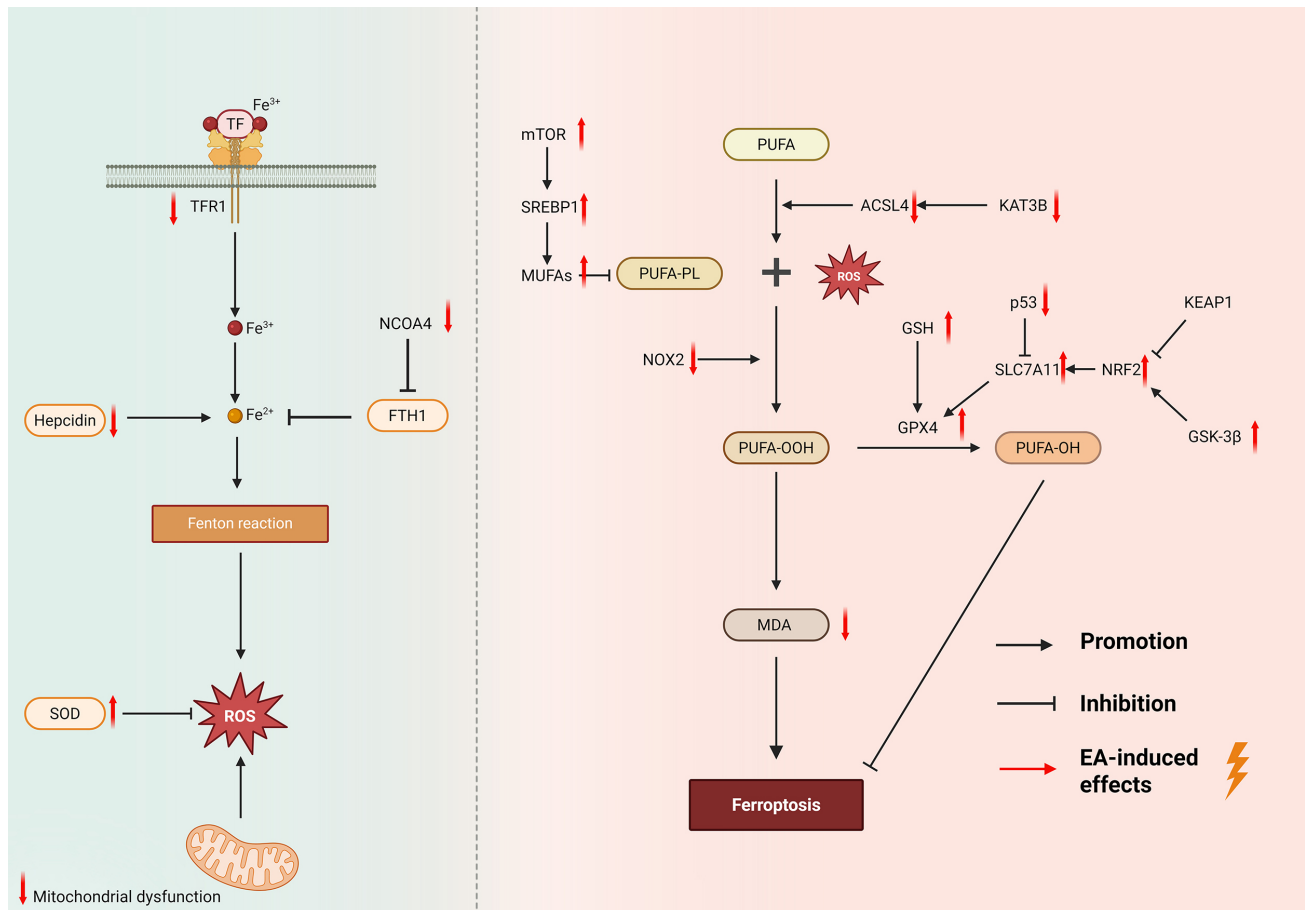


Fig. 5. EA regulates post-stroke ferroptosis by modulating iron metabolism, lipid peroxidation, and oxidative stress. EA reduces Fe^{2+} accumulation, inhibits lipid peroxidation, and enhances antioxidant defenses, including glutathione (GSH) and glutathione peroxidase 4 (GPX4), thereby attenuating ferroptotic cell death after stroke. Created with BioRender with permission to publish. NCOA4, nuclear receptor coactivator 4; FTH1, ferritin heavy chain 1; SOD, superoxide dismutase; SREBP1, sterol regulatory element-binding protein 1; MUFAs, monounsaturated fatty acids; ACSL4, acyl-CoA synthetase long-chain family member 4; KAT3B, lysine acetyltransferase 3B; MDA, malondialdehyde; p53, tumor protein p53; SLC7A11, solute carrier family 7 member 11; KEAP1, Kelch-like ECH-associated protein 1.

including FAS and DR5 [21]. NF- κ B, a key nuclear transcription factor, is activated in PSCI [108], while BAX and FAS are important downstream targets of NF- κ B signaling [134]. Feng et al. [119] reported that EA suppressed NF- κ B signaling in the brains of PSCI models, accompanied by reduced BAX and FAS expression, decreased neuronal apoptosis, and improved cognitive function [118]. Death receptor (DR)-mediated apoptosis is associated with caspase-8-dependent degradation of cIAP-1 [135]. Correspondingly, decreased DR5 expression together with increased cIAP-1 and cIAP-2 expression has been observed following EA treatment in PSCI model rats [21]. Overall, current evidence suggests that EA may inhibit the initiation phase of apoptosis primarily through attenuation of excitotoxicity and suppression of death receptor-related signaling.

4.1.2 Modulating BCL2 Family Balance

EA may regulate mitochondrial apoptotic signaling through modulation of BCL2 family protein expression and maintenance of mitochondrial homeostasis. The BCL2 family includes anti-apoptotic proteins such as BCL2 and BCL-xL, as well as pro-apoptotic proteins including BAX, BAK, BAD, and BID [80]. The relative expression levels of these proteins collectively determine the status of mitochondrial outer membrane permeabilization (MOMP). BCL2 is a membrane-associated protein that stabilizes organelle membranes by suppressing reactive oxygen species (ROS) generation and intracellular calcium overload, thereby reducing MOMP, preventing cytochrome c release, and inhibiting downstream caspase activation, including caspase-3. Following stroke, formation of BAX/BCL2 heterodimers antagonizes the anti-apoptotic function of BCL2 [136,137].

Studies have shown that EA treatment significantly upregulates BCL2 and downregulates BAX in PSCI model mice, accompanied by reduced caspase-3 activity, attenuated neuronal apoptosis, and improved cognitive function [21,61]. These effects may be associated with activation of cAMP response element-binding protein (CREB) [138,139] and modulation of H3K9/H3K27 acetylation occupancy within gene promoter regions [92]. Notably, following administration of a NOTCH3 inhibitor, the regulatory effects of EA on BCL2/BAX balance were markedly attenuated, together with reduced neuroprotective efficacy, suggesting that NOTCH3 signaling may participate in EA-mediated anti-apoptotic effects [55]. In addition, increased expression of the anti-apoptotic protein BCL-xL has also been observed following EA treatment, further contributing to mitochondrial membrane stabilization [21].

EA also appears to regulate BAX-associated mitochondrial events. Mitochondrial translocation of cofilin cooperates with activated BAX to promote mitochondrial permeability transition pore (mPTP) opening and subsequent cytochrome c release, representing a critical step in mitochondrial apoptosis [140]. Experimental studies have shown that cofilin silencing markedly attenuates neuronal apoptosis under oxygen-glucose deprivation conditions [141]. Following EA treatment, decreased cofilin expression together with reduced mitochondrial translocation of cofilin has been observed [27], suggesting that cofilin may participate in the mitochondrial anti-apoptotic effects of EA. Overall, current evidence suggests that EA may regulate mitochondria-mediated apoptotic signaling through restoration of BCL2 family balance and maintenance of mitochondrial homeostasis.

4.1.3 Inhibition of Terminal Apoptotic Events

During the execution phase of apoptosis, EA may suppress caspase cascade activation and subsequent apoptotic body formation, thereby attenuating terminal apoptotic signaling. These effects are mainly associated with regulation of the inhibitor of apoptosis protein (IAP) family. Members of the IAP family, including cIAP-1, cIAP-2, and XIAP, suppress apoptosis through negative regulation of caspase activity [142]. Previous studies have reported that EA increases XIAP expression, accompanied by reduced activities of caspase-9, -3, and -7 [21,143]. In addition, increased expression of the anti-apoptotic proteins cIAP-1 and cIAP-2, together with decreased activities of caspase-3, -8, and -9, has also been observed in the cortices of EA-treated rats [21]. Overall, current evidence suggests that EA may interfere with the execution phase of apoptosis through modulation of the IAP family, thereby alleviating post-stroke neuronal injury.

4.2 Autophagy

Autophagy may exert both protective and detrimental effects following stroke, and current studies on EA have

primarily focused on its regulatory effects on aberrantly activated autophagy. Studies have shown that EA intervention reduces the numbers of autophagosomes, autolysosomes, and lysosomes following stroke [144]. Mechanistically, EA-mediated autophagy regulation mainly involves mTOR-, SIRT1-, HIF-1 α -, and ERS-related signaling pathways, whereas mitophagy appears to exhibit distinct regulatory characteristics.

4.2.1 mTOR-Related Regulation of Autophagy

Regulation of autophagy by EA is mainly associated with modulation of the PI3K/AKT/mTOR axis. mTORC1 is a central negative regulator of autophagosome formation and autophagic processes [145]. Activation of mTORC1 leads to ULK complex inactivation and downregulation of LC3 II and Beclin1 expression, thereby suppressing subsequent autophagosome formation [105,144]. Following stroke, reduced oxygen, glucose, and growth factor supply suppresses PI3K/AKT activity and subsequently decreases mTORC1 activity [146]. Studies have demonstrated that EA treatment enhances PI3K expression as well as AKT and mTOR phosphorylation levels, accompanied by reduced autophagy in MCAO/R rats [147]. Notably, these effects can be reversed by PI3K/AKT/mTOR pathway antagonists, suggesting that this signaling pathway may participate in EA-mediated autophagy regulation [147]. Furthermore, proteomic analyses revealed that EA treatment downregulated expression of the AKT inhibitory factor PTEN while increasing expression of the AKT-promoting factors EFNB2 and PAK4 [42], suggesting that EA may modulate autophagy through upstream regulatory networks associated with the PI3K/AKT/mTOR axis.

In addition, Wnt signaling has also been implicated in EA-mediated autophagy regulation. Wnt signaling is known to regulate neurogenesis, synaptogenesis, neuronal and synaptic plasticity, and angiogenesis, effects that may partially depend on autophagic regulation. Studies have shown that EA treatment increases GSK-3 β phosphorylation levels, accompanied by enhanced mTOR activity and reduced autophagy [148,149,150], suggesting that Wnt/GSK-3 β signaling may participate in EA-mediated autophagy regulation. Overall, current evidence suggests that EA may suppress excessive post-stroke autophagy primarily through modulation of PI3K/AKT/mTOR- and Wnt/GSK-3 β -related signaling pathways.

4.2.2 SIRT1-Related Regulation of Autophagy

Silent information regulator 1 (SIRT1) is an NAD⁺-dependent deacetylase that regulates inflammation, oxidative stress, apoptosis, and autophagy through deacetylation of histone substrates, such as histone H4 lysine 16 (H4K16), as well as non-histone proteins including Forkhead box O1 (FOXO1) [151]. Following stroke, oxidative stress promotes cytoplasmic accumulation of acetylated FOXO1 (Ac-FOXO1), which interacts with autophagy-related gene

7 (ATG7) to activate autophagy [152]. Studies have shown that EA pretreatment increases SIRT1 and FOXO1 expression while reducing Ac-FOXO1 levels, thereby attenuating FOXO1-ATG7-associated autophagic activation. Notably, these effects are abolished by the SIRT1 inhibitor EX527 [135].

In addition, EA may also alleviate ERS-related autophagy. Studies have shown that EA intervention increases mRNA expression of the endoplasmic reticulum chaperone GRP78, while reducing expression of CHOP/GADD153, p-eIF2 α , and caspase-12, accompanied by decreased infarct volume [153]. These findings suggest that EA may modulate ERS-related injury. Furthermore, EA pretreatment has been associated with activation of NOTCH signaling and upregulation of HIF-1 α expression, accompanied by reduced autophagy levels [154]. Overall, current evidence suggests that EA may participate in post-stroke autophagy regulation through modulation of SIRT1-, ERS-, and HIF-1 α -related signaling pathways.

4.2.3 Regulation of Mitophagy

Mitophagy can be broadly classified into ubiquitin-dependent and receptor-mediated pathways, both of which function to maintain mitochondrial quality through fine regulation of autophagic activity. Ubiquitin-dependent mitophagy is primarily mediated by the PINK1/Parkin pathway [155]. Studies have shown that EA treatment enhances PINK1/Parkin-mediated mitophagy, accompanied by reduced accumulation of damaged mitochondria and improved mitochondrial function [156].

In contrast, receptor-mediated mitophagy depends on mitochondrial outer membrane proteins such as FUNDC1 and BNIP3. Following stroke, ULK1 induces mitophagy through phosphorylation of FUNDC1 [157]. Tian et al. [158] reported that EA pretreatment reduced expression of LC3 II, p-ULK1, and FUNDC1 while increasing levels of p-mTORC1 and LC3 I, suggesting that EA may suppress excessive receptor-mediated mitophagy prior to ischemic injury. Notably, rapamycin, an activator of the mTOR-ULK1/FUNDC1 axis, effectively reversed the effects of EA, suggesting that this signaling axis may participate in EA-mediated regulation of mitophagy [158]. Overall, current evidence suggests that EA may exert bidirectional regulatory effects on mitophagy, and its specific effects may depend on the stage of stroke, the degree of autophagic activation, and the extent of mitochondrial injury.

4.3 Neuroinflammation and Pyroptosis

Accumulating evidence suggests that EA alleviates post-stroke neuroinflammation and pyroptosis, thereby improving PSCI (Table 2). EA treatment suppresses upregulation of pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β , while promoting expression of anti-inflammatory cytokines such as IL-4 and IL-10, accompanied by reduced expression of pyroptosis-related proteins

[159,160]. Mechanistically, these effects involve broad suppression of inflammatory cascades, targeting inflammatory initiation, signal transduction, propagation, and the execution phase of pyroptosis (Fig. 4).

4.3.1 Disruption of Pyroptotic Cascades

The TLR4/NF- κ B/NLRP3 signaling pathway is considered a central axis in the initiation and progression of neuroinflammation. Studies have shown that EA treatment downregulates expression of TLR4, NF- κ B, and the NLRP3 inflammasome, accompanied by reduced downstream caspase-1 mRNA expression and improved learning and memory function [19,30]. Mechanistically, NF- κ B consists of NF- κ B1 (p50) and RelA (p65) subunits and regulates transcription of multiple pro-inflammatory cytokines [161]. Studies have shown that EA treatment increases expression of the negative regulatory factor OTULIN, accompanied by reduced nuclear translocation of p65 [162]. In addition, EA enhances neuronal A20 expression and downregulates TRPV1 levels, thereby attenuating excessive NF- κ B activation [162,163]. Notably, Jin et al. [164] found that the inhibitory effects of EA on NF- κ B-mediated inflammation were almost completely abolished in MCP1 knock-out mice, suggesting that MCP1 may serve as an important molecular mediator involved in EA-mediated regulation of NF- κ B-related inflammation.

EA also markedly suppresses NLRP3 inflammasome assembly. In MCAO rats, EA treatment was associated with reduced expression of NLRP3 and its mRNA [30]. Current evidence suggests that EA-mediated regulation of the NLRP3 inflammasome may involve multiple mechanisms, including oxidative stress modulation and cholinergic anti-inflammatory signaling. In oxidative stress-related mechanisms, thioredoxin-interacting protein (TXNIP) is considered an important molecular bridge linking oxidative stress to NLRP3 activation [165]. Studies have shown that EA suppresses TLR4/NF- κ B/TXNIP/NLRP3-related signaling, accompanied by reduced pyroptosis levels [166]. In addition, EA upregulates FTO expression and activates NRF2 signaling, thereby attenuating NLRP3-related inflammatory responses. Notably, these effects can be reversed by the FTO knockdown using shRNA-FTO, suggesting that FTO/NRF2 signaling may participate in EA-mediated regulation of pyroptosis [167]. Cholinergic anti-inflammatory signaling may likewise participate in EA-mediated regulation of NLRP3. As an important target of the cholinergic anti-inflammatory pathway, α 7 nicotinic acetylcholine receptor (α 7nAChR) plays a critical role in suppressing systemic inflammation. Studies have shown that EA treatment enhances α 7nAChR activity, accompanied by reduced NLRP3 activation and decreased expression of the pro-inflammatory mediator HMGB1 [168,169,170].

During the execution phase of pyroptosis, EA may further suppress activation of pyroptotic effector molecules.

Studies have shown that EA treatment significantly reduces expression of pyroptosis-related molecules, including ASC, caspase-1, gasdermin D (GSDMD), and IL-1 β [171]. Liu et al. [172] further demonstrated that EA decreases co-expression of GSDMD and MMP9 in brain tissue, accompanied by alleviation of blood–brain barrier injury and extension of the thrombolytic treatment window. EA may also regulate noncanonical inflammasome-related pyroptosis. Nuclear paraspeckle assembly transcript 1 (*Neat1*) interacts with the NLRP4 inflammasome, promotes caspase-1 maturation, and increases IL-1 β /IL-18 production, thereby facilitating pyroptosis [173]. Lin et al. [174] reported that *Neat1* overexpression partially reversed the inhibitory effects of EA on pyroptosis, suggesting that *Neat1*/NLRP4 signaling may participate in EA-mediated regulation of pyroptosis. Overall, current evidence suggests that EA may interfere with post-stroke pyroptotic cascades at multiple levels through suppression of inflammatory initiation, inhibition of NLRP3 inflammasome assembly, and attenuation of caspase-1-mediated execution signaling.

4.3.2 Inhibition of Glial Cell Activation

Microglia and astrocytes undergo marked activation following stroke and constitute important components of neuroinflammation and pyroptotic cascade amplification. Among them, microglia, the principal resident immune cells of the central nervous system, are rapidly activated after cerebral ischemia and release pro-inflammatory cytokines, thereby amplifying neuroinflammatory responses [175]. Studies have shown that EA modulates microglial phenotypic balance by suppressing pro-inflammatory M1 polarization while promoting anti-inflammatory M2 polarization, thereby improving the post-stroke inflammatory microenvironment [176]. Mechanistically, EA treatment reduces p38 MAPK phosphorylation in microglia, accompanied by attenuated M1 polarization and enhanced M2 polarization [48].

In addition to MAPK-related signaling, purinergic receptor-associated inflammatory pathways may also participate in EA-mediated regulation of microglia. Studies have shown that EA downregulates P2X7R and P2Y1R expression, thereby promoting microglial M2 polarization, accompanied by enhanced NRF2 activity and reduced NLRP3 inflammasome activation. Notably, intracerebroventricular injection of the P2 agonist BzATP partially reversed these effects of EA [47]. In addition, STAT family signaling also plays an important role in EA-mediated microglial remodeling. EA enhances STAT6/PPAR- γ signaling activity, thereby promoting M2 polarization and anti-inflammatory cytokine release. In contrast, the M1-associated p-STAT3/NOX2 signaling axis is suppressed following EA treatment, accompanied by reduced oxidative stress and inflammatory responses [177,178].

Beyond microglia, EA also suppresses excessive astrocyte activation [176]. Recent studies have shown that

neurotoxic astrocytes can be activated by inflammatory mediators such as interleukin-17A (IL-17A) [179]. Following EA treatment, reduced expression of IL-17A and its associated signaling molecules has been observed, accompanied by decreased formation of neurotoxic astrocytes and improved neurological outcomes [180]. Overall, current evidence suggests that EA may indirectly interfere with post-stroke pyroptotic cascades through modulation of glial inflammatory phenotypes, suppression of pro-inflammatory signaling, and attenuation of NLRP3-related neuroinflammation.

4.4 Ferroptosis and Oxidative Stress

EA exerts significant regulatory effects on three critical aspects of ferroptosis, including correction of iron metabolism imbalance, suppression of lipid peroxidation cascades, and enhancement of cellular antioxidant defenses (Fig. 5). Regarding iron metabolism, studies have shown that EA reduces Fe³⁺ levels and transferrin receptor 1 (TFR1) expression, thereby limiting iron uptake into neurons [126]. Meanwhile, EA increases ferritin heavy chain 1 (FTH1) expression to reduce intracellular free iron accumulation. These effects may be associated with inhibition of nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy by EA [126,181]. In addition, EA regulates systemic iron homeostasis by down-regulating hepcidin, a key regulator of intestinal iron absorption and cellular iron export, thereby alleviating iron overload [182,183]. Notably, compared with conventional deferoxamine (DFO) treatment, EA shows superior effects in attenuating ferroptosis-related neuronal injury, suggesting potential advantages as a multitarget regulatory strategy [184].

In addition to iron metabolism, EA also attenuates lipid peroxidation cascades. Studies have shown that EA inhibits KAT3B/p300-mediated succinylation of ACSL4, thereby reducing ACSL4 activity and limiting conversion of PUFAs into PUFA-PLs [185]. Sterol regulatory element-binding protein 1 (SREBP1) promotes monounsaturated fatty acid (MUFA) synthesis, which competitively incorporates into membrane lipids and replaces oxidation-prone PUFA-PLs, thereby reducing PUFA-OOH accumulation and suppressing ferroptosis [186]. EA has also been shown to activate the mTOR/SREBP1 signaling axis [187]. Meanwhile, EA downregulates expression of NOX2, a key enzyme involved in lipid peroxidation, accompanied by reduced levels of malondialdehyde (MDA), a terminal product of lipid peroxidation [126].

Enhancement of antioxidant defense is likewise an important mechanism underlying the anti-ferroptotic effects of EA. NRF2, a central transcription factor in cellular antioxidant responses, regulates multiple ferroptosis-related genes, including *SLC7A11*, *GPX4*, and *FTH1* [188]. Under homeostatic conditions, NRF2 is sequestered by Kelch-like ECH-associated protein 1 (KEAP1) and remains in-

active. Under oxidative stress conditions, NRF2 dissociates from KEAP1, translocates into the nucleus, and initiates transcription of antioxidant genes [189]. Studies have shown that EA promotes NRF2 nuclear translocation and activates the NRF2/SLC7A11/GPX4 pathway in ischemic stroke, thereby attenuating ferroptosis-related injury [190]. Notably, EA-mediated activation of NRF2 does not appear to rely exclusively on the classical KEAP1 pathway. Studies have further demonstrated that EA enhances antioxidant defenses through GSK-3 β /NRF2-related signaling [45]. The p53/SLC7A11 axis also participates in EA-mediated regulation of ferroptosis. Studies have shown that EA treatment decreases p53 protein levels while increasing expression of SLC7A11 and GPX4, accompanied by attenuation of oxidative stress and lipid peroxidation [191]. Furthermore, EA pretreatment prior to MCAO significantly activates NRF2-related signaling, suggesting potential preventive effects of EA against ferroptosis [192]. Overall, current evidence suggests that EA may participate in post-stroke ferroptosis regulation at multiple levels through coordinated modulation of iron homeostasis, lipid peroxidation, and antioxidant defense networks.

Beyond the classical forms of PCD described above, necroptosis, PARP1-dependent cell death (parthanatos), and phagoptosis have also been implicated in post-stroke neuroinflammation, synaptic injury, and cognitive dysfunction, and may contribute to the pathogenesis of PSCI [193,194,195,196,197]. Emerging evidence suggests that EA may likewise exert regulatory effects on these nonclassical forms of PCD. For example, EA has been shown to suppress RIPK1/RIPK3/MLKL-related signaling and improve mitochondrial function. In addition, its regulatory effects on oxidative stress, NAD⁺ metabolism, and aberrant microglial phagocytosis further suggest that EA may indirectly interfere with parthanatos- and phagoptosis-related processes [27,156,198,199,200,201]. However, current evidence is still largely derived from other neurological injury models, and the direct mechanisms and causal relationships underlying these effects in PSCI remain to be further elucidated.

5. Discussion

5.1 Crosstalk Among Different Forms of PCD

Increasing evidence suggests that different forms of PCD following stroke do not occur independently, but rather constitute a dynamically interconnected cell death network. During the development and progression of PSCI, extensive crosstalk exists among apoptosis, autophagy, pyroptosis, ferroptosis, and necroptosis, which share common upstream injurious stimuli, signaling mediators, and downstream effector mechanisms. Neuroinflammation driven by microglial activation and glutamate-mediated excitotoxicity are currently considered two major upstream pathological processes underlying the formation of this PCD network [78].

Within this network, shared signaling nodes may govern the dynamic transition among different forms of PCD. Among these, p53 has emerged as a critical regulatory hub linking apoptosis, autophagy, and ferroptosis. In addition to mediating mitochondrial apoptosis through BAX activation, p53 can regulate autophagy via the AMPK/TSC2–mTOR axis and participate in ferroptosis by suppressing SLC7A11 expression [202,203,204]. Notably, dysregulated autophagy itself may further promote ferroptosis through ferritin degradation and intracellular iron accumulation, suggesting that certain forms of ferroptosis may exhibit “autophagy-dependent” characteristics [78]. Members of the MAPK family also display prominent network-level interactions. Both JNK and p38 MAPK participate in oxidative stress amplification and inflammatory signaling while directly regulating BCL2 family proteins and mitochondrial function, thereby coordinately influencing apoptosis, autophagy, and pyroptosis [205,206,207].

Beyond classical protein signaling pathways, non-coding RNAs may also serve as important intermediates linking different PCD processes. Emerging evidence indicates that lncRNA *MEG3* is involved not only in post-stroke neuronal apoptosis, but also in the regulation of pyroptosis and autophagy through multiple miRNA–mRNA regulatory axes, suggesting that it may function as an upstream coordinator of multiple PCD programs [208,209,210]. In addition, substantial crosstalk exists between autophagy and inflammasome activation. Moderate autophagy may restrict NLRP3 inflammasome activation through mTOR-related mechanisms, whereas the accumulation of damaged mitochondria and impaired mitophagy can further enhance ROS generation and amplify NLRP3-dependent pyroptosis. Therefore, autophagy may exert both protective and detrimental effects at different stages after stroke, and its specific role may depend on the post-stroke temporal window and cellular stress state [211].

Based on the evidence above, the neuroprotective effects of EA are unlikely to rely solely on modulation of a single PCD pathway. Instead, EA may exert system-level regulatory effects through coordinated intervention at multiple shared stress-response nodes, thereby reshaping the overall PCD network. Current studies suggest that EA can suppress microglial activation, downregulate p53- and JNK/p38 MAPK-related signaling, activate mTOR while inhibiting aberrant NLRP3 inflammasome activation, and modulate non-coding RNA networks such as *MEG3*, collectively attenuating the reciprocal amplification among apoptosis, dysregulated autophagy, pyroptosis, and ferroptosis [28,31,212]. Accordingly, we speculate that EA may improve PSCI through a multilevel regulatory framework involving “stress response modulation–PCD network remodeling–neural circuit protection”. Nevertheless, most existing studies remain focused on individual pathways or single forms of PCD, whereas the temporal and causal interactions among different PCD processes remain insuf-

ficiently characterized. Future studies integrating multi-omics approaches, longitudinal neuroimaging, and causal intervention strategies are still needed to establish a unified mechanistic framework underlying EA-mediated regulation of PSCI.

5.2 Clinical Translation Implications

Current evidence suggests that the effects of EA on PSCI extend beyond empirically improving cognition and may instead represent a time window-dependent and parameter-sensitive neuromodulatory process. As summarized in Table 2 and **Supplementary Table 2**, the regulatory effects of EA on different PCD pathways appear to be closely associated with the post-stroke stage, stimulation parameters, and regional brain status, yet these relationships have not been systematically established in the current literature.

From the perspective of intervention timing, most available studies have focused on the hyperacute to subacute stages after stroke. In most animal experiments, EA intervention was initiated within 2 or 24 h after model induction, whereas only a limited number of studies delayed treatment initiation to 7–28 d post-stroke. Overall, the available evidence suggests that early EA preferentially targets acute injury-related PCD processes, particularly inflammatory cell death and mitochondria-associated injury pathways. For example, when EA was initiated within 24 h after stroke, improvements were primarily observed in NLRP3 inflammasome activation, IL-1 β , IL-18, ROS accumulation, and microglial polarization, suggesting that EA during the acute phase may mainly attenuate secondary injury by suppressing pyroptosis and oxidative stress-related damage. In contrast, when intervention was initiated days to weeks after stroke, EA exerted more pronounced effects on synaptic plasticity, dendritic spine remodeling, mitochondrial function, and hippocampal neurogenesis, indicating a potential shift toward neural network reconstruction and long-term cognitive recovery. These findings imply that the predominant forms of PCD may vary across different stages after stroke. During the acute phase, inflammatory cascades, oxidative stress, and metabolic collapse are likely to dominate, rendering pyroptosis and ferroptosis more prominent; by contrast, the subacute and chronic stages are characterized more by persistent neuronal loss, synaptic degeneration, and network disconnection, in which apoptosis, dysregulated autophagy, and impaired neuroplasticity may become central pathological processes. Therefore, the timing of EA intervention itself may determine its predominant mechanistic targets, rather than simply following a “the earlier, the better” paradigm.

Although previous studies have reported cognitive benefits of EA (Tables 1,2), few have directly compared the efficacy of different EA parameter settings or evaluated differential benefits across specific mechanistic domains. Commonly used protocols include GV20 and GV24 as core

acupoints combined with dense–sparse wave stimulation at 2/100 Hz or 1–20 Hz, with treatment durations generally set at 30 min/day for 7–14 d. However, substantial heterogeneity remains in waveform selection, stimulation frequency, and current intensity across studies, while most investigations merely confirm therapeutic efficacy without addressing why a given parameter combination may be more suitable for a specific PCD process. Nevertheless, several potential patterns can still be identified. Low-frequency or alternating low–high frequency stimulation (e.g., 2/100 Hz dense–sparse waves) appears to be more frequently associated with suppression of inflammation, regulation of NLRP3 signaling, and microglial polarization, suggesting that such paradigms may be more suitable for acute inflammatory states dominated by pyroptosis. In contrast, continuous-wave or relatively stable-frequency stimulation (e.g., 20 Hz continuous wave) has more commonly been linked to mTOR signaling, autophagic flux, and mitochondrial regulation, indicating a potentially greater role in chronic-stage neural network remodeling. Moreover, lower stimulation intensities (0.2–1 mA) are more commonly used in hippocampus-related studies, whereas higher intensities (2–6 mA) are more frequently applied in models of extensive cerebral ischemia, implying that stimulation intensity may be associated with regional excitability thresholds and the extent of network recruitment.

Different patient subtypes may further require distinct EA parameter strategies. Most current studies are based on ischemic stroke models, whereas evidence related to hemorrhagic stroke remains limited. However, the pathological basis of these two stroke subtypes differs substantially. Ischemic stroke is more prominently characterized by excitotoxicity, oxidative stress, and mitochondrial dysfunction, making ferroptosis, dysregulated autophagy, and inflammasome activation particularly relevant. In contrast, intracerebral hemorrhage is accompanied by hemoglobin degradation, iron deposition, and a persistent inflammatory microenvironment, in which ferroptosis and inflammation amplification may persist for longer periods. Therefore, future EA protocols may require stratification according to stroke subtype rather than relying on a uniform stimulation paradigm. Lesion location may also influence parameter selection. Current studies most commonly involve the hippocampus, prefrontal cortex, cingulate cortex, and white matter networks. Patients with hippocampal injury predominantly exhibit learning and memory impairment and may therefore require interventions targeting synaptic plasticity, autophagic homeostasis, and mitochondrial function. By contrast, damage involving frontoparietal and white matter networks is more often associated with executive and attentional dysfunction, where EA strategies may need to place greater emphasis on network connectivity efficiency and inflammatory regulation.

Based on current evidence, we speculate that EA may not regulate a single form of PCD in isola-

tion, but instead dynamically coordinate the interaction network among multiple PCD processes through a continuous “inflammation–oxidative stress–mitochondrial dysfunction–synaptic plasticity” regulatory axis. On this basis, a stage-specific “time window–parameter–pathological effect” framework may be provisionally proposed. During the hyperacute and acute stages, EA may primarily target early neuroprotection, using a relatively streamlined set of core cranial acupoints together with low-frequency or alternating low–high-frequency stimulation, with particular emphasis on NLRP3 inflammasome activation, ROS accumulation, and pyroptosis- and ferroptosis-related secondary injury. During the subacute stage, the therapeutic focus may gradually shift toward restoration of autophagic homeostasis, mitochondrial function, and synaptic remodeling. In addition to cranial acupoints such as GV20, GV24, EX-HN1, and GB20, HT7, PC6, ST36, and SP6 may be selected according to the predominant cognitive deficits, while repeated treatment courses may facilitate cognitive recovery and brain network restoration. During the chronic stage, a more individualized strategy combining core cranial acupoints with systemic acupoints may be considered, with adjunct acupoints selected according to cognitive, emotional, sleep-related, and motor dysfunction. Particular attention should be paid to the sustained effects of prolonged or maintenance treatment on domain-specific cognition, activities of daily living, and brain network reconstruction. Correspondingly, clinical and biomarker endpoints may evolve from neurological function, inflammation, and oxidative stress measures in the acute stage to indices of autophagy, mitochondrial function, and neuroplasticity in the subacute stage, and further to domain-specific cognitive outcomes, functional ability, and fMRI/DTI-based network measures in the chronic stage. The specific components of this stage-specific framework are summarized in **Supplementary Table 3**. Importantly, this framework is primarily derived from cross-study synthesis of the existing literature and is intended to provide hypotheses and a design basis for future stage-stratified and parameter-controlled studies rather than to constitute a definitive clinical treatment protocol. The proposed associations among stimulation parameters, acupoint combinations, and PCD pathways therefore require further validation through prospective, multimodal studies incorporating multiple post-stroke time points.

5.3 Limitations and Future Perspectives

Although current evidence suggests that EA may improve PSCI-related cognitive impairment and modulate PCD-associated pathways, these conclusions should still be interpreted with caution. Most available clinical studies are small-scale, single-center trials with insufficient reporting of randomization procedures, allocation concealment, and blinding implementation, resulting in an overall high risk of bias. In addition, the definition of PSCI base-

line status remains inconsistent across studies. Several investigations failed to adequately stratify patients according to stroke severity, degree of cognitive impairment, or affected cognitive domains, thereby limiting the comparability of therapeutic outcomes. With respect to efficacy evaluation, most studies continue to rely primarily on changes in MoCA or MMSE scores, whereas effect sizes, minimal clinically important differences (MCIDs), and longitudinal cognitive trajectories are rarely reported. Consequently, it remains unclear whether the observed improvements induced by EA represent sustained and clinically meaningful cognitive benefits. Sham acupuncture controls also present substantial methodological challenges. Different studies have employed superficial needling, non-acupoint stimulation, sham electrical stimulation, or no-current stimulation protocols, many of which may still generate sensory input or neuromodulatory effects, thereby complicating the distinction between specific therapeutic effects and placebo-related responses.

Publication bias may further influence the current interpretation of EA efficacy. Both clinical and preclinical studies on EA for PSCI predominantly report positive findings, whereas negative or nonsignificant results remain comparatively underrepresented, suggesting a potential tendency toward preferential publication of positive outcomes. This concern may be particularly relevant in animal studies, where preregistration, sample size estimation, blinded outcome assessment, and independent replication are often lacking, potentially leading to overestimation of the effects of EA on PCD pathways and cognitive outcomes. Moreover, most existing studies focus on short-term behavioral or cognitive improvements, while long-term follow-up data remain scarce. It therefore remains uncertain whether EA can sustainably modify the cognitive trajectory or disease progression of PSCI.

Another major limitation is the substantial heterogeneity of EA protocols. Considerable variability exists across studies regarding acupoint selection, stimulation frequency, waveform, current intensity, treatment duration, therapeutic course, and intervention timing. Such heterogeneity limits direct comparisons between studies and complicates both parameter optimization and evidence integration. More importantly, most studies merely demonstrate that EA is “effective”, while few investigate whether specific stimulation parameters preferentially regulate particular PCD pathways or cognitive domains. As a result, mechanism-based EA parameter recommendations remain largely unavailable.

In addition, current studies have insufficiently addressed the intrinsic heterogeneity of PSCI itself. PSCI is not a uniform pathological entity; different stroke subtypes, lesion locations, and cognitive impairment patterns may involve distinct cell death processes and network dysfunction profiles. For example, hippocampal injury is more commonly associated with memory impairment, whereas

frontoparietal and white matter network damage more frequently affects executive and attentional functions. Similarly, ischemic and hemorrhagic stroke differ substantially in oxidative stress burden, iron metabolism, inflammatory responses, and dominant PCD signatures. However, few studies have stratified patients according to stroke subtype, lesion location, or cognitive phenotype, potentially obscuring the specific populations and mechanistic contexts in which EA may be most beneficial.

Future studies should move beyond simply asking whether EA is effective and instead address more clinically and mechanistically relevant questions: when intervention should be initiated, which patient populations are most responsive, which PCD pathways are preferentially targeted, and which parameter combinations produce optimal effects. At the mechanistic level, future investigations should shift from descriptive pathway analyses toward causal validation strategies. Approaches such as conditional gene knockout models, cell-specific interventions, and viral tracing techniques may help determine whether modulation of key nodes including NLRP3, GPX4, Beclin1, and mTOR is required for EA-mediated cognitive improvement. At the parameter optimization level, dose-finding factorial designs may enable systematic evaluation of the main and interaction effects of stimulation frequency, waveform, intensity, and treatment duration, thereby establishing clearer “parameter–PCD pathway–cognitive domain” relationships.

From the perspective of clinical trial design, efficacy assessment of EA for PSCI should no longer rely solely on global cognitive scales such as the MoCA or MMSE. Instead, a hierarchical evaluation framework should be developed to capture clinical benefit, brain network recovery, and potential mechanisms of action. In addition to global cognitive assessment, primary endpoints could incorporate domain-specific measures of memory, attention, and executive function, together with fMRI- and DTI-derived indices of cognition-related functional connectivity, white matter integrity, and network efficiency. Such an approach may provide a more comprehensive assessment of whether EA promotes cognitive network reorganization and help identify the cognitive domains most responsive to treatment. Secondary endpoints may be used to characterize accompanying changes in brain function and neural tissue during network recovery [213]. These may include BDNF, regional brain activity, cerebral perfusion, and electrophysiological measures already examined in existing studies, while future trials could additionally incorporate NfL and GFAP to reflect neuroplasticity, axonal injury, and glial responses.

PCD-related measures may be more appropriately positioned as supplementary endpoints for elucidating the mechanisms underlying EA. Preclinical studies have reported changes in multiple PCD-related molecules. Among these, the BAX/BCL2 ratio and caspase-3 may be used

to assess apoptotic tendency, whereas LC3-II/I and p62 may reflect autophagic status. Given the central role of the NLRP3 inflammasome in post-stroke inflammatory cascades and pyroptosis, NLRP3, caspase-1, IL-1 β , and IL-18 may have relatively high translational potential. For ferroptosis, future studies should move beyond lipid peroxidation markers such as MDA and place greater emphasis on GPX4 and ACSL4 to improve mechanistic specificity. In particular, GPX4, as a key component of the cellular defense system against ferroptosis, may serve as an important candidate marker linking EA stimulation parameters to ferroptosis-related effects. Compared with behavioral outcomes alone, these biomarkers may detect EA-induced modulation of post-stroke PCD-related pathological processes at an earlier stage; however, their reliability as pharmacodynamic endpoints remains to be established in standardized clinical trials.

Accordingly, future high-quality EA clinical trials should establish multidimensional composite endpoint systems integrating behavioral scales, peripheral biomarkers, and brain network imaging, rather than relying solely on changes in cognitive scores. Finally, real-world translational studies should place greater emphasis on PSCI populations with comorbid hypertension, diabetes mellitus, atherosclerosis, sleep disorders, or depression, while incorporating corresponding composite animal models and multicenter longitudinal cohorts to evaluate the robustness and generalizability of EA under clinically complex conditions. Overall, EA demonstrates considerable neuromodulatory potential for PSCI; however, current evidence remains largely confined to efficacy observations and pathway-level associations. Only through rigorous bias control, standardized parameter reporting, causal mechanistic validation, and long-term objective outcome assessment can it be determined whether EA may ultimately evolve into a mechanism-driven precision intervention strategy for PSCI management.

6. Conclusion

In conclusion, this review summarizes the clinical characteristics and potential mechanisms of EA in PSCI. Current evidence suggests that EA may influence neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired synaptic plasticity by modulating interconnected PCD pathways, including apoptosis, autophagy, pyroptosis, and ferroptosis. By integrating clinical and preclinical findings, we further highlight the potential influence of intervention timing, stimulation parameters, and treatment strategies on cognitive and pathological outcomes, underscoring the importance of patient stratification and protocol optimization.

We therefore propose a “time window–parameter–pathological effect” framework to explain the stage- and parameter-dependent effects of EA. However, this framework is based mainly on heterogeneous preclinical evidence

and limited clinical data. Incomplete reporting, inconsistent intervention protocols and outcome measures, limited causal validation, and insufficient long-term objective outcomes restrict the clinical translation of current findings. Thus, the proposed framework should be regarded as a biologically plausible but still unvalidated mechanistic hypothesis. Future studies should combine standardized EA protocols, refined patient stratification, and longitudinal multi-dimensional assessments to clarify its clinical benefits and underlying mechanisms.

Author Contributions

HA designed the review. SX and YJ (co-first authors) conducted the literature search, collected relevant information, and wrote the manuscript. JL and YC contributed to literature collection, reference organization, the design and preparation of figures and tables, and manuscript revision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary Material

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