Detailed analysis of the effects of PNS and PGS on key metabolic pathways in six brain regions (Supplementary Text S1)

Hypothalamus (Table S2-S5):

As a critical hub regulating vital functions (body temperature, feeding, drinking, mood), hypothalamic impairment post-stroke disrupts physiological homeostasis. Oxidative phosphorylation, the primary cellular energy production pathway, is targeted by PNS to enhance hypothalamic ATP generation, facilitating functional recovery of damaged brain cells in acute ischemic stroke. Additionally, PNS negatively regulates the Platelet-Derived Growth Factor Receptor signaling pathway to mitigate inflammation and abnormal cell proliferation, while slowing the Negative Regulation of Microtubule Polymerization to stabilize the cytoskeleton and protect neurons from stroke-induced damage. In contrast, PGS promotes the Ribonucleotide Biosynthetic Process to support RNA/DNA repair and synthesis, restoring damaged neurons. It also enhances mitochondrial function and antioxidant capacity by facilitating protein targeting to mitochondria. Furthermore, PGS modulates behavior-related neural pathways to counteract stroke-induced behavioral and cognitive dysfunction, offering a unique therapeutic perspective for post-ischemic brain repair. Collectively, both PNS and PGS protect against ischemic brain injury by regulating hypothalamic metabolic pathways, with PNS emphasizing platelet activity and cytoskeletal stability, and PGS focusing on nucleic acid/protein synthesis, mitochondrial function, and potential behavioral modulation.

Thalamus (Table S6-S9):

The thalamus is pivotal for regulating consciousness, sleep, alertness, and sensory information processing; post-stroke damage leads to sensory abnormalities, attention/memory deficits, and sleep disturbances. PNS plays a key role in regulating the Actin Filament-based Process, which maintains cellular structural stability, migration, and division—supporting the restoration of neuronal structural integrity and repair of damaged cells. By promoting the assembly of mitochondrial respiratory chain complexes, PNS enhances energy metabolism in damaged thalamic cells, increasing ATP production to sustain cell survival and functional recovery. PGS, on the other hand,

promotes cellular homeostasis to help thalamic cells cope with stroke-induced stress and injury. It also regulates tight junction function, which forms intercellular barriers to maintain tissue integrity and selective permeability—critical for preserving intracellular environment balance and normal cellular function. Protecting or restoring tight junctions prevents blood-brain barrier breakdown, reducing further brain tissue damage. In the thalamus, PNS mechanisms focus on improving cellular structural integrity and energy metabolism (via actin fiber regulation and mitochondrial respiratory chain enhancement), while PGS prioritizes cellular homeostasis maintenance and tissue barrier protection (e.g., tight junctions), suggesting PGS may have specific efficacy in blood-brain barrier restoration post-stroke.

Hippocampus (Table S10-S13):

As one of the brain regions most sensitive to hypoxia, the hippocampus sustains severe damage in acute ischemic stroke, leading to cognitive impairment. PNS improves mitochondrial organization to enhance energy metabolism and reduce oxidative stress, counteracting ischemic cell damage. It also regulates glial cell differentiation to promote neuroprotective and repair mechanisms, which are essential for maintaining the neuronal microenvironment and facilitating nerve regeneration. Additionally, PNS modulates microtubule-based movement to preserve intracellular substance transport, and regulates apoptotic signaling pathways and ferroptosis to reduce ischemia-induced cell death, protecting the hippocampus from damage. PGS directly targets cognitive process-related pathways, implying potential benefits for post-stroke learning and memory improvement. It also regulates Golgi apparatus organization to modulate protein processing and secretion, contributing to energy metabolism regulation. Both PNS and PGS protect and repair the hippocampus by targeting cell death and cellular structure-related pathways, particularly in promoting energy metabolism and organelle organization. The key difference lies in PNS favoring cell survival and structural maintenance (e.g., reducing apoptosis, regulating glial differentiation, protecting mitochondrial structure), while PGS focuses on directly improving cognitive function to counteract stroke-induced cognitive deficits.

Cerebral Cortex (Table S14-S17):

The outermost layer of the brain, the cerebral cortex, is essential for higher-order functions (thinking, perception, memory, consciousness); post-stroke damage causes

complex neurological impairments (motor, sensory, olfactory deficits). PNS enhances mitochondrial energy production via oxidative phosphorylation, restoring the function of ischemic cortical cells. It regulates the IRE1-mediated unfolded protein response to help damaged cortical cells cope with stroke-induced protein folding disorders, and promotes mitophagy to eliminate damaged mitochondria and reduce oxidative stress. PGS improves and protects blood-brain barrier integrity by enhancing tight junction function, mitigating inflammation and further post-stroke damage. It also activates the neurotrophin signaling pathway to promote neuronal growth and regeneration—critical for neuronal survival, development, and repair. Both PNS and PGS counteract acute ischemic stroke injury by regulating cortical cell survival and repair mechanisms via improved energy metabolism and cellular stress responses. However, PNS focuses on direct enhancement of intracellular energy metabolism and reduction of internal stress, while PGS prioritizes protection and repair at a more macro level (e.g., blood-brain barrier, neurotrophin signaling).

Striatum (Table S18-S21)：

PGS helps maintain normal function of damaged striatal cells by improving cellular respiration and increasing energy production. Excessive release of the excitatory neurotransmitter glutamate is a key driver of stroke-induced cell death; PNS regulates glutamate secretion to reduce neurotoxicity, and negatively modulates apoptotic signaling pathways and ferroptosis to inhibit striatal cell death. PGS enhances energy efficiency via proton motive force-driven mitochondrial ATP synthesis, providing essential energy for striatal cell recovery. It also regulates cysteine-type endopeptidase activity (e.g., caspases, which trigger/execute apoptosis or participate in inflammatory responses by cleaving specific peptide bonds) to modulate the apoptotic process and reduce cell death. In summary, PNS and PGS protect and repair damaged striatal cells by promoting energy production and inhibiting cell death pathways, critical for post-stroke recovery. PNS directly targets ischemia-induced cell injury mechanisms (energy metabolism enhancement, excitatory neurotoxicity reduction, ferroptosis prevention), while PGS indirectly modulates apoptosis via specific enzyme activity and metabolic pathway regulation.

Amygdaloid Nucleus (Table S22-S25)：

A component of the limbic system, the amygdaloid nucleus primarily mediates emotional responses, fear processing, and memory; post-stroke damage impairs these functions. PNS enhances amygdaloid cellular energy metabolism via improved cellular respiration, supporting the survival and functional recovery of damaged cells. By increasing energy efficiency, PNS maintains normal amygdaloid activity, which in turn improves post-stroke emotional and cognitive function. PGS regulates dopamine metabolism—closely linked to emotion regulation, reward, and attention—to exert positive effects on amygdaloid emotion and fear processing, benefiting emotional stability and cognitive function recovery after stroke.