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Perspectives on Transcranial Direct Current Stimulation (tDCS) and Its Potential Integration With Nuclear Medicine as a Therapeutic Approach

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Abstract: Transcranial direct current stimulation (tDCS) is a non-invasive technique that modifies cortical excitability and induces neuroplasticity using low-intensity electrical currents. Nuclear medicine technologies like positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can quantify cerebral metabolism and other dynamics. Evidence suggests that combining tDCS with these imaging methods enhances understanding and outcomes for neurological and psychiatric conditions. This review highlights how nuclear medicine can objectively characterize tDCS effects, map network modulation, and identify predictive biomarkers. PET and SPECT indicate changes in glucose metabolism and neurotransmitter activity post-tDCS, demonstrating their value in validation. While the co-application of these methodologies is still in conceptual stages, their integration may advance precision neuromodulation and inform rehabilitation strategies.

Keywords: Depression; Nuclear Medicine; Transcranial Direct Current Stimulation; Cortical Excitability; Neuronal Plasticity; Tomography

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1.Introduction

Transcranial direct current stimulation (tDCS) has emerged over the past two decades as a non-invasive neuromodulation technique capable of altering cortical excitability and inducing neuroplastic changes through the application of weak, constant electrical currents to the scalp. Originally conceptualized in electrophysiological research, tDCS has since expanded into clinical neuroscience, rehabilitation, psychiatry, and cognitive enhancement, largely due to its safety, portability, and steadily accumulating evidence of therapeutic potential. The technique primarily operates by modulating neuronal membrane potentials like anodal stimulation promotes depolarization and increased excitability, whereas cathodal stimulation generally produces hyperpolarization and reduced excitability (Lang et al., 2005). These effects interact with synaptic plasticity mechanisms, including NMDA receptor–dependent pathways, long-term potentiation (LTP), long-term depression (LTD), and changes in neurotransmitter systems such as glutamate and GABA. In parallel, nuclear medicine has advanced considerably in its ability to quantify functional and molecular brain processes through imaging modalities such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) (Kwon & Jang, 2011). These tools allow

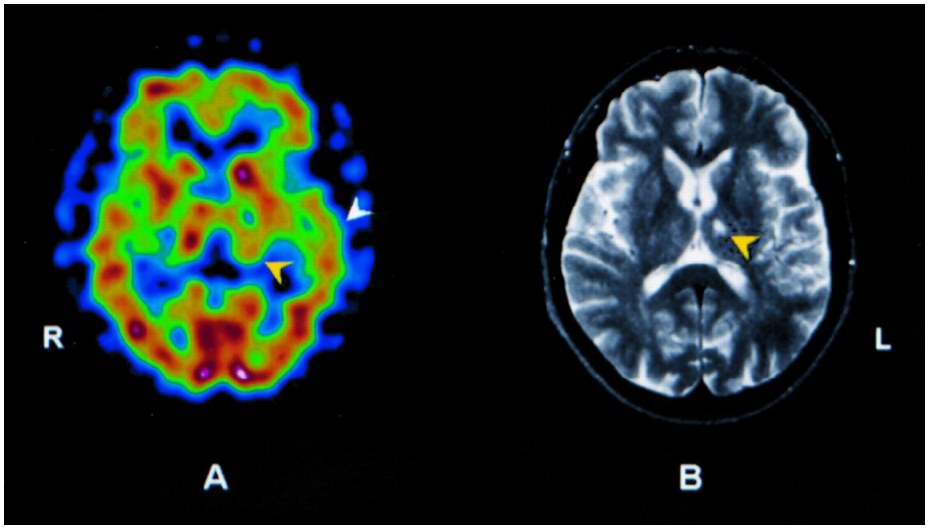
investigators to observe cerebral glucose metabolism, neurotransmitter receptor activity, neuroinflammation, regional cerebral blood flow, and neurodegenerative protein deposition with remarkable sensitivity. As personalized medicine and precision neurotherapeutics evolve, a compelling question arises: whether nuclear medicine can not only characterize the mechanisms and effects of tDCS but also contribute to optimizing its therapeutic application across neurological and psychiatric diseases (Stagg et al., 2011).

2.Methods

This manuscript adopts a narrative literature review approach focusing on mechanistic, clinical, and imaging research involving tDCS and nuclear medicine. Peer-reviewed studies were extracted from PubMed, Scopus, and Web of Science using combinations of terms including transcranial direct current stimulation, PET imaging, SPECT imaging, neuromodulation, cerebral blood flow, brain metabolism, and neurotransmitter receptors. Priority was given to studies employing PET or SPECT to investigate brain activity changes following tDCS, as well as nuclear medicine research addressing biomarkers relevant to neuromodulation and neuroplasticity. The conceptual framework guiding this review centers on three thematic domains: 1. nuclear medicine as a mechanistic tool to visualize tDCS-induced physiological and molecular changes. 2. nuclear imaging as a predictive and personalized medicine approach for tailoring tDCS interventions. 3. the hypothetical therapeutic integration of tDCS with nuclear medicine, particularly in conditions in which neuromodulation and molecular neuroimaging intersect, such as stroke, dementia, mood disorders, and movement disorders. While tDCS itself does not require imaging for administration, nuclear medicine provides a unique window into brain-wide functional modulation that may enhance the precision, dosing, and targeting of tDCS interventions. Because no standardized protocols exist for combining these modalities, this review synthesizes available evidence to outline future possibilities rather than provide statistical meta-analysis.

3.Results

Figure 1. SPECT (A) and MRI (T2-weighted) (B) slices at basal ganglia level of patient with ischemic lesion in left thalamus (yellow arrowheads). Patient developed aphasia, which could not be explained by localization of anatomic lesion only. MRI of left temporal cortex was normal, but decreased tracer uptake in region can be seen in SPECT image (white arrowhead). This was interpreted as ipsilateral subcorticocortical deafferentation (Catafau, 2001).

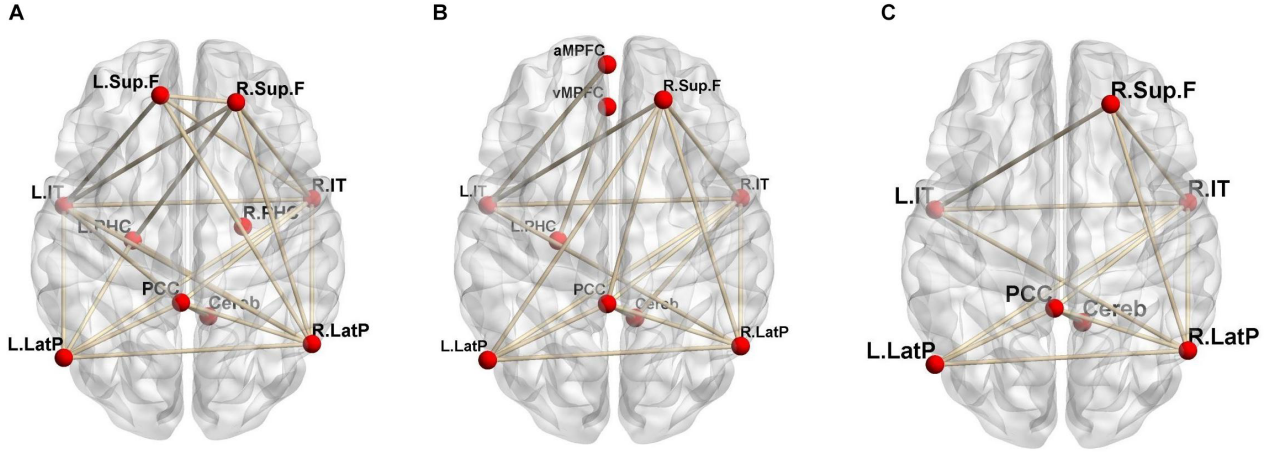


Available nuclear medicine studies demonstrate that tDCS induces measurable and regionally specific changes in brain metabolism, perfusion, and neurotransmitter systems. Early work using PET provided foundational evidence that tDCS modulates cortical glucose metabolism. Lang et al. (2005) showed that anodal stimulation over the motor cortex increases regional cerebral blood flow and enhances excitability in both stimulated and connected motor regions, suggesting network-level propagation rather than purely focal effects. Kwon et al. (2011) later reported that tDCS produced detectable changes in regional cerebral blood flow using SPECT in patients with stroke, highlighting imaging's ability to reveal interhemispheric

rebalancing important for recovery. Complementary PET research by Stagg et al. revealed that anodal tDCS reduces GABA concentration in the stimulated cortex, providing a neurochemical explanation for enhanced plasticity (Stagg et al., 2011). Further evidence comes from dopaminergic PET imaging, where studies demonstrated that prefrontal tDCS can alter striatal dopamine release—a finding relevant for depression and Parkinson's disease (Fonteneau et al., 2018). Collectively, these imaging results confirm that tDCS influences multiple physiological domains measurable through nuclear medicine, including metabolism, neurotransmission, and network function.Transcranial direct current stimulation (tDCS) operates by delivering low-intensity electrical currents to modulate cortical excitability, while nuclear medicine techniques such as PET and SPECT allow precise visualization of metabolic, perfusion-based, and molecular changes within the brain. Together, these methods provide complementary insights into how neuromodulation influences neural circuits at both functional and biochemical levels (Figure 1).

In addition to mechanistic characterization, nuclear medicine offers biomarkers that can potentially be used to personalize tDCS therapy. FDG-PET, for example, is commonly used to identify regions of hypometabolism in dementias, which may help guide stimulation targets for cognitive enhancement trials. Amyloid and tau PET imaging provide disease staging information that may determine whether neuromodulation is likely to be beneficial in early versus late Alzheimer disease. Perfusion SPECT has been explored in major depressive disorder to characterize fronto-limbic dysregulation, which aligns with common tDCS targets such as the dorsolateral prefrontal cortex (DLPFC). Studies in stroke using SPECT or perfusion PET frequently reveal areas of diaschisis—remote hypoperfusion due to focal lesions—which may guide individualized electrode montages. Nuclear medicine's ability to quantify synaptic density using tracers such as C-CUB-J similarly raises the possibility of tracking neuroplasticity induced by repeated tDCS sessions (Fonteneau et al., 2018). The clinical integration of tDCS with nuclear medicine is supported by imaging evidence demonstrating how molecular and perfusion patterns can guide stimulation strategies across neurological and psychiatric disorders. PET and SPECT biomarkers—including hypometabolism in dementia, perfusion deficits in stroke, and dopaminergic loss in movement disorders—provide objective maps that can help identify optimal stimulation targets, personalize electrode placement, and predict treatment responsiveness. These imaging-derived insights illustrate how tDCS can be aligned with molecular pathology and network dysfunction to achieve precision neuromodulation (Figure 2).

Figure 2. Significant positive functional correlations involving the DMN. (A) Correlations based on CBF; (B) $CMRO_2$; (C) the overlap between CBF and $CMRO_2$ (reprint from Aoe et al., 2018; permission obtained from the Annals of Nuclear Medicine in accordance with their open access policy) (Watabe & Hatazawa, 2019).



4.Discussion

The convergence of tDCS and nuclear medicine presents several promising but underexplored pathways for both mechanistic insight and therapeutic innovation. From a mechanistic standpoint, nuclear medicine provides objective, quantifiable measures of brain function that can validate and expand current understanding of how tDCS modulates neural circuits. PET and SPECT imaging can elucidate whether tDCS effects remain localized to the stimulation site or extend through broader networks, enabling refined selection of stimulation parameters. Moreover, neurochemical imaging offers the

potential to correlate neurotransmitter changes with clinical outcomes, contributing to the development of biomarker-driven neuromodulation strategies. Clinically, imaging biomarkers may also help identify responders to tDCS before treatment begins—a major challenge in neuromodulation research. Patients with preserved metabolic activity in targeted networks may be more likely to respond, whereas those with advanced neurodegeneration or extensive diaschisis may require modified protocols.

The therapeutic integration of nuclear medicine and tDCS remains largely conceptual but holds significant promise. For example, neuromodulation-induced increases in cerebral perfusion or receptor expression could theoretically enhance uptake of therapeutic radiopharmaceuticals in targeted brain regions. Reciprocal approaches, in which radiotracers identify optimally responsive regions or receptor populations, could further guide tDCS application. Beyond neurological disease, psychiatric conditions such as treatment-resistant depression, bipolar disorder, and addiction may benefit from combined imaging and stimulation approaches that address both functional dysregulation and molecular abnormalities. Nevertheless, major challenges remain, including the logistical and ethical considerations associated with repeated exposure to ionizing radiation, the cost of PET/SPECT imaging, and the need for standardized stimulation–imaging protocols. Despite these limitations, the growing sophistication of neuromodulation and molecular imaging technologies suggests that combined approaches may facilitate precision neurotherapy in the future.

5.Conclusion

Transcranial direct current stimulation and nuclear medicine represent complementary modalities within modern neuroscience one providing an accessible means of modulating neural activity, the other offering the most sensitive tools for visualizing and quantifying functional and molecular processes in the human brain. Evidence from PET and SPECT studies demonstrates that tDCS produces measurable changes in cerebral metabolism, cerebral blood flow, neurotransmitter systems, and network dynamics. These findings support the potential use of nuclear medicine not only to elucidate tDCS mechanisms but also to personalize treatment, monitor therapeutic response, and identify candidates most likely to benefit from stimulation. While direct therapeutic integration of tDCS and nuclear medicine remains a future possibility requiring substantial research, the conceptual framework is increasingly supported by advances in neuroimaging and neuromodulation science. The synergy between these fields may ultimately lead to more precise, biologically informed interventions for neurological and psychiatric disorders.

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Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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