Journal of Integrative Neuroscience

J. Integr. Neurosci. **2026**; 25(10): 52368
https://doi.org/10.31083/JIN52368

Review

A Neuro-endocrine-immune Network Perspective on Transcranial Direct Current Stimulation for Metabolic Dysregulation in Schizophrenia

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Academic Editors: Natalia Gulyaeva and Bettina Platt
Submitted: 28 March 2026 Revised: 20 May 2026 Accepted: 26 May 2026 Published: 10 October 2026

Abstract

Individuals with schizophrenia (SCZ) frequently exhibit glycolipid metabolic disorders. This clinical issue cannot be fully explained by the high metabolic risk associated with antipsychotic medications alone. It is increasingly recognized to involve complex multi-system interactions, particularly those linking the central nervous system with peripheral endocrine and immune regulation. Existing interventions have shown limited efficacy, underscoring the need for novel adjunctive strategies. Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation (NIBS) technique that modulates cortical excitability, has accumulated preliminary evidence for metabolic regulation in non-psychiatric populations and has generated several mechanistic hypotheses. However, direct evidence regarding its efficacy in SCZ remains limited, and the lack of comparison with existing interventions has hindered the recognition of its neurobiological mechanisms and potential advantages. Current challenges include methodological limitations, outcome heterogeneity, and insufficient mechanistic understanding, highlighting the need for further research and standardization of this clinical intervention. In light of these gaps, we synthesize the latest evidence on the metabolic and weight regulatory effects of tDCS, and further propose an integrative neuro-endocrine-immune network framework to conceptualize how central neuromodulation may influence peripheral metabolic regulation through interconnected biological systems. Moreover, we identify key methodological limitations in current tDCS research and outline directions for improvement, aiming to enhance the quality of future direct evidence. This framework provides a theoretical direction for future interventional studies applying tDCS to glycolipid metabolic disorders in SCZ, while acknowledging that further direct evidence is still warranted.

Keywords: transcranial direct current stimulation; schizophrenia; lipid metabolism disorders; glucose metabolism disorders; neuroimmunomodulation

1. Introduction

Glycolipid metabolic disorders, characterized by weight gain, hyperglycemia, and hyperlipidemia, are common among individuals with schizophrenia (SCZ) receiving long-term antipsychotic medication treatment [1]. The global disease burden of SCZ is substantial, accounting for 1.1% of disability-adjusted life years (DALYs) and 2.8% of years lived with a disability (YLDs) [2]. This burden is further exacerbated by comorbid glycolipid metabolic disorders, which are key risk factors for metabolic syndrome and cardiovascular disease (CVD), leading to a reduced life expectancy of 15–20 years [3]. These metabolic disorders are also associated with significant cognitive impairment, leading to poor functional performance and decreased quality of life [4]. Moreover, metabolic syndrome (MetS) predicts a 3-fold higher risk of psychiatric relapse within one year of follow-up [5]. A systematic review reported that SCZ patients with physical comorbidities incur inpatient costs up to 2.7 times higher and medication costs up to 8.1 times higher than those with mental health disorders alone [6]. Taken together, glycolipid metabolic disorders not only aggravate clinical outcomes in SCZ populations, but also incur significant economic costs. Current management strategies primarily rely on pharmacological interventions, including switching antipsychotics and the adjunctive use of anti-diabetic (e.g., metformin) or lipid-lowering agents (e.g., statins) [7]. However, these approaches often raise concerns about the risk of psychiatric symptom fluctuation, potential drug-drug interactions that may compromise antipsychotic efficacy, and other side effects [8,9]. Therefore, elucidating the mechanisms underlying glycolipid metabolic disorders in SCZ is critical for identifying novel therapeutic targets and developing more targeted interventions.

In recent years, non-invasive brain stimulation (NIBS), especially transcranial direct current stimulation (tDCS), has received increasing attention. tDCS delivers low-intensity direct current to target neurons through

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scalp electrodes, modulating cortical excitability through subthreshold shifts in resting membrane potential without generating action potentials [10,11]. The sustained current can modulate neural network function by promoting synchronized neuronal activity and strengthening synaptic connectivity [12]. Through indirect influences on deeper brain structures and extensive neural networks, tDCS induces alterations in neurotransmitters and peripheral physiological activities, linking central nervous system activity to peripheral metabolism [10,13,14]. In line with this framework, the dorsolateral prefrontal cortex (DLPFC) has emerged as a key target for tDCS because of its extensive connection with structures known to regulate peripheral metabolism and immune responses, such as the hypothalamus and striatum [15,16,17]. Moreover, tDCS is easy to operate and highly safe, with few reports of serious adverse effects. It is suitable for the elderly, children, and individuals with mental disorders, as well as for home-based settings, demonstrating broad application potential [18]. Several meta-analyses have indicated that tDCS regulates the eating behavior of obese individuals and promotes weight loss by normalizing reward neural circuits, but its impact on biomarkers such as metabolic parameters has been insufficiently explored [19,20,21]. Similarly, although the mechanisms underlying glycolipid metabolic disorders in SCZ have been extensively studied from diverse perspectives, including genetics, neuroimaging, and inflammation, few studies have integrated these findings into a framework linking central nervous system activity with peripheral metabolism [22,23,24].

Taken together, these two gaps highlight the need for a neuro-endocrine-immune network perspective to interpret metabolic dysregulation in SCZ. This review aimed to (1) establish this perspective by synthesizing evidence on tDCS-induced changes in metabolic biomarkers, providing mechanistic support for the research hypothesis that tDCS can effectively treat glycolipid metabolic disorders in SCZ, and (2) review the progress made and suggest future directions.

2. Methods

This narrative review followed the guidelines of the Scale for the Assessment of Narrative Review Articles (SANRA) [25]. A comprehensive literature search was performed in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), and ClinicalTrials.gov (https://clinicaltrials.gov/) for publications between January 1, 2015, and April 30, 2026. The complete search string for each database is provided in **Supplementary Table 1**. Briefly, the search strategy combined terms for the intervention ("transcranial direct current stimulation" OR "tDCS"), the metabolic outcomes ("obesity" OR "overweight" OR "metabolic diseases" OR "weight gain" OR "lipid metabolism disorders" OR "glucose metabolism disorders"), and the population ("schizophrenia" OR "SCZ" OR "psychotic disorders"). Eligible study designs included controlled and observational studies (both human and animal) with outcomes reporting alterations in glycolipid metabolism, body weight, body mass index (BMI), inflammatory markers, or hormones. Conference proceedings, abstracts, or non-peer-reviewed publications were excluded. One study protocol without reported results was identified; however, none of the completed clinical trials met the inclusion criteria. Therefore, to provide the best available human evidence, we included clinical trials conducted in obese populations without psychiatric disorders, to extrapolate the potential metabolic effects of tDCS on SCZ. Ultimately, ten studies met the eligibility criteria and were included in the clinical evidence synthesis. Relevant data, including the tDCS stimulus protocol, study procedures, primary outcomes, and secondary outcomes, were extracted, as shown in Table 1 (Ref. [16,26,27,28,29,30,31,32,33,34]). The findings from animal studies were incorporated to support the mechanistic discussion. The following sections will: (Section 3) delineate the neuro-endocrine-immune mechanisms underlying glycolipid metabolic disorders in SCZ; (Section 4) synthesize clinical evidence and mechanistic insights; (Section 5) discuss tDCS as a potential intervention for glycolipid metabolic disorders in SCZ; and (Section 6) address limitations and future directions.

3. Neuro-Endocrine-Immune Mechanisms Underlying Glycolipid Metabolic Disorders in SCZ

Although SCZ-related metabolic dysregulation shares overlapping mechanisms with common obesity, including insulin resistance, hormonal dysregulation (e.g., leptin and cortisol), and shared genetic pathways, it is more severe and less responsive to standard interventions due to the SCZ-specific pathological features of cortico-thalamo-striatal-midbrain circuits and dopaminergic transmission [35,36]. Neuroimaging and neurophysiological studies have discovered over-activation of the prefrontal cortex (PFC) and premotor cortex during inhibitory control tasks in individuals with SCZ, reflecting impaired inhibitory control and reduced cognitive restraint over food intake, which are significant behavioral contributors to increased appetite, weight gain, and metabolic disorders in this population [37]. Notably, premotor cortex continuous theta burst stimulation (cTBS) has been validated to prevent olanzapine-induced weight gain in drug-naïve first-episode SCZ patients [38]. Furthermore, abnormal dopaminergic transmission in the ventral tegmental area (VTA) (whether enhanced or disrupted) alters PFC synaptic plasticity and leads to functional deficits [39,40]. Second-generation antipsychotics (SGAs) further compound these vulnerabilities by inducing gray matter reduction in PFC [41], altering default-mode network (DMN) functional connectivity [42], and changing synaptic plasticity [40,43], thereby significantly increasing

Table 1. Summary of clinical studies examining the effects of tDCS on metabolic characteristics in obese populations (n = 10).

Study	Stimulation settings	Other interventions	Study participants	Grouping	Primary Outcome	Secondary outcome	Key findings (Statistical significance)
Gluck et al. (2015) [26]	Study 1: Anodal: right supraorbital, Cathodal: L-DLPFC, 2 mA for 40 min, Consecutive 3 days; Study 2: Anodal: L-DLPFC, Cathodal: right supraorbital, 2 mA for 40 min, Consecutive 3 days; (6 sessions)	/	Male or female, aged between 18–60, BMI (kg/m^2) ≥25, no mental illness	Active: n = 5 Sham: n = 4	Less energy intake (kcal/d) during anodal tDCS	Greater reduction in weight during anodal compared with cathodal tDCS; no direct comparison between active and sham groups was performed.	Trend improvement (primary outcome, $p = 0.07$; all other outcomes significant improved, all $p < 0.05$)
Heinitz et al. (2017) [27]	Anodal: L-DLPFC, Cathodal: right supraorbital, 2 mA for 40 min, Consecutive 3 days during hospitalization; 3 sessions per week for 4 weeks during outpatient period (15 sessions)	/	Male or female, aged between 18–60, BMI (kg/m^2) ≥25, no mental illness	Hospitalization phase: Active: n = 14 Sham: n = 17 Outpatient phase: Active: n = 9 Sham: n = 14	No significant differences in energy intake and body weight between active and sham groups.	Reduced hunger and urge to eat in active group after repetitive stimulation	Trend improvement (primary outcomes, all $p \geq 0.18$; secondary outcomes showed significant improvements after repetitive anodal tDCS, all $p < 0.05$)
Fassini et al. (2020) [28]	Anodal: L-DLPFC, Cathodal: right supraorbital, 2 mA for 30 min, PhaseI: single session; PhaseII: 5 sessions per week for 2 weeks; Phase III: 3 sessions per week for 2 weeks; (17 sessions) 6-month follow-up	Phase III: tDCS+low-calorie diet	Female, aged between 20–40, BMI (kg/m^2) 30–35, no mental illness	Active: n = 20 Sham: n = 18	No differences in body weight between active and sham groups; less weight loss in active group during the follow-up	Reduced hunger and urge to eat in the *COMT Met* carriers subgroup	Overall: all $p > 0.05$ (weight, hunger/urge). *COMT Met* subgroup: reduced hunger and urge to eat ($p < 0.05$).
Amo Usanos et al. (2020) [29]	Anodal: L-DLPFC, Cathodal: right supraorbital, 2 mA for 20 min 5 sessions on week 1, 3 sessions on week 2 (8 sessions)	tDCS+low-calorie diet	Female, aged between 45–65, BMI (kg/m^2) 25–35, no mental illness	Active: n = 20 Sham: n = 18	Greater reduction in body weight in active group (2.32%) compared with sham group (1.29%)	Greater reduction in urge to eat and improvement in inhibitory control performance in active group	Significant improvement ($p < 0.05$)

Table 1. Continued.

Study	Stimulation settings	Other interventions	Study participants	Grouping	Primary Outcome	Secondary outcome	Key findings (Statistical significance)
de Araujo et al. (2020) [30]	Anodal: R-DLPFC, Cathodal: L-DLPFC, 2 mA for 20 min 5 sessions per week for 4 weeks (20 sessions)	tDCS+low-calorie diet	Male or female, aged between 20–50, BMI (kg/m^2) 25–35, no mental illness	Active: n = 14 Sham: n = 14	No significant difference in body weight between active (–4.5 kg) and sham (–2.3 kg) groups	Reduction in the desire to eat sweet foods in active group. No other significant differences were observed.	Trend improvement (significant weight loss in pooled sample ($p < 0.001$); no significant between-group difference ($p = 0.786$); reduced desire for sweet foods ($p = 0.005$)
Forcano et al. (2020) [31]	Anodal: R-DLPFC, Cathodal: L-DLPFC, 2 mA for 20 min Consecutive 4 days (4 sessions)	tDCS+computerized cognitive training	Male or female, aged between 18–60, BMI (kg/m^2) >40 or BMI (kg/m^2) >35, combined with diabetes or hypertension, no mental illness	Active: n = 9 Sham: n = 9	Greater reduction in energy intake in active group compared with sham group	Reversed left-dominant frontal asymmetry and increased frontal coherence in the γ band in active group; decreased eCB level in active group	d = 0.85, p not reported.
de Araujo et al. (2022) [16]	Anodal: R-DLPFC, Cathodal: L-DLPFC, 2 mA for 20 min 5 sessions per week for 4 weeks (20 sessions)	tDCS+low-calorie diet	Male or female, aged between 20–50, BMI (kg/m^2) 25–35, no mental illness	Active: n = 14 Sham: n = 14	No significant difference in body weight between active (–4.5 kg) and sham (–2.3 kg) groups	Significantly decreased FPG, insulin levels, and increased MISI in the active group	Trend improvement (no significant weight loss, $p = 0.786$; improved metabolic changes, all $p < 0.05$)
Araújo de Oliveira Figueirêdo et al. (2024) [32]	Anodal: R-DLPFC, Cathodal: L-DLPFC, 2 mA for 20 min, Consecutive 10 days (10 sessions)	/	Female, aged between 45–65, BMI (kg/m^2) 25–35, no mental illness	Active: n = 25 Sham: n = 25	No differences in energy intake (kcal/d) and urge to eat between active and sham groups	No significant difference in body weight between active and sham groups	Trend improvement (not statistically significant, $p > 0.05$)
Aydin et al. (2024) [33]	Anodal: L-DLPFC, Cathodal: right supraorbital, 2 mA for 40 min Consecutive 3 days (3 sessions)	/	Male or female, aged between 18–60, BMI (kg/m^2) ≥25, no mental illness	Active: n = 13 Sham: n = 16	Greater reduction in IL-6 in active group compared with sham group, independent of ad libitum intake	No differences in body weight, energy intake, and hormones between active and sham groups	Significant improvement in inflammatory marker ($p = 0.03$)
Ester-Nacke et al. (2025) [34]	12 channel network tDCS anode/cathode stimulation of hypothalamic functional network area, 2 mA per electrode for 25 min, consecutive 3 days (3 sessions)	/	Male or female, aged between 20–65, BMI (kg/m^2) 25.5–39, female waist circumference ≥80 cm, male waist circumference ≥94 cm, no mental illness	Anodal active: n = 15 Cathodal active: n = 14 Sham: n = 15	Significant improvement in inhibitory control performance and reduction in the desire for sweet foods in active group	No differences in glucose metabolism, peripheral insulin sensitivity, energy intake (kcal/d), and urge to eat between active and sham groups	No metabolic changes (all $p > 0.05$); significant cognitive function improvement ($p < 0.05$)

Abbreviations: COMT, catechol-*O*-methyltransferase; DLPFC, dorsolateral prefrontal cortex; R/L-DLPFC, right/left dorsolateral prefrontal cortex; BMI, body mass index; FPG, fasting plasma glucose; MISI, Matsuda insulin sensitivity index; eCB, endocannabinoid; tDCS, transcranial direct current stimulation; IL-6, interleukin-6.

the risk of metabolic dysregulation [44]. However, strategies merely suppressing appetite or inhibiting lipid absorption have proven insufficient to prevent SGA-induced glycolipid metabolic disorders [45]. This limited efficacy of peripheral-focused interventions highlights the need for central neuromodulation strategies targeting the underlying brain circuitry to restore metabolic homeostasis. Evidence from obese individuals without mental disorders has demonstrated that tDCS can modulate PFC excitability and reward circuits, providing a mechanistic rationale for its potential efficacy in SCZ, while also establishing preliminary safety and tolerability profiles [28,29,30,31,34]. However, understanding the mechanisms underlying metabolic disorders in SCZ requires a more comprehensive central-peripheral synergistic perspective. An increasing body of evidence pertaining to this research question points toward a unifying neuro-endocrine-immune framework, aiming to provide further theoretical support for the application of tDCS in SCZ.

The neuro-endocrine-immune network is an integrated system in which the nervous, endocrine, and immune systems function as a coordinated whole through bidirectional communication [46]. The brain integrates peripheral metabolic signals and regulates hormone secretion through several endocrine systems, including the hypothalamic-pituitary-adrenal (HPA) axis [47]. Immune cells and peripheral organs such as adipose tissue secrete cytokines and other mediators that influence insulin sensitivity and chronic inflammation [48,49]. Disruption of this network is increasingly being recognized as a key driver of metabolic disorders, including obesity, diabetes, and metabolic syndrome [46]. Accumulating evidence indicates that SGAs disrupt hormone secretion and systemic inflammatory responses through the neuro-endocrine-immune network, leading to glycolipid metabolic disorders [23,44,50,51]. Therefore, tDCS has emerged as a promising theoretical treatment. Preclinical studies have shown that tDCS promotes axonal growth and facilitates neural repair, while clinical evidence also supports that tDCS can induce durable neuroplastic changes [52,53,54]. Consequently, it may normalize brain function and peripheral physiological processes by stimulating key regions such as the DLPFC (Fig. 1).

3.1 Neuro-Endocrine Axis

The HPA axis connects central and peripheral physiological processes and regulates energy metabolism, with glucocorticoids (GCs) secretion playing a critical role. Elevated GC levels resulting from hyperactivity of the HPA axis induce insulin resistance in key metabolic tissues, such as the liver and adipose tissue [55,56]. This promotes hepatic gluconeogenesis and lipolysis, while triggering systemic inflammatory responses, thereby further exacerbating glycolipid metabolic disorders. Chronic exposure to high GC levels also reduces cortical neuron volume, dendritic complexity, and synaptic protein expression, which may result in white matter defects in specific brain regions, such as the prefrontal-amygdala pathway, increasing the risk of SCZ [57,58]. In addition, studies have found significantly reduced expression of glucocorticoid receptors (GR) in the DLPFC of individuals with SCZ, indicating HPA axis dysfunction [59,60]. The effects of pharmacotherapy warrant further attention. SGAs act on the hypothalamus to regulate the secretion of neurotransmitters, including dopamine and serotonin. These drugs induce hyperphagia, weight gain, and metabolic disorders [44]. In summary, both brain abnormalities and long-term pharmacological effects contribute to HPA axis hyperactivity and peripheral metabolic disorders in SCZ, which in turn exacerbates brain damage, forming a vicious cycle between worsening psychiatric symptoms and metabolic disorders. This neuro-endocrine pathway provides a theoretical foundation through which central neuromodulation may help improve peripheral metabolic health.

3.2 Neuro-Immune Axis

Systemic chronic low-grade inflammation is a key contributing factor to the pathogenesis and progression of SCZ [61]. Adipose tissue functions as an endocrine organ that secretes pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which further activate systemic inflammatory responses [62]. The hypothalamus is particularly susceptible to peripheral inflammation because of its lack of protection from the blood-brain barrier. Acute inflammation may temporarily restore energy metabolism homeostasis by activating interactions among glial cells, thereby exerting neuroprotective effects. However, as it progresses to chronic inflammation, persistent gliosis impairs myelin formation and axon growth in the surrounding neurons, leading to disruption of the hypothalamic network connectivity [63]. Consequently, impaired negative feedback regulation of GC levels by the HPA axis leads to peripheral glycolipid metabolic disorders. In addition to affecting the hypothalamus, elevated levels of pro-inflammatory markers in the blood and cerebrospinal fluid of individuals with SCZ are associated with reduced gray matter volume and connectivity abnormalities [64]. Abnormalities in brain structure and functional connectivity disrupt the normal regulation of the endocrine axis, triggering various metabolic issues [22]. Therefore, suppressing systemic inflammation is beneficial for both psychiatric and metabolic disorders, and inflammatory cytokines may serve as biomarkers for disease prediction and treatment evaluation.

3.3 Endocrine-Immune Axis

The bidirectional interaction between the endocrine and immune systems completes the neuro-endocrine-immune network, revealing the mechanism underlying

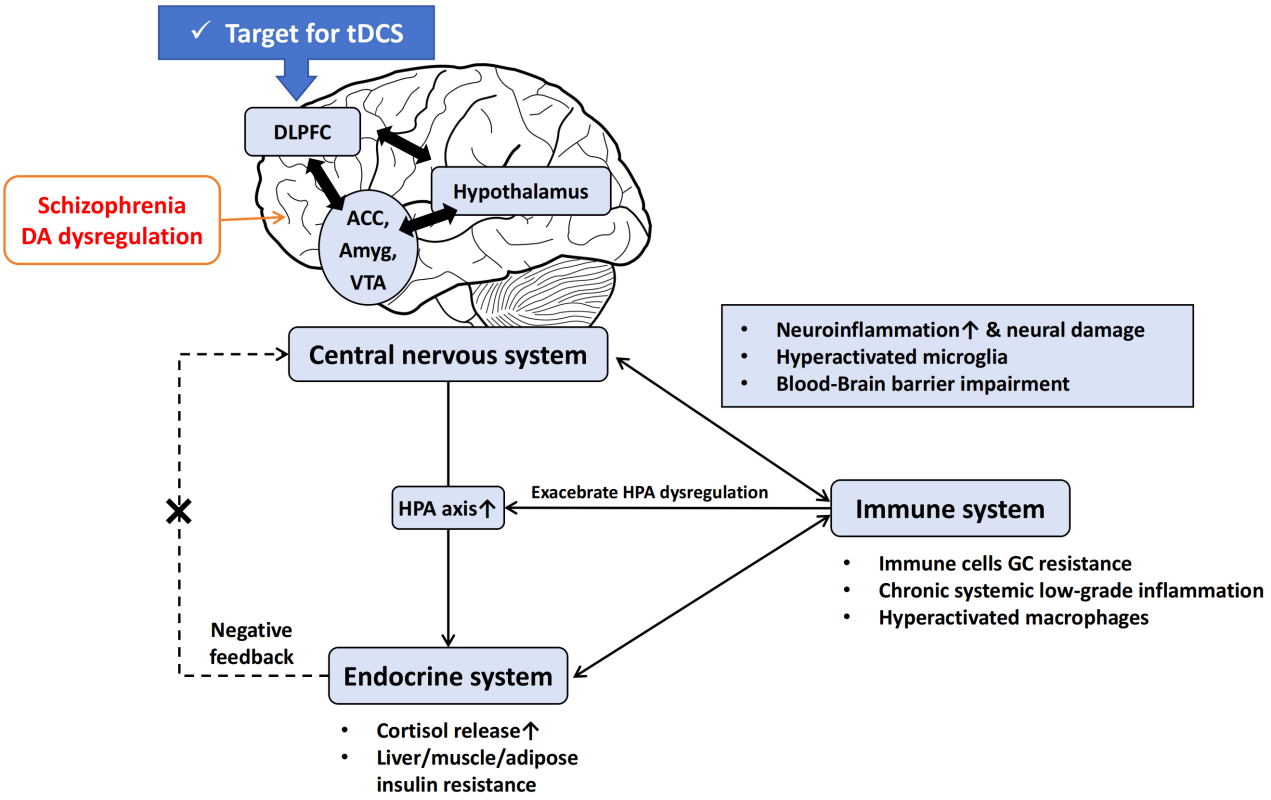


Fig. 1. The neuro-endocrine-immune mechanism linking central nervous system abnormalities to peripheral metabolic disorders in SCZ and the potential target of tDCS. Abbreviations: ACC, Anterior Cingulate Cortex; Amyg, Amygdala; VTA, ventral tegmental area; DA, dopamine; GC, glucocorticoid; HPA, hypothalamic-pituitary-adrenal; SCZ, schizophrenia. Solid arrows indicate established direct regulatory pathways among these systems (bidirectional or unidirectional as shown). Dashed lines represent anticipated feedback pathways from the endocrine system to the central nervous system; these are marked with "×" to indicate that such feedback loops are disrupted under pathological conditions. Thick double-headed arrows indicate functional connectivity among brain regions. "↑" indicates upregulation or increased activity; "×" indicates disruption or inhibition of the pathway.

the susceptibility of individuals with SCZ to glycolipid metabolic disorders. Persistently elevated GC levels not only directly affect metabolic organs but also weaken the anti-inflammatory capacity of immune cells by reducing their sensitivity to GCs, consequently perpetuating low-grade inflammation [65,66]. Additionally, dysfunctional adipose cells release pro-inflammatory cytokines and promote macrophage infiltration, further amplifying the inflammatory response [62,65]. A vicious cycle emerges: immune dysfunction associated with excessive GCs exacerbates metabolic disorders, promotes the release of inflammatory factors, and causes systemic damage, including impairment of the blood-brain barrier. Consequently, activated microglia promote neuroinflammation, leading to cumulative structural and functional damage in multiple brain regions, potentially increasing the risk of SCZ [67,68]. This multi-system interaction indicates that neuromodulation targeting the central nervous system may interrupt this cycle and improve metabolic and immune functions.

4 tDCS for Glycolipid Metabolic Disorders: Evidence From Non-Psychiatric Populations

4.1 Clinical Research Progress and Theoretical Analysis

Existing tDCS studies have primarily targeted obese individuals without mental disorders, investigating the effects of tDCS on weight loss and energy intake, as shown in Table 1. It should be noted that direct clinical validation of tDCS for metabolic regulation in SCZ populations remains lacking, and caution against over-extrapolation of existing findings is warranted. Most studies have employed a current intensity of 2 mA. The earliest two studies found that the effectiveness of short-term interventions (e.g., ≤10 sessions) was limited, with the montage of placing the anode over the left DLPFC and the cathode over the right supraorbital area [26,27]. In contrast, extended treatment duration and increased numbers of sessions appeared to improve metabolic parameters and response inhibition, although there was still no significant weight loss. Notably, Fassini et al. [28] first reported in a 6-month follow-up study that tDCS combined with a low-calorie diet led to

appetite and energy intake reduction, but only in carriers of the catechol-*O*-methyl transferase (*COMT*) *Met* allele, who exhibited higher dopamine concentrations in the PFC and a better response to tDCS. These findings suggest that tDCS may regulate the dopaminergic pathway and induce corresponding central and peripheral physiological activities. Neuroimaging studies have shown that tDCS targeting the DLPFC increases dopamine release in the ventral striatum, which further supports this hypothesis [15]. de Araujo et al. [30] conducted a longer intervention period of four weeks (20 sessions) and observed weight loss and reduced consumption of sweet foods among participants, employing a montage with the anode placed over the right DLPFC, which is the inverse of the conventional left-sided placement. This finding suggests that long-term and repeated interventions may induce long-lasting synaptic plasticity changes and promote the functional reorganization of neural circuits for self-control [30]. Subsequent studies further demonstrated that tDCS improves glucose homeostasis and insulin sensitivity, indicating its potential therapeutic value in treating insulin resistance or diabetes in obese individuals [16]. Several recent short-term studies using tDCS alone (3 [34], 4 [31], and 10 [32] sessions, respectively) only reported changes in metabolic parameters and cognitive function without statistically significant weight loss. Nevertheless, tDCS has demonstrated certain benefits in obese individuals, and may prevent further weight gain. A feasibility trial protocol specifically targets antipsychotic-induced weight gain and assesses whether tDCS can help prevent further metabolic deterioration, which aligns with our observation that tDCS may halt weight progression even when significant weight loss is not achieved [69]. While this protocol signals an initial interest in applying tDCS to metabolic dysregulation in SCZ, direct evidence from completed trials remains scarce, underscoring the need for future research.

Several factors may account for the lack of significant weight loss in most of the ten studies reviewed. First, the intervention duration and the total number of sessions were likely insufficient. Although still not statistically significant, studies with extended treatment (≥20 sessions) showed improvements in secondary metabolic parameters, suggesting that longer interventions may be necessary to translate tDCS effects into clinically detectable weight changes. Second, genetic heterogeneity may influence individual responses to tDCS, and failing to consider such variability could obscure positive signals. Third, the primary endpoint of weight loss may be less immediately sensitive to tDCS effects than the secondary endpoints (e.g., food craving and glucose homeostasis), as body weight regulation involves complex homeostatic mechanisms that may require sustained behavioral changes over longer periods. These considerations do not negate the potential of tDCS, but highlight areas for protocol optimization. Future studies should expand the study population and design long-term intervention protocols to validate efficacy and clarify the exact mechanisms, as small samples reduce detection probability and long-term protocols (≥10 sessions) yield greater effects [70,71].

4.2 Comparative Effectiveness With Pharmacological Interventions and Repetitive Transcranial Magnetic Stimulation (rTMS)

Overall, a range of NIBS and pharmacological interventions have been investigated for the management of glycolipid metabolic disorders in SCZ, each with distinct mechanisms, efficacy profiles, and practical considerations. When comparing these approaches, the overall body of evidence remains substantially larger for pharmacological interventions, including metformin, glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., semaglutide), and statins, as supported by numerous randomized clinical trials (RCTs) and meta-analyses [72,73,74,75]. However, despite achieving practical therapeutic effects, pharmacological interventions have raised considerable concerns, including individual variations in efficacy, poor long-term adherence, side effects, and limited accessibility [73,76,77,78]. It is crucial to recognize that drug targets are primarily focused on peripheral metabolic pathways rather than on the dysfunction of central regulatory mechanisms. Emerging precision strategies, including AI-assisted psychobiotics and NIBS, seek to bridge this gap by restoring neuro-endocrine-immune homeostasis [79]. Notably, NIBS is distinguished by its direct modulation of the aberrant central neural circuits underlying the disease, providing a more proximate intervention.

Among NIBS techniques, tDCS and rTMS are the two most commonly used approaches [20]. Regarding outcomes, rTMS appeared to be more effective than tDCS in reducing food cravings and energy intake [20,80]. Notably, rTMS has been applied to induce weight loss in individuals with SCZ, while no tDCS-related studies have been conducted. High-frequency rTMS over the DLPFC was observed to significantly reduce body weight and BMI within four weeks [81,82], and continuous theta burst stimulation was shown to prevent antipsychotic-induced weight gain [38]. Collectively, these findings support the overlapping brain mechanisms between obesity and SCZ, and demonstrate that central neuromodulation can positively ameliorate metabolic disorders in this population. However, rTMS requires expensive and bulky equipment and administration by trained professionals in clinical settings, which critically limits its treatment frequency and real-world accessibility. Given that tDCS shares the core advantage of direct modulation of the central nervous system, it may offer a viable alternative. tDCS offers distinct advantages, including portability, simple operation, high safety, and suitability for home-based and long-term community management, thereby addressing the many practical barriers associated with rTMS. However, tDCS still has limitations for clinical

applications. It may not be as effective as rTMS and requires further optimization of the stimulation protocols and individualized treatment. Currently, evidence regarding its therapeutic effects and long-term use in home settings is accumulating.

4.3 Quality of Existing Literature and Recommendations

The variability in the clinical efficacy of tDCS may result from inconsistent stimulation parameters, including target location, treatment duration, and current intensity, as well as small sample sizes, short follow-up periods, and limited population diversity. Future research should be more cautious about methodological quality, such as implementing reliable blinding procedures and refining strategies to minimize participant dropout, as these issues are particularly critical in non-pharmaceutical intervention studies. Recent methodological advances have proposed ActiSham, a model-driven multi-electrode approach that offers better participant blinding than traditional bifocal tDCS by mimicking real stimulation sensations without affecting the corticospinal excitability [83]. Another study developed a specification-grade checklist to help reduce trial variability and strengthen cross-study syntheses in mechanistic and clinical research [84]. Notably, remote supervision and home-based tDCS protocols have been shown to improve adherence and reduce dropout rates in other clinical populations [85,86]. Increasing stimulation frequency or sessions [87] and incorporating neuroimaging and electrophysiological techniques are recommended for protocol optimization [88,89]. Furthermore, studies should explore combined interventions, such as cognitive tasks or lifestyle changes, which may develop synergistic effects [90,91,92]. Participant stratification based on baseline characteristics may be beneficial for developing personalized stimulation protocols [93,94]. These strategies will facilitate the clarification of tDCS mechanisms and support the establishment of standardized stimulation protocols and evaluation systems.

In summary, efforts should be directed toward enhancing methodological rigor to supplement reliable evidence, utilizing objective biomarkers to optimize stimulation protocols, and exploring the underlying mechanisms. Previous study have established the abnormal neuro-endocrine-immune network as the underlying pathological mechanism of glycolipid metabolic disorders in SCZ and potentially as an effective target for tDCS modulation [46]. Therefore, exploring the feasibility of tDCS in restoring metabolic homeostasis and serving as an adjunct therapeutic strategy for SCZ holds a theoretical basis and has broad application prospects. The following sections elaborate on the specific mechanisms and supporting evidence of this argument.

5 Theoretical Basis and Preliminary Evidence Supporting tDCS as A Potential Intervention for Glycolipid Metabolic Disorders in SCZ

5.1 Normalize HPA Axis Activity

Brunoni et al. [95] first demonstrated that tDCS applied to the L-DLPFC reduced cortisol levels, with greater stimulation intensity linked to larger cortisol decreases. Antal et al. [96] found that anodal tDCS increased regional cerebral blood flow in the right medial PFC and right amygdala during psychosocial stress, suggesting precise brain targets of tDCS effects. Direct evidence for tDCS engagement of the DLPFC-Anterior Cingulate Cortex (ACC) circuit comes from a task-based fMRI study, which found that prefrontal tDCS increased right DLPFC and ACC activity specifically in response to negative outcomes and reduced whole-brain connectivity of the right ACC, confirming that tDCS exerts effects on distal brain regions and can bidirectionally modulate the functional architecture of the DLPFC-ACC circuit [97]. In real-world contexts, a study of elite archers under competitive conditions showed that a single session of anodal L-DLPFC tDCS replicated the cortisol-lowering effect [98]. Integrating these findings, we propose that tDCS may influence cortisol secretion by stimulating DLPFC and modulating the brain networks implicated in HPA axis regulation [99]. Given the close association between HPA axis dysregulation and glycolipid metabolic disorders, the ability of tDCS to modulate cortisol secretion raises the possibility that tDCS may serve as a potential intervention for metabolic disorders, particularly in populations with HPA axis dysfunctions.

5.2 Improve Glucose Homeostasis

tDCS may influence whole-body glycolipid metabolism by modulating cerebral metabolic processes. Human trials have shown that repeated tDCS induced localized cerebral energy consumption and directly promoted systemic glucose uptake through an insulin-independent mechanism [100,101]. Animal studies have provided valuable insights into the underlying mechanisms. Specifically, hypothalamic glucose-sensing neurons detect elevated glucose levels via ATP-sensitive potassium (K-ATP) channels and suppress hepatic gluconeogenesis to maintain glucose homeostasis [102]. These neurons also control autonomic nervous activity, hormone secretion, and the hedonic value of food through interactions with the mesolimbic dopamine system [103]. Dysfunction in central glucose sensing may precede and cause the development of obesity and diabetes, representing a promising target for improving systemic metabolism. Notably, beyond its effects on cortical excitability, tDCS has been shown to modulate the deep subcortical nuclei, including the hypothalamus [99]. Regarding lipid metabolism, animal studies have indicated that tDCS can reduce hepatic steatosis and inflammation in obese mice [104]. Although research on lipid metabolism in humans remains limited, these animal findings suggest

a potential role for tDCS in improving lipid metabolism, which may be considered as an exploratory outcome in future studies of SCZ individuals with comorbid glycolipid metabolic disorders.

5.3 Inhibit Systemic Inflammation

Although tDCS does not directly stimulate deep brain regions or peripheral cells, it may indirectly modulate peripheral immune and inflammatory responses through multi-systemic interactions. Early studies often failed to capture significant changes in biomarkers, constrained by short intervention durations, inadequate sessions, and small sample sizes. However, emerging evidence suggests that inflammatory status may influence the efficacy of tDCS. Goerigk et al. [10] first found that IL-6 and IL-8 levels were positively correlated with depression severity in patients with bipolar disorder and predicted the response to tDCS [10]. Optimized tDCS protocols, featuring increased sessions and longer treatment durations, have demonstrated reductions in serum IL-6 and improvements in glycolipid metabolism [10,33]. These findings suggest that inflammatory cytokines may serve as promising biomarkers for evaluating tDCS efficacy. Future research should expand the sample sizes, develop high-intensity stimulation protocols, and conduct long-term follow-up studies to clarify the causal relationship between tDCS-induced anti-inflammatory mechanisms and metabolic improvement.

6. Limitations and Future Directions

Individuals with SCZ frequently exhibit glycolipid metabolic disorders, which are increasingly recognized as integral components of the biological phenotype of SCZ, rather than mere somatic comorbidities. These metabolic abnormalities reflect complex dysregulation across the interconnected neural, endocrine, and immune systems. The limitations of the existing pharmacotherapy highlight the importance of developing non-pharmacological interventions. tDCS is an NIBS technique that enhances neuroplasticity and helps restore brain network function. Accumulating evidence suggests that tDCS mainly functions through top-down indirect mechanisms, rather than direct peripheral metabolic regulation. Given its neuroprotective properties, tDCS may induce significant and persistent changes in neural activity when integrated with complementary interventions that engage overlapping neural systems, such as cognitive training, behavioral modulation, or biofeedback. Such combined approaches offer synergistic strategies targeting shared neurobiological mechanisms, thereby amplifying the system-level regulation and therapeutic impact [90,91,92].

Future research should address several critical challenges: (1) conducting clinical trials in individuals with SCZ and glycolipid metabolic disorders to provide direct evidence of tDCS effects on metabolic regulation and to elucidate its neurobiological mechanisms, especially by identifying relevant cortical targets and neuro-endocrine-immune pathways; (2) optimizing experimental designs and stimulation protocols to enhance interpretability and reproducibility; and (3) establishing biomarkers to evaluate tDCS efficacy, facilitating standardized and personalized intervention strategies within the framework of biological psychiatry. Notably, most registered ClinicalTrials.gov studies on tDCS in SCZ have focused on negative symptoms or cognitive function, with only one suspended trial (NCT04518319) targeting SCZ in metabolic syndrome. This gap underscores the need for further studies in this specific population. Additionally, a recent study reported that individuals with psychosis receive lower electric field strength during tDCS than healthy controls, suggesting the necessity of establishing an electric field model and adopting individualized montages to improve tDCS effectiveness given the increased risk of obesity [105]. Although tDCS is generally well tolerated with no reported serious adverse events, mild and transient side effects (e.g., local itching, tingling, or fatigue) may occur [85,106]. Future long-term studies are needed to comprehensively evaluate the safety profile of tDCS, particularly in the context of higher stimulation intensities, repeated sessions, and diverse populations.

7. Conclusion

In summary, this review synthesizes current evidence and proposes a neuro-endocrine-immune network framework to elucidate tDCS effects on metabolism in individuals with SCZ. Our synthesis suggests that direct clinical evidence remains preliminary and highly heterogeneous, constrained by methodological variability, inconsistent protocols, and small samples, although the biological rationale is plausible. Large-scale, standardized trials with optimized parameters are urgently needed to establish its efficacy. Currently, tDCS should be viewed as a promising but unproven experimental approach, warranting further validation rather than routine clinical use.

Author Contributions

Conceptualization, HYT, CL and JHC; investigation, HYT, CL; writing—original draft preparation, HYT; writing—review and editing, JHC; visualization, HYT; supervision, JHC; funding acquisition, CL, JHC. 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.

Acknowledgment

Not applicable.

Funding

This work is supported by the Shanghai Shen-Kang Hospital Development Center (SHDC12025118), the Shanghai Municipal Health Commission (2026PT006), the Fundamental Research Funds for the Central Universities (YG2025QNB32), the Program of Chen Frontier Lab for AI and Mental Health (TCCI) - Shanghai Mental Health Center (SMHC) (2023-TX-018), and the Integrated Innovation Team Project of Shanghai Mental Health Center.

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN52368.

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