tDCS for Depression: A 22 514-Patient Retrospective Analysis with Integrated Sleep-Outcome Sub-study

Aria Banazadeh

BSc (Hons) Artificial Intelligence

University of Northampton

10th October 2025

Supervisor: Prof Mu Mu

Abstract

Background: Although home-use transcranial direct current stimulation (tDCS) shows promise as a scalable treatment adjunct for major depressive disorder (MDD) and frequently co-occurring insomnia, comprehensive long-term, real-world evidence is lacking. This study presents the first population-scale evaluation of the self-administered Flow FL-100 tDCS device, analyzing trajectories of depression symptoms, sleep quality, and the influence of dose and adherence.

Methods: We analyzed a retrospective cohort of 22 514 adults who purchased and used the Flow FL-100 device between 2020–2024. Weekly self-reported Montgomery–Åsberg Depression Rating Scale (MADRS-S) scores, device stimulation logs, and basic demographic data were collected for up to 50 weeks. Co-primary endpoints included remission (MADRS-S ≤ 12), achieving a minimal clinically important difference (MCID; $\geq$ 6-point score reduction), $\geq 50\,\%$ symptom response, and relapse. Secondary analyses investigated predefined stimulation schedules, adherence patterns, comorbidities, and concurrent treatments. Sleep-specific remission was evaluated in a nested sub-study of 6 229 users with baseline insomnia (MADRS-S sleep item ≥ 4). Primary analyses employed mixed-effects models and stratified summaries based on available data, without imputation.

Results: Participants typically presented with moderate depression (baseline mean MADRS-S 27.4 ± 8.3). Mean scores significantly decreased, reaching the mild severity range by week 10 (16.8) and remaining stable through week 50. Key week-10 outcomes for all users included: 33.9 % remission rate, 66.1 % achieving MCID, and 34.6 % showing a $\geq 50\,\%$ response. Relapse occurred in 12.2 % of those who had previously remitted. Users adhering to recommended stimulation (≥ 4 stimulations wk^{-1} in weeks 1–3 and ≥ 1 thereafter) demonstrated superior outcomes (e.g., 38.0 % remission, 70.9 % MCID response at week 10). Higher initial stimulation intensity (4–5 sessions/wk) was linked to greater week-20 remission (42 % vs. 36 % for minimal protocols) and longer remission retention (6.0 vs. 5.5 weeks). While treatment efficacy was broadly consistent across demographic and clinical subgroups, observed variability suggests potential benefits for personalized dosing. In the insomnia sub-cohort, sleep-item remission was rapid (36.1 % by week 1, 63.2 % by week 10) and moderately correlated with improvements in total MADRS-S scores

($r = 0.47$–0.63).

Conclusions: This large real-world dataset ($> 22\,000$ users) indicates that self-directed bifrontal tDCS can provide clinically meaningful and durable relief from depressive symptoms, while also substantially improving sleep in individuals with comorbid insomnia. Treatment benefit is strongly associated with initial stimulation intensity and sustained adherence, suggesting that adaptive dosing strategies could further enhance outcomes. These findings warrant pragmatic clinical trials and cost-effectiveness studies to better integrate home-use tDCS into stepped-care pathways for depression and related insomnia.

Lay Summary

People with depression often wait months for therapy or must cope with medication side-effects. We looked at anonymous data from more than 22,000 people who bought and used a small headset that gives the brain a very mild electrical current (called tDCS) at home. Users answered a short mood questionnaire every week. On average, symptoms improved quickly during the first ten weeks and stayed better for a year if people kept using the headset once or twice a week. About one in three users became free of depression, and results were similar regardless of age or gender. This shows that self-directed brain-stimulation could become a practical extra tool alongside talking therapy or tablets, especially for people on waiting lists. We also checked sleep, a common partner of low mood. Among users who began with insomnia, one-quarter hit 'good-sleep' scores by week ten, with lasting gains. Gains were greatest in people who stuck to four sessions a week up front and weekly top-ups after, showing the value of adherence. Side-effects were usually mild tingling and no serious problems appeared. Though not a randomised trial, these real-world data offer a view of at-home use and suggest that tailoring dose could boost results.

Declarations

Ethics approval. All analyses were performed on a fully-anonymised dataset supplied by Flow Neuroscience AB. The study protocol was approved by the University of Northampton Faculty of Arts, Science and Technology Research Ethics Committee (FREC2425005).

Funding. This work was supported by a short-term analytic consultancy paid to Aria Banazadeh by Flow Neuroscience AB. The company also supplied the fully-anonymised dataset. No additional external funding was received.

Conflicts of interest. I received consultancy fees from Flow Neuroscience AB for the data-analysis phase of this project. There were regular meetings and discussions with the flow team but they had no direct role in interpretation of the results, or the writing of this report.

Data availability. Analysis scripts are available in the project's private GitHub repository. Raw data remain under the custody of Flow Neuroscience AB and cannot be publicly released for GDPR reasons.

Acknowledgements

I extend my sincere gratitude to my supervisor, Professor Mu Mu, for his invaluable guidance throughout this project.

I also thank Chris Griffiths of Northamptonshire Healthcare NHS Foundation Trust for his collaboration.

Finally, my appreciation goes to Flow Neuroscience AB for providing the anonymised dataset essential for this research and for the consultancy opportunity during the analysis phase. Particular thanks are due to their data-engineering team for preparing the data.

Contents

List of Figures

List of Tables

Chapter 1

General Introduction

1.1 Clinical Burden of Depression

Major depressive disorder (MDD) is one of the most prevalent and debilitating illnesses worldwide. Current estimates from the World Health Organization (2023 briefing) suggest that **around 280 million adults, approximately 5% of the global population, experience depression at any given time**. This makes depression the largest single contributor to the global burden of mental illness [World Health Organization, 2023]. Its prevalence continues to rise across all Global Burden of Disease (GBD) regions, influenced by factors such as population growth, conflict, economic instability, and the lingering psychosocial consequences of the COVID-19 pandemic.

The health impact is profound. The *Global Burden of Disease 2019* study linked depressive disorders to **49 million years lived with disability (YLDs)**, ranking depression **second among individual conditions contributing to YLDs and thirteenth overall for disability-adjusted life years (DALYs)** when premature death is considered [GBD 2019 Diseases and Injuries Collaborators, 2020]. In terms of non-fatal health loss, depression is surpassed only by musculoskeletal pain and anaemia. The economic consequences mirror this clinical burden. The WHO estimates that depression and anxiety collectively cost the global economy **US$1 trillion each year in lost productivity**, stemming primarily from absenteeism, reduced workplace performance (presenteeism), and lower labour force participation [World Health Organization, 2023].

Depression typically emerges relatively early in life, with a median onset in the mid-twenties, and often follows a relapsing course that accumulates social and medical costs over time. Furthermore, it is the leading risk factor for suicide, a tragedy claiming over 700,000 lives annually. Despite the existence of effective treatments,

the WHO highlighted in 2023 that access to care remains inadequate. Fewer than half of those affected in high-income nations, and often **less than 10% in low- and middle-income countries**, receive even basic care [World Health Organization, 2023]. Significant barriers include shortages of trained healthcare professionals, insufficient primary care training, enduring stigma, long waiting lists, and the challenges associated with medication side-effects.

In summary, MDD imposes a disproportionate share of global disability and economic loss, persists as a major driver of suicide, and remains largely untreated for the majority of affected individuals. The disparity between the immense need for mental health support and the capacity of existing services has fuelled interest in developing scalable treatment alternatives. Options suitable for self-direction or delivery outside conventional clinical settings, such as low-intensity neuromodulation like home-use transcranial direct current stimulation (tDCS), alongside app-based therapies and other digital tools, are emerging as potentially valuable components of care pathways. However, robust evidence regarding their long-term effectiveness and safety is still required.

1.2 Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation, commonly abbreviated as *tDCS*, is a simple and established non-invasive brain stimulation technique employed in both research and clinical practice. A standard session involves placing two saline-soaked sponge electrodes on the scalp, connected to a small, battery-powered device. This device administers a constant, very low-level electrical current, typically between 0.5 and 2 mA, for approximately twenty minutes. Unlike stimulation methods that use pulses, this direct current does not directly cause neurons to fire (action potentials). Instead, it subtly modifies the resting electrical state (membrane potential) of neurons located beneath the electrodes. The positive electrode (anode) induces slight depolarization, bringing the neuron closer to its firing threshold, while the negative electrode (cathode) causes mild hyperpolarization, making it less likely to fire. Although this electrical shift is minor—around one millivolt—it is sufficient to influence the activation probability of targeted brain circuits in response to normal inputs.

While the immediate impact is modest, the effects of tDCS can be lasting. The induced changes in neuronal excitability appear to engage known mechanisms of brain plasticity. These include modulating the activity of N-methyl-D-aspartate (NMDA) receptors, temporarily reducing local levels of the inhibitory neurotrans-

mitter γ-aminobutyric acid (GABA), and producing short-term adjustments in brain wave patterns (cortical oscillations). Cumulatively, these processes allow the behavioural effects of a single tDCS session to extend for hours beyond the stimulation period itself. With repeated daily applications, these effects can accumulate and persist for weeks. This capacity for inducing lasting change has prompted research into *tDCS* for various conditions, including stroke rehabilitation, chronic pain management, treatment-resistant depression, and even cognitive enhancement in healthy individuals.

Historically, tDCS was primarily utilized within specialized laboratories. More recently, clearer regulatory frameworks and advancements in technology have facilitated the use of *tDCS* in home settings. The voluntary "LOTES" guidelines published in 2023 classified limited-output transcranial electrical stimulators (delivering under 4 mA for less than 60 minutes within specific charge limits) as low-risk devices. This classification encouraged the creation of lightweight, application-guided headsets designed for self-administration, sometimes conducted under remote professional supervision. Such systems are now used by healthcare providers in several countries, and regulatory bodies are approving large-scale clinical trials based entirely on home use. Consequently, market analysts forecast steady growth for this technology, driven by mental health demands and increasing interest in wellness and cognitive enhancement applications.

The expanding use of home-based tDCS naturally raises considerations about safety. Fortunately, the existing evidence is largely reassuring. Meta-analyses encompassing tens of thousands of stimulation sessions primarily report transient and mild side effects, most commonly tingling, itching, or slight redness of the skin under the electrodes. No serious neurological complications have been associated with tDCS protocols that adhere to established safety parameters. Furthermore, commercial devices typically include automatic current cut-offs as an additional safety measure. Nevertheless, best practices continue to emphasize the importance of correct electrode preparation, accurate placement, and appropriate dosing, especially when the device is used outside of a supervised clinical environment.

In essence, *tDCS* functions subtly, modulating brain circuit activity rather than forcing it. Its straightforward hardware, robust safety profile, and favourable regulatory outlook have enabled its transition from a laboratory instrument to an accessible technology for remote therapy and research.

1.3 The Bidirectional Relationship Between Depression and Insomnia

Major depression and chronic insomnia often coexist, and epidemiological research indicates that each condition increases the risk of developing the other. A significant meta-analysis integrating findings from 21 longitudinal studies reported that individuals initially without insomnia who later developed persistent sleep difficulties had more than double the odds of subsequently developing depression (random-effects $OR = 2.60$, 95% CI 1.98–3.42) [Baglioni et al., 2011]. This finding was corroborated by a 2023 umbrella review, which rated the evidence for insomnia predicting new-onset depression as *high*, particularly concerning difficulties initiating or maintaining sleep [Al-Abri, 2023].

This relationship is bidirectional. A separate meta-analysis focusing on nine longitudinal studies found that the presence of baseline depressive symptoms significantly elevated the risk of later developing new or worsened insomnia (pooled $OR = 1.55$, 95% CI 1.23–1.94), leading researchers to conclude there was *moderate* support for this direction of the association [Li et al., 2016]. Several studies within that review observed that even after depressive symptoms had improved, residual mood issues could still predict future sleep problems, suggesting depression might leave a persistent vulnerability or "sleep scar."

This connection is likely underpinned by shared biological mechanisms. Both depression and insomnia involve sustained activation of the body's stress-response system (the hypothalamic–pituitary–adrenal [HPA] axis), low-grade neuro-inflammation, and alterations in neurotransmitter systems, particularly monoaminergic dysregulation. All these factors can disrupt the natural regulation of sleep-wake cycles (both homeostatic and circadian processes). From a cognitive perspective, the hyperarousal and worry characteristic of insomnia overlap significantly with the repetitive negative thinking (rumination) common in depression, potentially creating a self-perpetuating cycle. Neuroimaging studies further reveal that sleep deprivation increases the reactivity of the amygdala (the brain's emotion centre) while diminishing control from the prefrontal cortex, thereby increasing susceptibility to low mood. Conversely, individuals with depression frequently exhibit altered sleep architecture, such as a shortened latency to REM sleep and more fragmented deep (slow-wave) sleep, which can exacerbate feelings of being unrested.

Clinically, these interactions imply that untreated insomnia can serve as a potent warning sign for depression, while persistent low mood can predict subsequent sleep difficulties. Fortunately, treatments can effectively target this link. Meta-analyses

demonstrate that cognitive–behavioural therapy for insomnia (CBT-I) not only alleviates sleep problems but also produces moderate reductions in depressive symptoms. Similarly, certain antidepressant therapies can enhance sleep consolidation. Consequently, best practice advocates for routine screening for both conditions and favours integrated treatment approaches designed to break the cycle, rather than addressing each issue in isolation.

1.4 Why Real-World, Device-Embedded Data Matter

Modern therapeutic tools connected to digital platforms—such as smartphone applications, wearable sensors, and the home-use tDCS headset featured in this study continuously record user interactions in real time. Every stimulation session, completed questionnaire entry, or logged activity measure is automatically timestamped and uploaded. Aggregated across thousands of users, these data streams create *population-scale cohorts* with minimal additional data collection cost. Such datasets present distinct advantages for mental health research:

a) **Ecological validity.** Data originates from users' everyday environments (e.g., home, work) rather than controlled research settings. This approach captures symptoms, adherence behaviours, and sleep patterns as they naturally unfold, potentially mitigating artificial study effects (like the Hawthorne effect) and enhancing the generalizability of the findings [Insel, 2020].

b) **Inclusive sampling.** Participation is based on device usage, not adherence to stringent research eligibility criteria. Consequently, these cohorts often include older adults, individuals with multiple health conditions, and those geographically distant from research centres, thereby helping to counterbalance the "healthy volunteer" bias frequently observed in clinical trials.

c) **Dense longitudinal coverage.** A user submitting weekly assessments over a year can contribute over 50 data points. This granularity significantly exceeds the typical data density of standard trials (often only a few visits) and enables detailed modelling of dose-response relationships, remission durability, and relapse predictors [Onnela, 2021].

d) **Scalable statistical power.** Data collection is largely passive once the system is operational. This scale facilitates the reliable investigation of infrequent

events (such as uncommon side effects) and allows for robust analysis of subgroup differences without incurring prohibitive additional costs.

While indispensable for establishing cause-and-effect relationships, randomised controlled trials (RCTs) have inherent trade-offs. Their rigorous methods, including strict participant selection, fixed dosing regimens, and clinic-based assessments, enhance *internal* validity (confidence in the study's results) but can restrict *external* validity (the applicability of findings to real-world settings). Treatment effects observed under the idealized conditions of an RCT often diminish when the intervention is implemented in routine clinical practice [Kraemer, 2019]. Furthermore, RCTs are typically smaller in scale and shorter in duration, making it challenging to detect delayed treatment effects, long-term loss of effectiveness (tachyphylaxis), or rare adverse events.

Device-embedded data collection offers a complementary perspective. It excels at revealing how treatments perform "in the wild"—demonstrating variations in user response and identifying safety signals that may only emerge at scale. RCTs, conversely, are designed to test specific therapeutic mechanisms under controlled conditions. A *hybrid evidence approach*, leveraging both methodologies, can accelerate discovery. Real-world data can generate hypotheses and inform the design of more efficient trials (e.g., using adaptive or Bayesian designs). Subsequently, RCTs provide causal confirmation. Ongoing real-world data collection can then monitor long-term performance, help refine clinical guidelines, and potentially inform the development of adaptive dosing algorithms.

In this framework, the present dissertation utilizes data from a cohort of 22,514 participants to provide the real-world perspective often absent in tDCS clinical trials. It aims to contribute a more comprehensive understanding of how home-use neuromodulation functions within the context of everyday depression care.

1.5 Aim and Objectives

Aim. To evaluate the long-term real-world effectiveness and sleep-related benefits of self-administered Flow FL-100 *t*DCS in a cohort of 22,514 adults diagnosed with depression.

Objectives

1. To map the weekly trajectories of depressive symptoms and calculate rates of remission, response, and relapse over a 50-week period.

2. To quantify the effects of treatment dose and adherence, examining different stimulation schedules to identify patterns potentially associated with sustained benefit.

3. To determine the baseline prevalence of insomnia within the cohort, monitor changes in sleep symptoms over time, and assess the correlation between improvements in sleep and mood.

4. To investigate the influence of demographic factors (age, sex), comorbidities, and previous treatment history on clinical outcomes.

5. To compare the findings from this real-world cohort with results from published RCTs, informing the potential integration of home-use tDCS into care pathways and guiding future trial designs.

1.6 Dissertation Road-map

This dissertation is structured into eight chapters, supplemented by appendices. **Chapter 1** has laid the groundwork, introducing the significant burden of depression, the principles and rationale behind home-use *t*DCS, the value of real-world evidence, and outlining the specific aims and objectives of this research. **Chapter 2** delves into the existing scientific literature, reviewing trial evidence for *t*DCS in treating depression and sleep disturbances, discussing the landscape of real-world evidence in mental health care, and pinpointing the specific knowledge gaps this study addresses. **Chapter 3** details the methodological framework, explaining the retrospective cohort design, the data sources and management procedures, the definition and selection of the study population, the outcome measures used (including primary and secondary endpoints), the approach to handling missing data, the statistical analysis plan, and the ethical considerations and approvals. **Chapter 4** presents the characteristics of the study sample derived from the real-world data. This includes the process of cohort assembly and filtering, a description of the baseline demographic and clinical profiles of the users, an overview of reported comorbidities, and the calculated prevalence of insomnia symptoms at the start of treatment based on the MADRS-S sleep item. **Chapter 5** focuses on the results pertaining to depression outcomes. It examines the overall trajectory of MADRS-S scores over 50 weeks, analyzes changes in specific symptom clusters, reports the rates of clinical remission, response (both MCID and 50% reduction), and relapse (the '3R metrics'), and investigates the influence of baseline depression severity, different stimulation protocols (dose-response), treatment adherence, comorbidities,

and concurrent therapies on these outcomes. **Chapter 6** presents the findings from the integrated sleep sub-study. It details the baseline prevalence of insomnia across different subgroups, tracks the rates of sleep symptom remission and improvement over time, explores the impact of adherence on sleep outcomes, quantifies the correlation between changes in sleep quality and overall depression severity, and examines the interaction between achieving sleep remission and overall depression remission. **Chapter 7** provides a discussion and interpretation of the findings from Chapters 5 and 6. It highlights the key results, compares them with existing evidence from clinical trials and other real-world studies, considers the study's strengths and inherent limitations, and explores the potential clinical and research implications arising from the analysis. **Chapter 8** concludes the main body by offering specific recommendations derived from the study's findings. These recommendations target clinical practice, healthcare policy and service delivery, and priorities for future research in the field of home-use tDCS for depression and associated insomnia. Finally, the **Appendices** contain supplementary materials, including detailed results from the imputation sensitivity analyses, documentation related to the data processing and analysis code, and copies of relevant ethics and consent documentation.

Collectively, these sections provide a comprehensive evaluation of the real-world use and impact of the Flow FL-100 *t*DCS device.

Chapter 2

Literature Review

2.0.1 tDCS for Depression: Trial Evidence

TDCS is increasingly explored as a non-invasive, portable neuromodulation approach for major depression. It delivers a low-intensity (1–2 mA) direct current via scalp electrodes to modulate cortical excitability [Nitsche et al., 2008]. In MDD trials, the anode is typically placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right DLPFC or other reference, aiming to normalise hypoactive frontal regions. Unlike antidepressant drugs or electroconvulsive therapy, tDCS produces no systemic side effects and does not require anaesthesia. Its relative affordability and ease of use make it suitable for community settings and helping broaden treatment access.

Several sham-controlled randomised trials (RCTs) have evaluated tDCS for MDD, yielding mixed results. In an early landmark trial (SELECT-TDCS), six weeks of tDCS monotherapy in 120 patients resulted in similar depression improvement to sertraline, and the combination of tDCS plus sertraline was more efficacious than either alone [Brunoni et al., 2013]. However, a larger non-inferiority RCT (ELECT-TDCS, $n = 245$) found that tDCS (2 mA, 15 daily plus 7 weekly sessions) was slightly less effective than escitalopram (mean HDRS-17 reduction 9.0 vs. 11.3) and failed to meet the non-inferiority margin, although both active treatments outperformed placebo [Brunoni et al., 2017]. Another multicentre trial in treatment-resistant depression showed no difference between active and sham tDCS after four weeks [Loo et al., 2018]. This aligns with a recent German study where adding tDCS to ongoing SSRI therapy provided no benefit over medication alone [Burkhardt et al., 2023].

Interest in home-based tDCS has grown because of its potential to extend therapy beyond clinics. Borrione et al. (2024) tested fully home-administered tDCS (unsupervised, $n = 210$) and found no significant difference versus sham after six

weeks [Borrione et al., 2024]. In contrast, Woodham et al. (2025) reported that a ten-week course of remotely supervised home tDCS ($n = 174$) led to a modest but significant advantage over sham (HDRS-17 improvement 9.4 vs. 7.1, p=0.01), corresponding to higher response rates (63 % vs. 45 %) [Woodham et al., 2025]. These differing outcomes suggest that while at-home use is feasible and acceptable, some level of professional monitoring might be critical to achieving efficacy outside the clinic.

Meta-analyses generally support a modest antidepressant effect for tDCS. An individual-patient-data meta-analysis (nine trials, $n = 571$) found active tDCS superior to sham, with roughly doubled odds of response (OR $\approx$ 1.9, 95 % CI 1.3–2.9; Hedges' $g \approx 0.30$) and remission (OR $\approx$ 1.9) [Moffa et al., 2020]. A conventional meta-analysis of 23 RCTs estimated a pooled Hedges' $g \approx 0.46$ for symptom improvement, with an NNT of $\approx$6 for response [Razza et al., 2020]. These effect sizes approach those of antidepressant drugs (OR $\approx$ 2.0 vs. placebo) and are somewhat lower than those reported for high-frequency rTMS (OR $\approx$ 3.0 in treatment-resistant samples) [Cipriani et al., 2018, Blumberger et al., 2018]. Figure 2.1 summarises pooled outcomes: roughly 30–35 % of patients respond to tDCS versus 15–20 % to sham. TDCS is also as acceptable as sham (no significant difference in dropout rates) across studies [Moffa et al., 2020, Razza et al., 2020].

In terms of dose-response, benefits appear to increase with sufficient treatment duration. Trials delivering >15 sessions tend to report larger effects than shorter protocols, and improvement continues to diverge from sham through week 6 [Nikolin et al., 2023]. Most studies used 2 mA with a bifrontal montage; there is no clear evidence that higher intensities or alternative electrode montages (e.g., extracephalic cathodes) substantially boost efficacy. Identifying strong patient-level predictors has proven difficult [Moffa et al., 2020], though tDCS appears less effective in highly treatment-resistant depression and perhaps more effective as monotherapy than augmentation. Figure 2.2 illustrates a trend that trials with more sessions tend to yield greater effects.

Safety is a key consideration; tDCS is generally well tolerated. The most common side effects are mild scalp tingling or erythema and transient headaches, which are more frequent with active tDCS than sham but generally self-limited. Unlike SSRIs, tDCS causes no systemic adverse effects (e.g., gastrointestinal or sexual problems), and no serious events have been attributed to tDCS in depression trials. Rare cases of hypomania have been reported (<2 %) [Brunoni et al., 2013], a rate comparable to that seen with antidepressants. Overall, tDCS's safety profile compares favourably with pharmacotherapy and rTMS. Key limitations include heterogeneous methods

and mixed results across populations, underscoring the need to refine stimulation parameters and identify responders. Overall, tDCS is a safe treatment option for depression. While its average efficacy is modest, there are clear ways it could be refined.

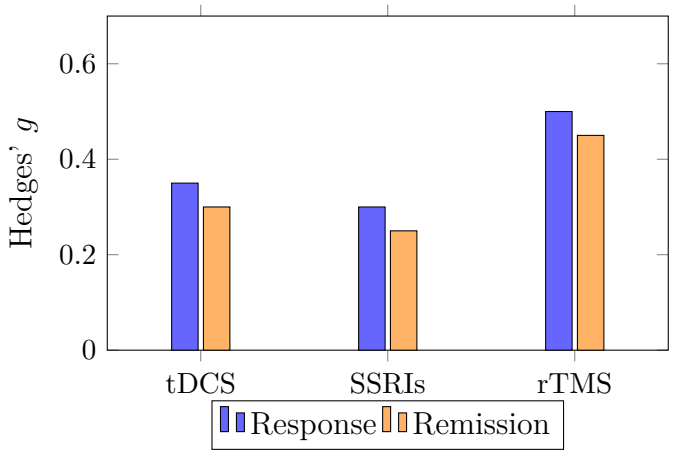

Figure 2.1: Pooled antidepressant effect sizes for tDCS, selective serotonin-reuptake inhibitors (SSRIs), and high-frequency rTMS. Bars show Hedges' g for symptom change corresponding to acute response and remission.

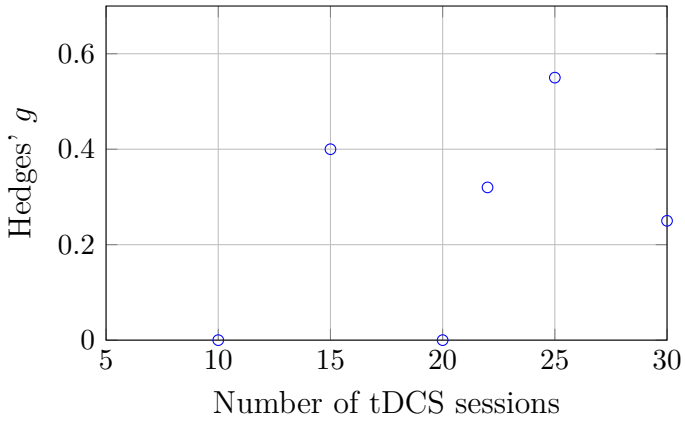

Figure 2.2: Relationship between treatment dose and efficacy in tDCS trials. Each bubble represents an RCT (bubble size $\propto$ 2 mA; colour indicates standard bifrontal montage). Longer courses (>15 sessions) tend to yield larger effects.

2.0.2 tDCS for Sleep Disturbance

TDCS is also being investigated as a portable, well-tolerated neuromodulatory technique potentially useful for the cortical hyperarousal that sustains insomnia. By delivering a low direct current (1–2 mA) across scalp electrodes, tDCS might

help down-regulate fronto-insular arousal circuits or, when timed to non-rapid-eye-movement (NREM) sleep, amplify slow-wave activity. This potential relevance to sleep connects with this dissertation's evaluation of novel adjuncts for chronic sleep disturbance, including cases complicated by depression.

Several key RCTs provide insight into the current evidence: Frase *et al.* applied slow-oscillatory bifrontal tDCS during NREM, increasing slow-wave sleep (SWS) by 33 min and lowering the Insomnia Severity Index (ISI) by three points [Frase et al., 2019]. Saebipour's clinic-based study delivered ten evening sessions (2 mA, anode left dorsolateral prefrontal cortex; DLPFC) and achieved a large symptom gain ($d = 0.80$) with 75 % of participants attaining a $\geq$8-point ISI drop versus 12 % on sham [Saebipour et al., 2015]. A home crossover trial replicated subjective improvements but found no polysomnographic change, suggesting montage-dose interactions [Frase et al., 2021]. Sá *et al.* compared slow-wave and bifrontal montages in primary insomnia, observing superior sleep-efficiency gains (+6 %) only with the slow-wave montage [Sá et al., 2023]. Conversely, Krone *et al.* reported that 15 afternoon sessions (2.5 mA) lengthened actigraphic total sleep time by 40 min in treatment-resistant depression, but objective SWS remained unchanged [Krone et al., 2024].

Pooled results from three recent meta-analyses point towards modest but significant benefits. Sheng *et al.* pooled nine RCTs and found Hedges' $g = 0.26$ (95 % CI 0.05–0.47) for insomnia severity [Sheng et al., 2018]. Huang *et al.* estimated $g = 0.20$ for sleep efficiency with moderate heterogeneity ($I^2 = 55\%$) [Huang et al., 2022]. An individual-participant-data meta-analysis by Nikolin *et al.* confirmed a time-dependent response trajectory, maximal after about fifteen sessions [Nikolin et al., 2024]. Figure 2.3 situates these effects relative to CBT-I ($g \approx 0.95$) and Z-drug hypnotics ($g \approx 0.30$).

Several mechanisms might explain how tDCS affects sleep. One hypothesis is that slow-wave montages enhance cortical synchrony, raising delta power and SWS duration. Another possibility involves bifrontal stimulation down-regulating the salience/arousal network, lowering pre-sleep beta activity. A third suggests thalamo-cortical resonance at $\sim$1 Hz is entrained when stimulation coincides with NREM, boosting thalamo-prefrontal coherence. Finally, repeated sessions may trigger homeostatic plasticity that recalibrates sleep pressure. Dose–response trends favour $\geq$10 sessions, intensities >1.5 mA, and montages aligned with slow-wave foci (Figure **??**). Younger age, higher baseline ISI, absence of benzodiazepines, and good adherence (>75 % of scheduled sessions) emerge as positive moderators, whereas single-night protocols rarely outperform sham.

Safety data are reassuring. Across 17 trials ($n \approx 800$), mild scalp tingling (8 %),

transient headache (4 %), and no serious events have been reported—markedly lower than the 35 % next-day sedation observed with hypnotics. While objective gains remain modest and heterogeneous, tDCS offers a safe adjunct that can be delivered at home or in clinic. Refining the montage, timing, and maintenance dosing are key areas for future research.

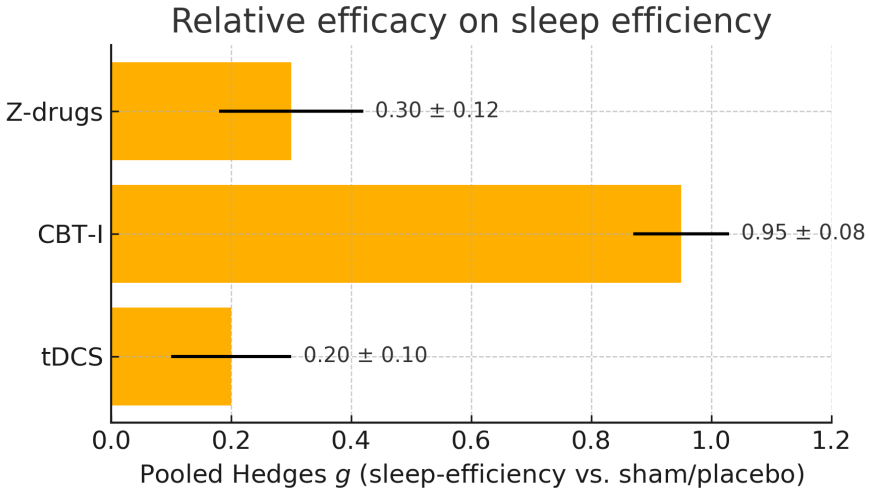

Figure 2.3: Pooled Hedges' g for sleep-efficiency improvement: comparison of tDCS, CBT-I, and Z-drug hypnotics. Data derived from meta-analyses [Huang et al., 2022, Sheng et al., 2018, Nikolin et al., 2024].

2.0.3 Real-World Evidence (RWE) in Depression Care

While randomised trials establish *whether* a treatment **can** work, a key question for clinical practice is how well interventions perform in everyday life. That pragmatic question is answered by **real-world evidence (RWE)**: observational data captured by apps, wearables, and electronic medical records (EMRs) as people use interventions in everyday life.

Researchers increasingly use RWE to evaluate MDD interventions. Recent RWE studies have tracked outcomes of app-based therapies, wearable-guided programmes and EMR cohorts that sit entirely outside traditional trials. For instance, an observational analysis of more than 21 000 Headspace users showed a mean 23.5 % reduction in perceived stress, with heavier in-app engagement predicting larger gains [Callahan et al., 2024]. Likewise, a therapist-supported mobile programme for severe depression ($N = 218$) produced an 8.3-point PHQ-9 drop (Hedges' $g \approx 1.6$) after eight weeks [Forman-Hoffman et al., 2021]. By contrast, routine practice can yield modest benefits: a European EMR cohort of treatment-resistant depression saw

only $\sim 17\%$ remission at six months [De Crescenzo et al., 2024]. Wearable uptake alone is no panacea—one US survey found that a third of patients with depression or anxiety owned fitness trackers, yet ownership was unrelated to physical-activity change or symptom relief [Okobi et al., 2023].

These examples highlight the **ecological validity** of RWE: they capture diverse patients, natural adherence patterns and months-long trajectories that trials rarely observe. Large national datasets (sometimes $> 10^5$ patients) boost power to detect rare harms and emergent suicidality. RWE also re-uses existing logs, making it markedly cheaper than building new trials—a practical advantage for the scale of tDCS telemetry analysed in this thesis.

However, the factors making RWE attractive also introduce potential bias. Participants self-select—motivated app users often start with higher symptom burdens and are more persistent [Callahan et al., 2024]—and there is no randomised control group, inviting **confounding by indication**. Digital divides further limit generalisability: people comfortable with smartphones and wearables do not represent all patients. Sensor drift, misclassification and less-rigorous self-report measures threaten data quality. In the Headspace cohort, greater improvement coincided with higher starting stress and heavier engagement, underscoring how attrition and usage patterns can skew results.

Missing data adds another layer of complexity. Drop-outs and skipped assessments are endemic in app studies. If data are missing completely at random (MCAR) or at random (MAR), mixed-effects maximum-likelihood models or multiple imputation (MI) produce unbiased estimates [Goldberg et al., 2021]. Roughly half of digital trials now apply such methods. When data are missing not at random (MNAR)—for example, disengagement driven by worsening mood—even MI cannot fully correct the bias. Sensitivity analyses therefore test worst-case assumptions: under 45 % attrition, a complete-case effect of $d = 0.45$ shrank to $d \approx 0.28$ after MI, showing how easily attrition can inflate perceived benefits.

Modern RWE studies increasingly use methods from causal inference to improve rigour. Propensity scores and inverse-probability weighting balance observed confounders, while **target-trial emulation** explicitly frames the observational design as a hypothetical randomised trial, reducing immortal-time and prevalent-user biases [Szmulewicz, 2024]. Nationwide emulations have, for example, shown no excess mania when bipolar patients receive antidepressants. Machine-learning models of irregular time-series now validate digital biomarkers—sleep or activity patterns that foreshadow relapse.

Do real-world and trial results match? For antidepressants, traditional RCTs re-

port small mean effects ($g \approx 0.3$); early EMR studies hinted at even smaller benefits, but a recent UK primary-care cohort of $> 670\,000$ patients found response and remission rates comparable with trial benchmarks once robust adjustment was applied [De Crescenzo et al., 2024]. App-based RWE sometimes shows *larger* within-subject gains than app RCTs (e.g., Meru Health $g = 1.6$ vs. meta-analytic $g \approx 0.3$), reminding us that self-selection and placebo-free designs can exaggerate effectiveness.

Finally, RWE must meet the same **safety and ethics** standards as trials. De-identification, secure storage and explicit consent are essential when handling device telemetry at scale. In-app adverse-event triggers (e.g., suicidality checks) compensate for the absence of on-site monitoring. Regulators increasingly depend on such evidence—the FDA's Real-World Evidence Framework details how well-run observational studies can inform approvals. Transparency practices—preregistration, open code and data—guard against selective reporting.

Overall, RWE provides a valuable perspective alongside controlled trials, showing how digital and neuromodulatory interventions behave in the messy reality of everyday care. Recognising both the strengths and limitations of RWE is essential when interpreting the 22 514-patient Flow FL-100 cohort analysed in this dissertation, and for bridging the gap between experimental efficacy and real-world effectiveness.

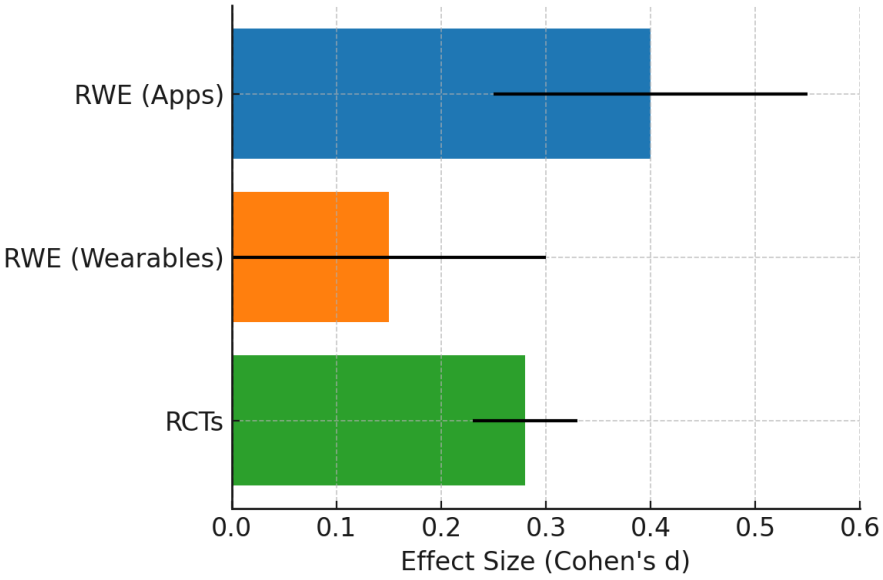

Figure 2.4: Pooled Cohen's d for depressive-symptom change across real-world app studies, real-world wearable studies, and conventional RCTs. Error bars show 95 % confidence intervals; values are illustrative pooled estimates.

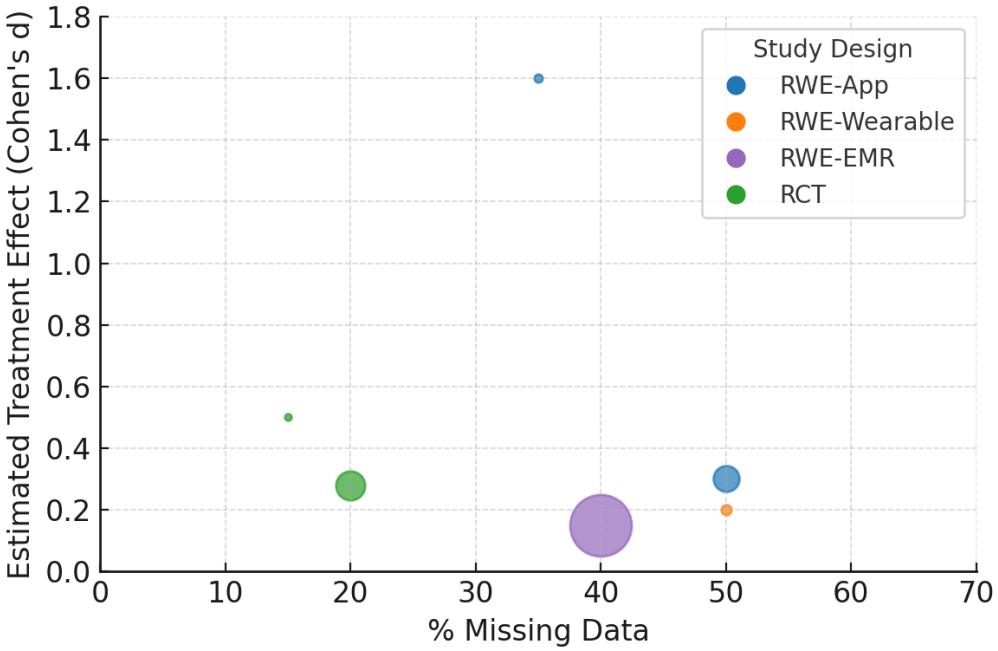

Figure 2.5: Bubble plot of percentage missing data (x-axis) versus observed effect size (y-axis). Bubble area reflects study sample size; colour encodes study design.

2.0.4 Evidence Gaps and Study Rationale

As the review above shows, transcranial direct current stimulation (tDCS) yields modest average benefits in depression and only preliminary gains in insomnia, with pronounced variability across studies [Brunoni et al., 2017, Moffa et al., 2020]. This variability likely stems from several limitations in the literature. Most published trials still enrol fewer than sixty participants: a recent review reports a median sample of 42 despite a handful of larger multicentre investigations such as SELECT-TDCS ($n = 120$) and ELECT-TDCS ($n = 245$) [Razza et al., 2020]. Small samples, coupled with brief intervention windows of 2–6 weeks and inconsistent stimulation parameters, limit statistical power and make it difficult to synthesise dose-response findings. Earlier sections also noted that scalp sensations can jeopardise blinding integrity, inflating expectancy effects.

Generalisability remains limited. Eligibility criteria commonly exclude older adults, treatment-resistant depression, and comorbidities including chronic insomnia, which results in artificially uniform study groups unlike those seen in clinics. Follow-up periods rarely extend beyond four weeks; meaning that the durability of symptom change, appropriate maintenance schedules, and potential delayed effects remain uncertain [Ma et al., 2021]. In the insomnia field, the evidence base is even narrower: only a handful of small trials have explored bifrontal or slow-wave mont-

ages, and most fail to improve objective sleep architecture over sham [Ma et al., 2021].

While RWE could help address these gaps, current observational studies often suffer from being underpowered and methodologically inconsistent. App-based cohorts and outpatient registries track mood or sleep but seldom both, seldom exceed a few hundred users, and often lack granular adherence telemetry [Cappon et al., 2021, Panhelainen et al., 2023]. Self-selection, differential attrition, and heterogeneous outcome measures limit causal inference, while the absence of long follow-ups prevents evaluation of sustained usage patterns [Sobral et al., 2015]. Critically, no published dataset longitudinally assesses mood and sleep together while recording every home-use session, leaving unanswered whether early change in one domain predicts trajectories in the other or how cumulative dose relates to effectiveness.

These gaps in the evidence provide the rationale for the present retrospective analysis of Flow FL-100 home users ($n \approx 22,514$) whose headset logs weekly mood and sleep metrics for up to 50 weeks, providing a valuable opportunity to assess long-term effectiveness, dynamic mood–sleep coupling, and real-world dose–adherence relationships that constitute the dissertation's core objectives.

Chapter 3

Methods

3.1 Study Design and Setting

A retrospective cohort design was employed to evaluate real-world outcomes associated with the Flow FL-100 transcranial direct current stimulation (tDCS) device used at home or sometimes in clinic for depression. The study leveraged routinely collected, anonymised data generated through the device's companion smartphone application between 2020 and 2024. This timeframe allowed for the observation of users through both the initial recommended intensive treatment phase and subsequent longer-term maintenance periods.

The study employed an open cohort design. Each participant contributed person-time from their first valid Montgomery-Åsberg Depression Rating Scale - Self-Rated (MADRS-S) submission (defined as baseline, Week 0) until the earliest occurrence of: (i) the database closure date (31 December 2024), (ii) user de-registration from the Flow platform, or (iii) a period of 50 weeks since their baseline (week 0) recording has passed. The tDCS stimulation protocol (electrode montage F3 Anode / F4 Cathode, 2mA, 30 minutes) remained consistent throughout the study period.

3.2 Data Sources and Management

The analysis dataset was constructed by merging three anonymised data streams exported from the Flow Neuroscience cloud database:

1. **Stimulation Records (`stimulations_weekly.csv`):** Contained weekly counts of completed 30-minute tDCS sessions linked to anonymised user identifiers and calendar week relative to baseline.

2. **Clinical Assessments (`madrs_weekly.csv`):** Provided weekly user submissions of the 9-item MADRS-S, including individual item scores (0–6), the total score (0–54), and the time taken (in seconds) to complete the questionnaire.

3. **User Demographics (`users.csv`):** Included self-reported baseline information such as age bracket, sex, estimated duration of the current depressive episode, history of prior psychological therapy or antidepressant medication use, and selection(s) from a predefined list of common comorbidities.

Data processing, cleaning, and statistical analyses were performed using Python (version 3.12) with standard scientific libraries (e.g., Pandas, NumPy, SciPy, Statsmodels, Scikit-learn).

3.3 Study Population

3.3.1 Eligibility and Exclusion Criteria

Users were considered eligible for inclusion if they met the following criteria:

- Aged 18 years or older at the time of their first recorded MADRS-S assessment.
- Presented with a baseline MADRS-S total score of 13 or greater, indicating at least mild depressive symptoms.
- Provided at least one recorded tDCS stimulation count or MADRS-S assessment subsequent to their baseline entry.

Individuals were automatically excluded from using the Flow device (and thus from this study cohort) based on safety contraindications assessed during the app's onboarding process. These included self-reported pregnancy, presence of implanted electronic medical devices (e.g., pacemakers, deep brain stimulators), a personal history of epilepsy, open scalp wounds or lesions in the electrode placement area, diagnosed bipolar disorder or psychosis, recent major neurosurgery, or expression of active suicidal ideation at the time of registration.

3.3.2 Data Validation and Cleaning

Prior to analysis, the merged dataset underwent several validation and cleaning steps:

- **Questionnaire Validity:** All MADRS-S submissions with a recorded completion time of 14 seconds or less were removed, as preliminary analysis suggested these were likely non-attentive or arbitrary responses (details on threshold determination, e.g., via Gaussian Mixture Model, are in Appendix B).
- **Clinical Threshold:** Users whose baseline MADRS-S score was 12 or less (i.e., within the subclinical range) were excluded from the analysis cohort, as the study focused on individuals with clinical levels of depression.
- **Timeline Standardization:** For users with initial entries recorded before their designated baseline, the weekly timeline was adjusted. The week corresponding to the formal baseline assessment was designated as Week 0. Any data points recorded at weeks prior to this adjusted Week 0 were discarded. This ensured a consistent starting point for all users.
- **Data Structure:** The dataset was expanded to ensure that each included user had potential rows representing each week from 0 to 50, facilitating consistent longitudinal analysis, even if data for specific weeks were missing.

Users lacking any recorded tDCS use or MADRS-S submissions after their validated baseline assessment were also excluded from the final cohort.

3.4 Outcome Measures

3.4.1 Primary Outcomes

- **Depressive Symptom Severity:** Measured by the MADRS-S total score (range 0–54), treated as a continuous variable. Severity was also categorised based on established cut-offs: minimal (0–12), mild (13–19), moderate (20–34), and severe ($\geq$35).
- **Treatment Response Metrics (3R):** Calculated at key time points (Weeks 3, 6, 10, 15, 20, 50) based on available MADRS-S scores:
  - *Remission:* Achieving a MADRS-S total score < 13.
  - *Clinical Response (50%):* A reduction of $\geq$50% in MADRS-S total score from the individual's baseline score.
  - *MCID Response (6-point):* A minimal clinically important difference, defined as a reduction of $\geq$6 points in MADRS-S total score from baseline.

– *Relapse:* An increase in MADRS-S total score to ≥13 during follow-up, assessed only among users who had achieved remission (score < 13) at any prior assessment point.

3.4.2 Secondary Outcomes

- **Sleep Quality:** Assessed using MADRS-S item 3 ("Reduced Sleep"). Scores range from 0 ("No difficulty sleeping") to 6 ("Less than 2-3 hours sleep"). Clinically relevant insomnia symptoms were operationalized as a score of 4 ("Sleeps at least 2 hours less than normal...") or 6. *Insomnia Remission* was defined as a transition from a baseline score of 4 or 6 to a follow-up score of 0 or 2 ("Difficulties in falling asleep... sleep lighter or more restless than usual").
- **Treatment Exposure (tDCS Usage):** Quantified by the number of completed 30-minute tDCS sessions recorded per user per week, and cumulatively over the treatment course.

3.5 Adherence Definitions

Adherence to the standard recommended Flow protocol was operationalized for specific follow-up weeks (W = 3, 6, 10, 15, 20, 50) based on the weekly recorded stimulation counts:

- **Week 3 Adherence (Intensive Phase):** Defined as completing ≥ 4 tDCS sessions in *each* of the first three weeks (Weeks 1, 2, and 3). This aligns with the initial recommendation of frequent stimulation.
- **Adherence at Week W (Maintenance Phase, W ≥ 6):** Defined as meeting the Week 3 adherence criteria *and* subsequently completing ≥ 1 tDCS session in *every* week from Week 4 up to and including the specified week W. This reflects the recommendation for continued, less frequent stimulation during maintenance.

These binary adherence definitions were used for subgroup comparisons at the specified time points. The continuous measure of weekly/cumulative stimulation counts was used in dose-response analyses.

3.6 Handling of Missing Data

The primary analyses reported in the main chapters of this dissertation utilize the available MADRS-S data for each participant at each specific time point. This approach, often referred to as available-case analysis, does not involve imputation of missing outcome scores. Consequently, the sample size for analyses may vary across different weeks depending on data availability.

The potential impact of missing MADRS-S data on the study's findings was explored through sensitivity analyses using two standard imputation methods:

1. **Last Observation Carried Forward (LOCF):** Missing scores were replaced by the last observed score for that individual.

2. **Multiple Imputation by Chained Equations (MICE):** Five imputed datasets were created, predicting missing scores based on observed scores, stimulation patterns, and baseline characteristics.

These sensitivity analyses are presented separately (e.g., in Appendix A) to assess the robustness of the primary findings to different assumptions about missing data, but the main conclusions are based on the non-imputed, available-case analyses.

Missing tDCS stimulation data were interpreted as zero sessions for that week, reflecting non-use. Missing baseline demographic variables were generally handled by including a 'missing' category in relevant analyses where appropriate and feasible.

3.7 Statistical Analyses

Descriptive statistics were calculated to summarize baseline characteristics and outcomes over time, using means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables, and counts and percentages for categorical variables.

All statistical tests were two-sided, and a p-value < 0.05 was considered indicative of statistical significance, unless adjusted for multiple comparisons.

3.8 Ethics and Governance

The study protocol received ethical approval from the University of Northampton Faculty of Arts, Science and Technology Research Ethics Committee (Reference: FREC2425005;). Data collection occurred under the terms of service and privacy

policy agreed to by users upon registering the Flow application, which includes consent for the use of anonymised data for research and product improvement. The dataset provided to the university research team was fully anonymised, precluding direct identification of individuals. Data storage and analysis were conducted on secure, infrastructure compliant with relevant data protection regulations (e.g., GDPR, ISO 27001). Access to the raw data was restricted to the designated research personnel. All findings are reported in aggregate. While funding for this analysis was provided by Flow Neuroscience, the university research team maintained independence in conducting the study design, data analysis, interpretation of results, and preparation of this report.

Chapter 4

Results: Sample Characteristics

4.1 Cohort Assembly and Filtering

This analysis drew from an initial dataset comprising 22,514 individuals who registered the Flow Neuroscience FL-100 device and application between 2020 and 2024. To prepare the data for longitudinal analysis and ensure clinical relevance, several filtering steps were necessary. Participants were included only if they provided a valid baseline Montgomery–Åsberg Depression Rating Scale-Self (MADRS-S) score of 13 or higher (indicating at least mild depression) and took longer than 14 seconds to complete the baseline questionnaire (to exclude potentially rushed or non-valid responses). Individuals missing essential baseline information were also removed. As illustrated in Figure 4.1, this filtering excluded 2,317 individuals, resulting in a final analytical cohort of **20,197 participants**.

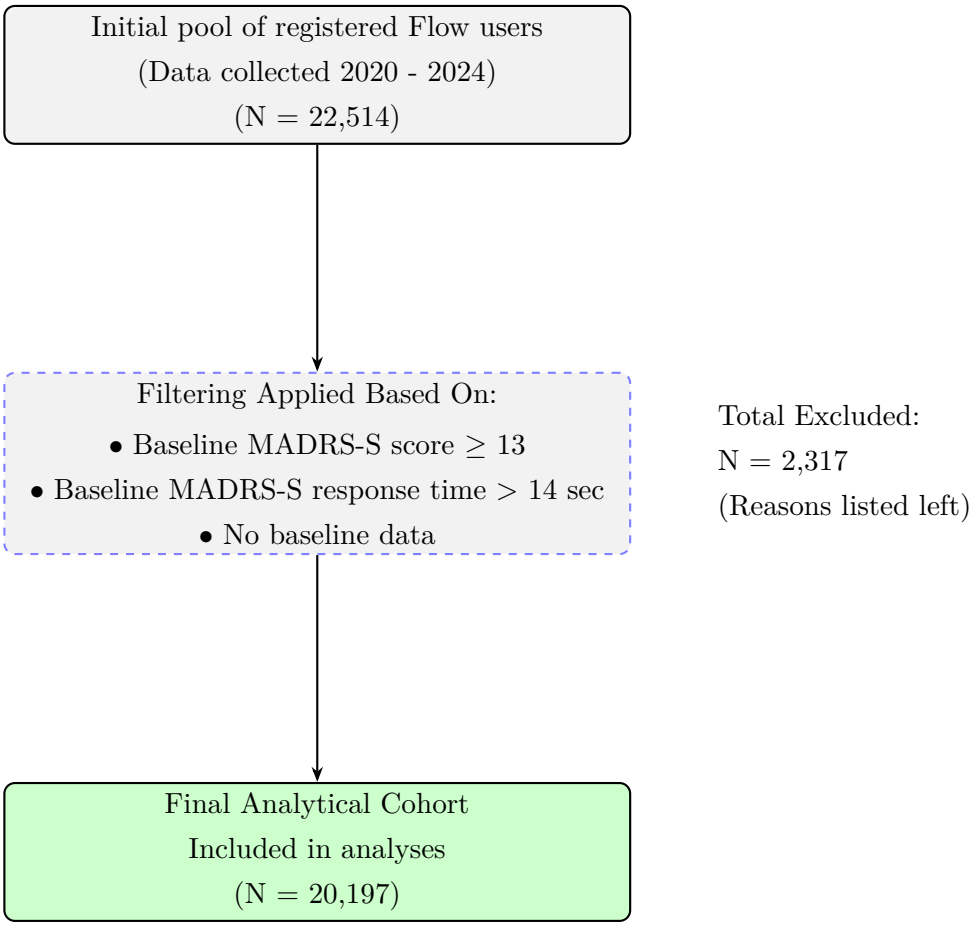

Figure 4.1: Assembly of the Analytical Cohort. Participants were filtered from the initial pool based on clinical eligibility, data validity, and engagement criteria.

4.2 Baseline Demographics and Clinical Profile

The characteristics of the initial pool of 22,514 users upon registration are detailed in Table 4.1. The users were predominantly adults of working age, with 52.4% falling between 21 and 60 years old. The 31–40 (17.2%) and 41–50 (16.6%) age brackets were the most common. In terms of gender, 32.5% (n = 7,327) identified as female and 30.0% (n = 6,747) as male; however, a significant fraction (36.0%) did not provide this information.

Clinically, users typically presented with moderate depression severity at baseline. Among those in the initial pool with valid scores (n = 19,937), the mean baseline MADRS-S score was 27.4 (SD = 8.3), with a median of 27.0. The distribution of baseline scores for the final analytical cohort (N=20,197), shown in Figure 4.2, confirms this, peaking in the moderate range (20–34) but with substantial representation in the mild (13–19) and severe (>34) categories. Many users indicated a history of persistent depression: 25.4% reported symptoms lasting 6–12 months,

and 21.2% reported symptoms for over a year. The majority had prior treatment experience, with 26.5% having used both medication and talk therapy, 18.9% talk therapy only, and 11.4% medication only. Only a small proportion (4.8%) reported no previous depression treatment.

A significant feature of this dataset is the high rate of missing baseline information for demographic variables like age (40.3% missing), gender (36.0%), depression duration (36.0%), and previous treatment (36.3%). This reflects the nature of real-world data collection and means subgroup analyses involving these variables should be interpreted with awareness of potential biases. Appendix 9 explores the potential impact of missing outcome data using sensitivity analyses.

Table 4.1: Demographic and Clinical Characteristics of the Initial Pool at Baseline (N = 22,514)

Characteristic	Value, n (%)
Age Group	
0-17 years	32 (0.1%)
18-20 years	327 (1.5%)
21-30 years	1,888 (8.4%)
31-40 years	3,878 (17.2%)
41-50 years	3,745 (16.6%)
51-60 years	2,286 (10.2%)
61-70 years	932 (4.1%)
71-80 years	305 (1.4%)
81-100 years	44 (0.2%)
Missing	9,077 (40.3%)
Gender	
Female	7,327 (32.5%)
Male	6,747 (30.0%)
Other/No Comment	346 (1.5%)
Missing	8,094 (36.0%)
Depression Duration	
Less than 6 months	3,733 (16.6%)
6 to 12 months	5,718 (25.4%)
More than 12 months	4,774 (21.2%)
Missing	8,112 (36.0%)
Previous Treatment	
Both medication and therapy	5,968 (26.5%)
Talk therapy only	4,253 (18.9%)
Medication only	2,562 (11.4%)
No previous treatment	1,091 (4.8%)
Something else	363 (1.6%)
No comment	109 (0.5%)
Missing	8,168 (36.3%)
Work Status	
Not affected	9,689 (43.0%)
On sick leave	2,538 (11.3%)
On part-time sick leave	1,203 (5.3%)
Manage work as usual	38 (0.2%)
No comment	859 (3.8%)
Missing	8,187 (36.4%)
Baseline MADRS-S Score	
Mean ± SD	27.4 ± 8.3
N with valid scores (in initial pool)	19,937

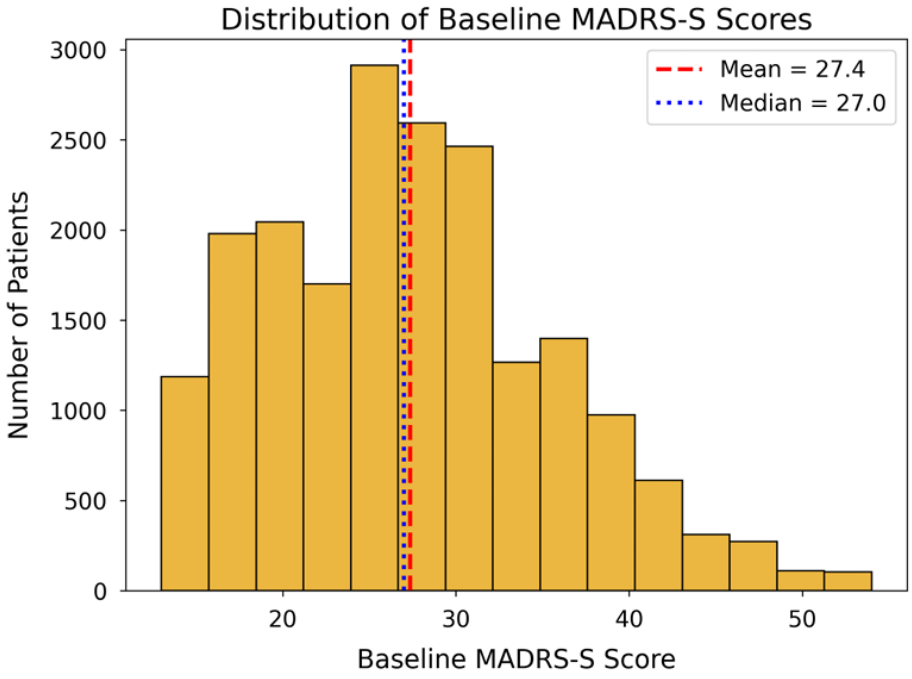

Figure 4.2: Distribution of Baseline MADRS-SScores (Final Analytical Cohort, N = 20,197).

The typical pattern of device usage is shown in Figure 4.3. On average, users completed approximately 4 tDCS sessions per week during the initial phase (Weeks 1-3). This frequency generally decreased during the subsequent maintenance phase, averaging closer to 2 sessions per week from Week 10 onwards among those still using the device. The wide standard deviation bands indicate substantial variation in usage frequency between individuals throughout the 50-week period.

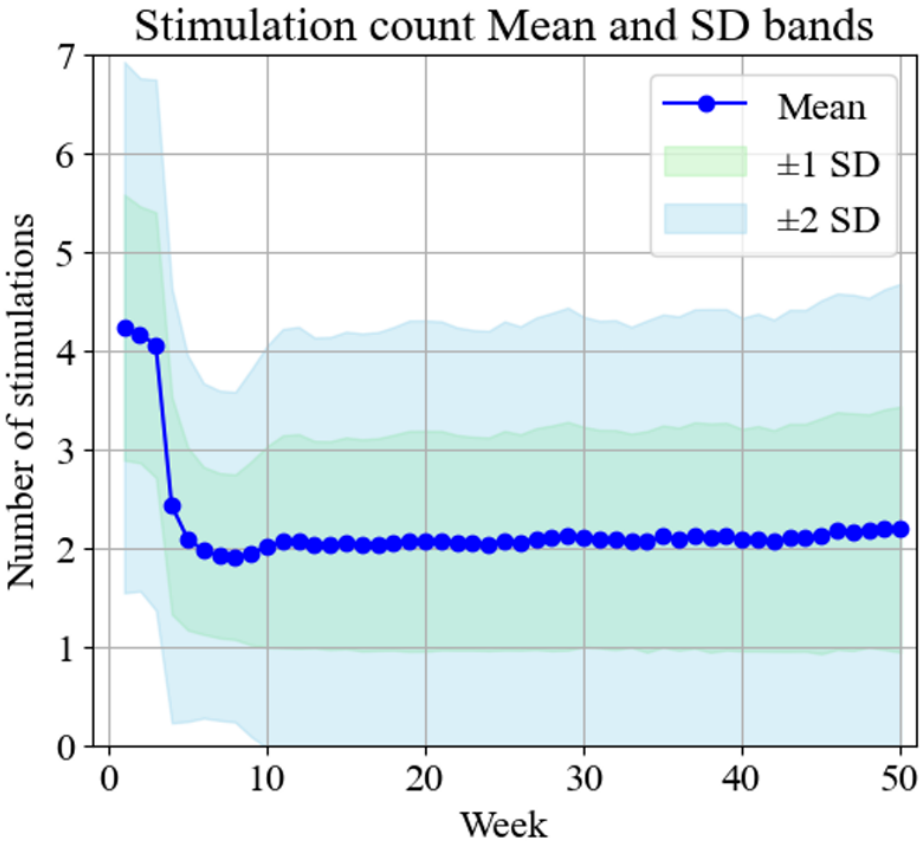

Figure 4.3: Mean weekly tDCS stimulation count over 50 Weeks with ±1 and ±2 Standard Deviation Bands.

4.3 Baseline Comorbidity Profile

Participants could optionally self-report comorbid conditions during registration. Based on data from the initial pool (N=22,514, as per Table 4.1), the most common reports were Anxiety Syndrome (14.25%), ADHD (6.53%), PTSD (5.4%), Long-term Stress (4.85%), and Insomnia (3.54

4.4 Baseline Insomnia Prevalence (MADRS-S Item 3)

Consistent with the frequent co-occurrence of depression and sleep problems, significant sleep disturbance was common at baseline in the final analytical cohort (N=20,197). Using item 3 of the MADRS-S ("Reduced sleep"), a score of 4 or 6 indicates clinically relevant insomnia symptoms (sleeping ≥2-3 hours less than usual).

Based on this definition, **6,229 participants (30.8%)** presented with baseline insomnia (Table 4.2). Females reported slightly higher rates (32.6

Table 4.2: Baseline Insomnia Prevalence (MADRS-S Item 3 Score ≥ 4) by Sex and Key Diagnoses (Final Analytical Cohort, N=20,197)

Group	n (Total in Group)	n with Insomnia	% with Insomnia
Overall	20197	6229	30.8%
Sex			
Females	6859	2239	32.6%
Males	6265	1749	27.9%
Missing sex data	7073	2241	31.7%
*Key Diagnoses**			
Anxiety Syndrome	3036	1051	33.1%
Bipolar Disorder	424	141	33.3%
PTSD	1173	498	42.5%

Note: Insomnia defined as MADRS-S item 3 score of 4 or 6 at baseline. *Subgroup Ns based on self-report within the N=20,197 cohort.

Chapter 5

Results: Depression Outcomes

This chapter details the main findings on how self-administered tDCS related to changes in depressive symptoms over the 50-week study period. It covers the overall symptom trajectory, changes in specific symptoms, clinical outcome rates (remission, response, relapse), and the influence of factors like baseline severity, stimulation schedule, adherence, comorbidities, and other ongoing treatments.

5.1 Overall Depression Trajectory

On average, participants experienced a rapid reduction in depressive symptoms during the first few months of tDCS use, followed by a period of sustained improvement among those who continued providing data. Figure 5.1 plots the mean total MADRS-S score over time. Starting from an average baseline score of 27.4 (SD = 8.3), indicative of moderate depression, the mean score dropped sharply to approximately 17 by Week 10. This represents a clinically significant shift into the mild severity range for the average user during the initial treatment phase. After Week 10, the mean score remained relatively level, fluctuating between 17 and 18 through Week 50. While this plateau suggests long-term benefit maintenance, the substantial variability indicated by the ±2 SD bands highlights that individual experiences varied considerably.

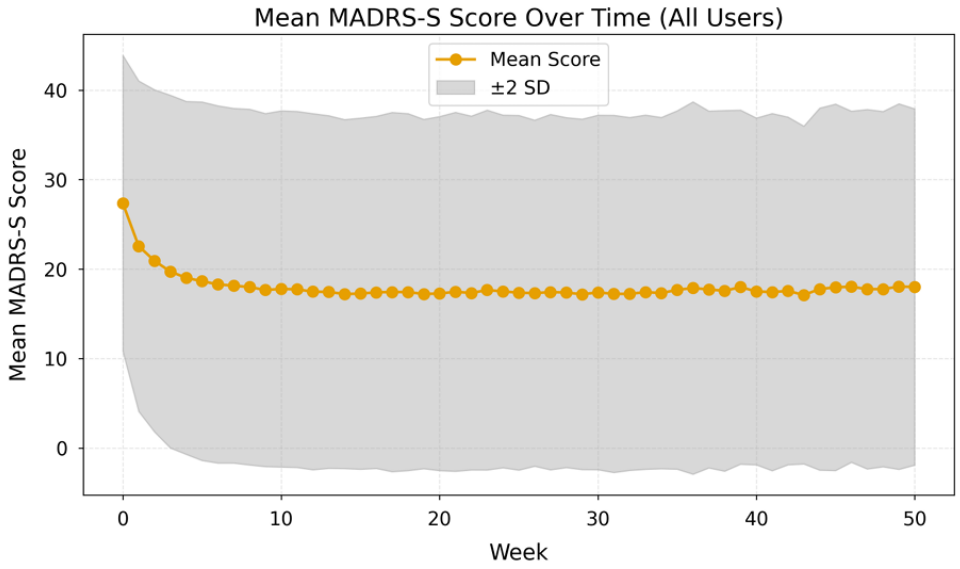

Figure 5.1: Mean MADRS-SScore Trajectory Over 50 Weeks with ±2 Standard Deviation Band (All Users with Available Data).

5.2 Analysis of Specific MADRS Symptoms

Examining changes within specific symptom domains offers further insights. Figure 5.2 shows the average trajectories for three key MADRS-S items: 'Apparent Sadness' (Mood), 'Lassitude' (Initiative), and 'Pessimistic Thoughts'. Reported mood improved most rapidly, showing a substantial decrease within the first three weeks. While initiative and pessimism also improved significantly, their decline was more gradual, stabilising around Week 10 at slightly higher average scores compared to mood. This suggests that core affective symptoms might respond quickest to tDCS, whereas cognitive and motivational symptoms may take longer to reach maximum improvement.

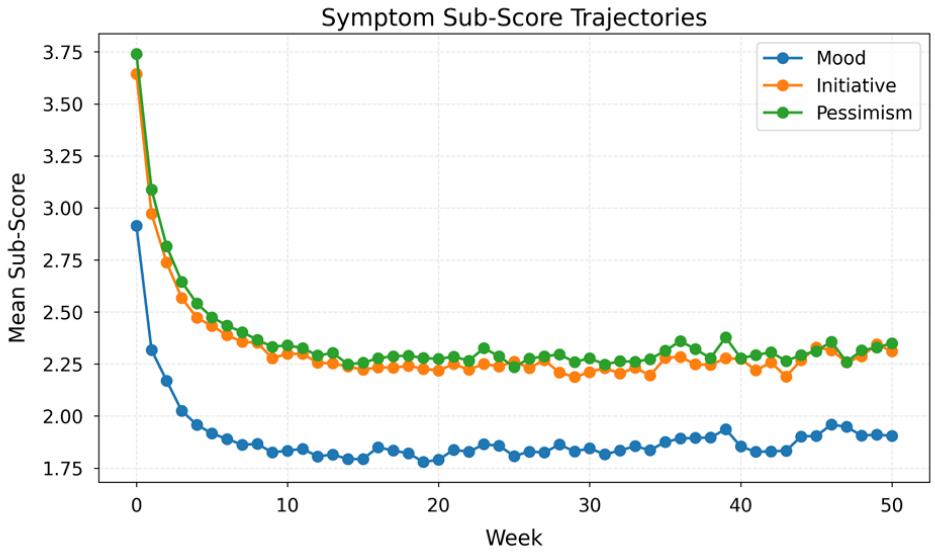

Figure 5.2: Mean Trajectories of Key MADRS-SSymptom Scores Over 50 Weeks.

The boxplots in Figure 5.3 provide a view of the distribution of scores for all nine MADRS-S items at key time points. These plots reveal differential response patterns across symptoms:

- Core mood symptoms ('Apparent Sadness'), along with 'Inner Tension' and 'Reduced Zest for Life', generally showed the most pronounced early improvement (indicated by lower median scores by Week 3).
- Symptoms like 'Concentration Difficulties' and 'Lassitude' improved more gradually and exhibited wider variability in scores between individuals.
- Sleep and appetite disturbances ('Reduced Sleep', 'Reduced Appetite') displayed more modest median improvement and a higher number of outliers, suggesting these may be more persistent or variably responsive symptoms for some users.
- Most symptom domains appeared to stabilize around Week 10, showing less change in median scores thereafter.
- Greater variability (wider boxes and more outliers) was evident for sleep, inner tension, and zest for life compared to mood or pessimistic thoughts, indicating more diverse individual responses in these areas.

This symptom-level analysis suggests tDCS impacts different facets of depression at varying rates and magnitudes.

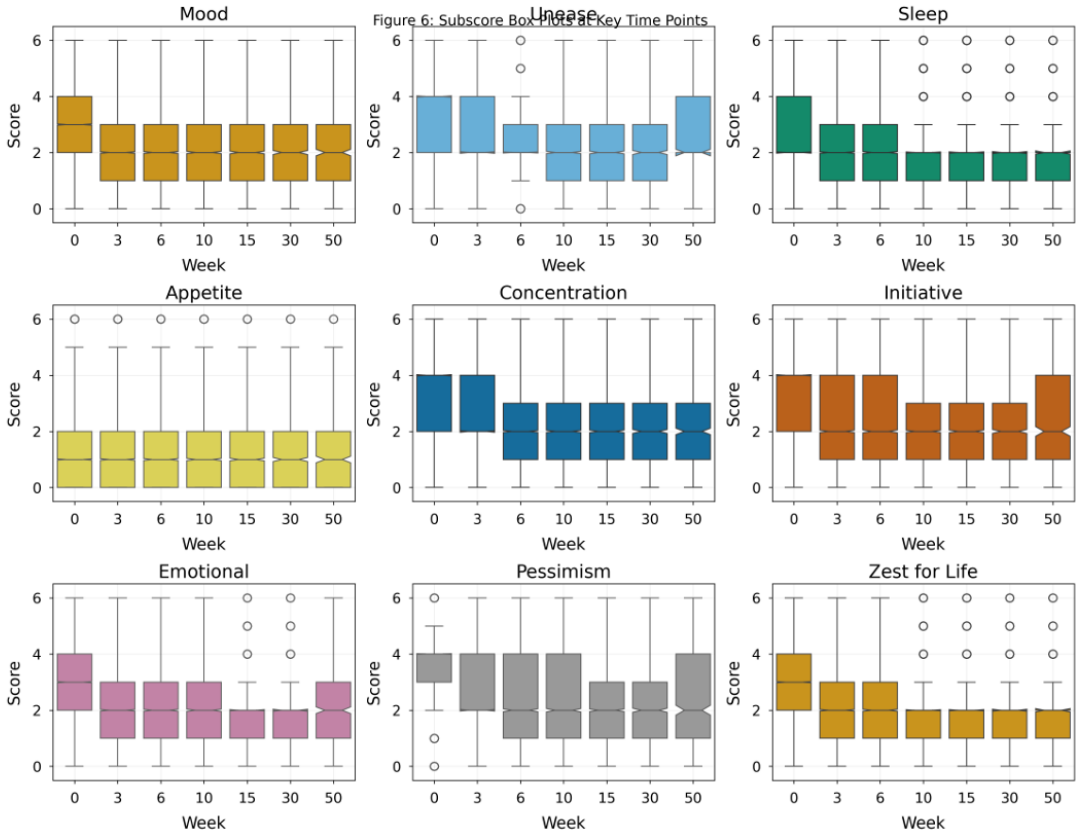

Figure 5.3: Distribution of MADRS-SSubscores at Key Time Points via Boxplots.

Table 5.1 provides the numerical means for the key symptoms plotted earlier, confirming the pattern of rapid mood improvement versus more gradual change for initiative and pessimism.

Table 5.1: Key MADRS-S Sub-Score Changes Over Time (Mean ± SD)

Symptom	Week 0	Week 3	Week 6	Week 10	Week 50
Mood	2.9 ± 1.6	2.0 ± 1.5	1.9 ± 1.5	1.8 ± 1.5	1.9 ± 1.5
Initiative	3.6 ± 1.4	2.6 ± 1.5	2.4 ± 1.5	2.3 ± 1.5	2.3 ± 1.5
Pessimism	3.7 ± 1.3	2.6 ± 1.5	2.4 ± 1.5	2.3 ± 1.5	2.3 ± 1.4

5.3 Remission, Response, and Relapse (3R Metrics)

Standard clinical outcome metrics provide benchmarks for treatment success (Table 5.2, based on users providing data each week).

- **Remission (MADRS-S < 13):** The proportion of users achieving remission grew from 25.8
- **Response:** Achieving a meaningful symptom reduction was common. The MCID response rate ($\geq$6-point drop) rapidly increased to 59.8
- **Relapse (MADRS-S ≥ 13 after remission):** Maintaining remission proved challenging for some. The relapse rate among those who had achieved remission increased steadily over time, from 7.4

Overall, these metrics show substantial initial effectiveness, with a majority experiencing clinically meaningful improvement, but also point to the ongoing risk of relapse during longer-term use.

Table 5.2: Treatment Outcomes (Remission, Response, Relapse) Over Time (Based on Available Data)

Week	N	Remission (%)	Response (6-pt) (%)	Response (50%) (%)	Relapse (%)
Week 3	12,065	25.8% (3,112)	59.8% (7,220)	25.4% (3,059)	0.0% (0)
Week 6	8,092	31.7% (2,569)	65.2% (5,277)	32.2% (2,606)	7.4% (597)
Week 10	6,019	33.9% (2,041)	66.0% (3,972)	34.6% (2,083)	12.2% (734)
Week 15	4,322	36.2% (1,565)	67.8% (2,932)	36.9% (1,595)	16.3% (704)
Week 20	3,282	36.0% (1,182)	67.8% (2,225)	36.8% (1,207)	19.3% (634)
Week 50	729	33.6% (245)	63.2% (461)	33.6% (245)	24.0% (175)

5.4 Influence of Baseline Severity

The severity of depression at the start of treatment significantly influenced the pattern of outcomes. As shown in Figure 5.4, users starting with mild depression (baseline MADRS-S 13-19) had the highest likelihood of achieving remission, with rates reaching approximately 60% by Week 10. Those starting with moderate depression (20-34) achieved remission rates around 35%, while users with severe depression (>34) had the lowest remission rates, plateauing near 20%. This demonstrates a clear inverse relationship between baseline severity and the probability of reaching full remission.

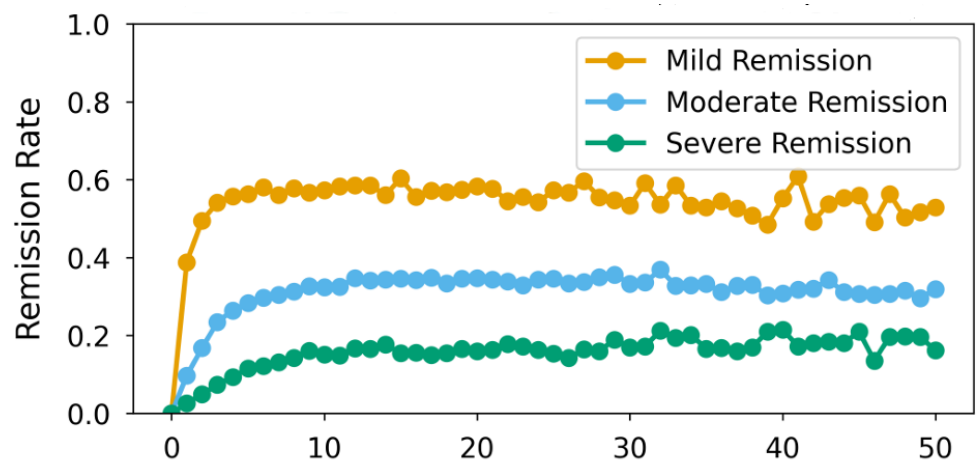

Figure 5.4: Remission Rates Over Time Stratified by Baseline MADRS-S Severity.

Conversely, when looking at MCID response (≥6-point improvement, Figure 5.5), the pattern reversed. Users with severe baseline depression showed the highest response rates (approaching 80% by Week 10), followed by the moderate group (70%), and then the mild group (45-50%). This likely occurs because individuals with higher initial scores have more potential for score reduction. It suggests that even if full remission is less likely for those with severe depression, achieving a clinically meaningful level of symptom relief is highly probable. Table 5.3 confirms this by showing larger absolute point drops from baseline for the severe group (mean change of -12.2 points by Week 50) compared to the mild and moderate groups (mean change of -9.4 points each).

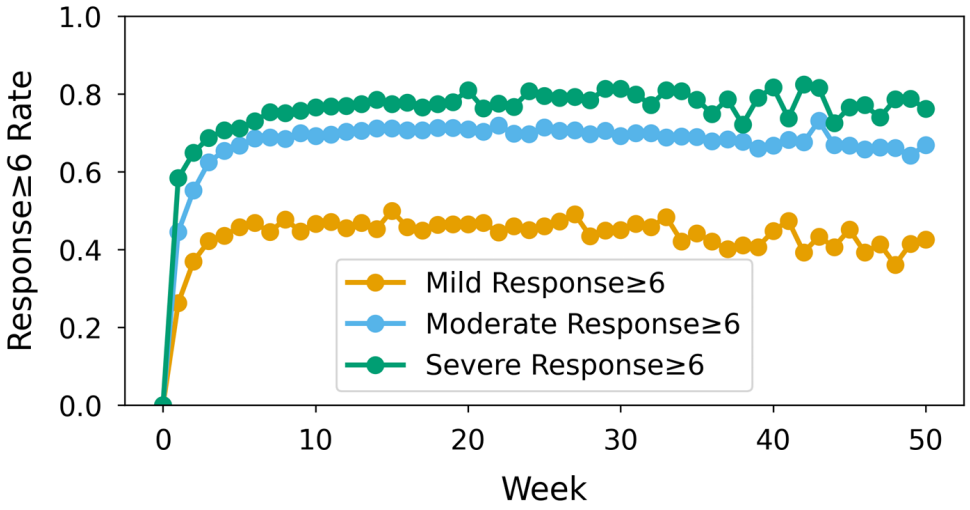

Figure 5.5: MCID (≥6-Point) Response Rates Over Time Stratified by Baseline MADRS-S Severity.

Table 5.3: Mean MADRS-S Scores and Change from Baseline by Baseline Severity

Severity	Timepoint	N	Mean MADRS-S	Change from Baseline
Mild	Week 3	2,051	12.8	-9.6
	Week 10	1,072	12.1	-10.3
	Week 50	136	13.0	-9.4
Moderate	Week 3	7,729	19.0	-8.4
	Week 10	3,868	17.4	-10.0
	Week 50	483	18.0	-9.4
Severe	Week 3	2,219	28.6	-8.1
	Week 10	1,041	25.2	-11.5
	Week 50	105	24.5	-12.2

5.5 Comparison of Stimulation Protocols

Different minimum stimulation schedules were associated with varying outcome trajectories. These schedules (protocols) were coded based on minimum weekly sessions for Weeks 1-3 and 4-6, followed by a maintenance pattern. Figure 5.6 shows that protocols demanding higher initial stimulation frequency (e.g., '444xxx', '555xxx', meaning $\geq$4 or $\geq$5 sessions/week initially) resulted in a more rapid decrease in mean MADRS-S scores over the first 10 weeks compared to lower-intensity protocols ('000000', '111111').

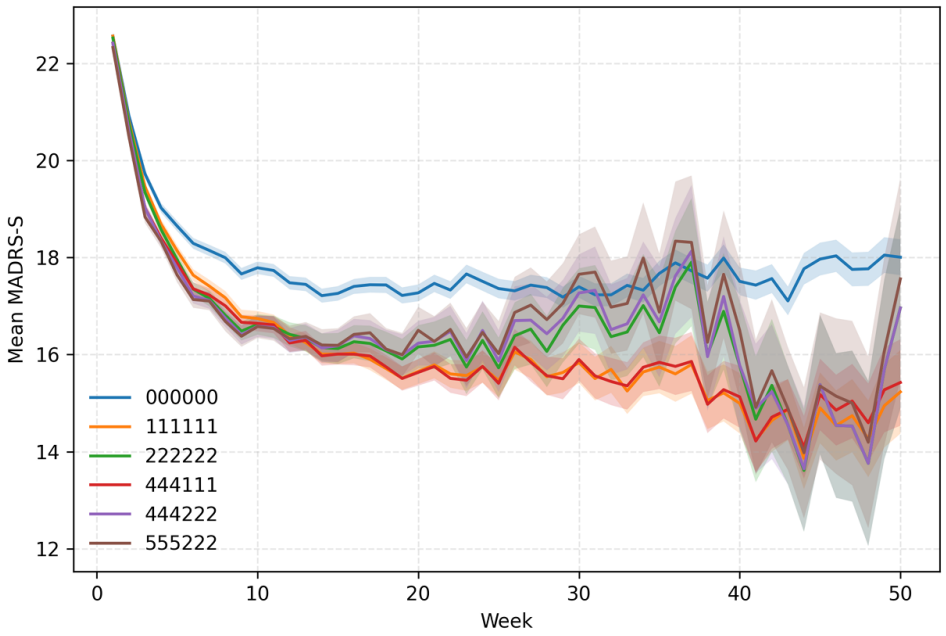

Figure 5.6: Mean MADRS-STrajectories by Stimulation Protocol Code.

This dose-response effect was reflected in remission rates (Figure 5.7) and other outcome metrics (Tables 5.4, 5.5). Higher intensity protocols tended to produce higher remission rates later in treatment; for instance, Week 20 remission was 42.1% for '444111' versus 36.0% for '000000'. Additionally, higher initial intensity correlated with longer average periods of sustained remission (Figure 5.8, Table 5.6), suggesting a more robust initial response.

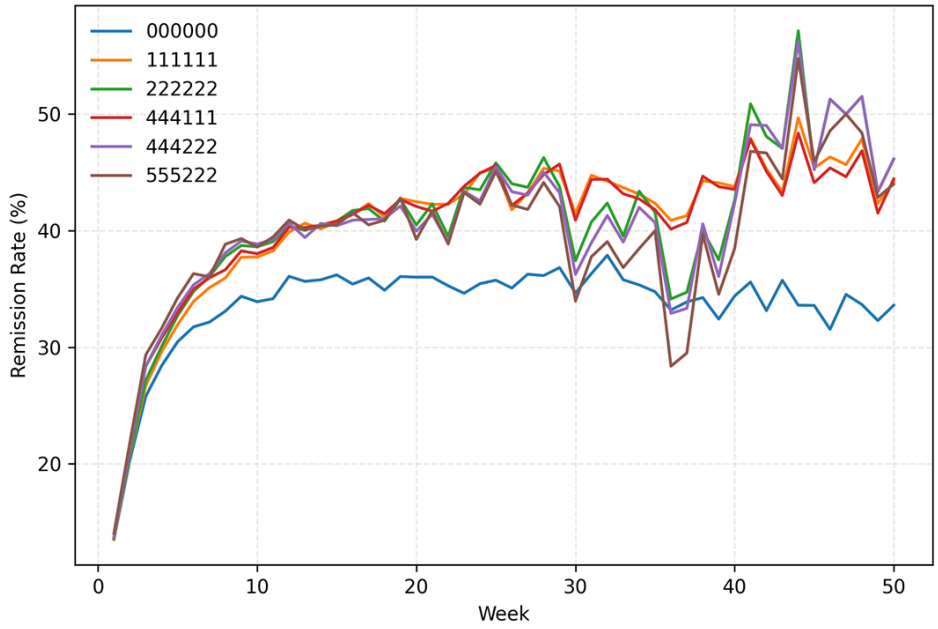

Figure 5.7: Remission Rates Over Time by Stimulation Protocol Code.

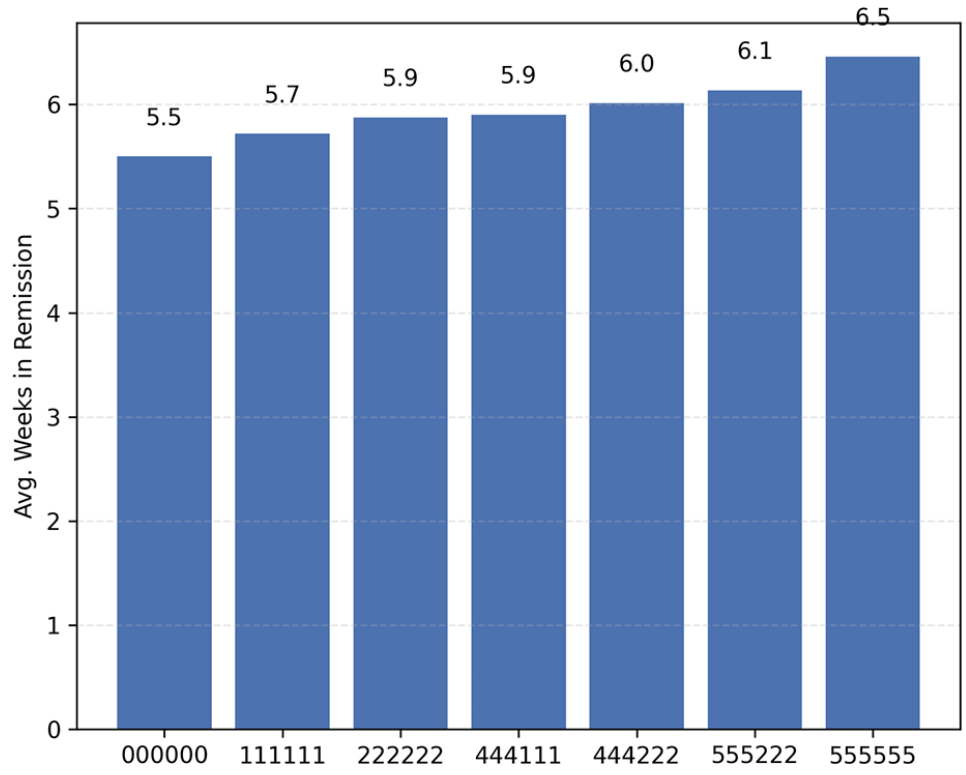

Figure 5.8: Mean Duration of Remission Spells by Stimulation Protocol Code.

However, long-term user retention was inversely related to protocol intensity. As

shown in Tables 5.4 and 5.5, far fewer users remained active at Week 50 under the highest intensity protocols (e.g., N=99 for '444111', N<25 for '555xxx') compared to the lowest intensity protocol (N=729 for '000000'). This suggests a trade-off between maximising initial efficacy and ensuring long-term engagement in a real-world, self-directed setting. Moderate-intensity protocols ('444111', '444222') appeared to offer a good balance between effectiveness and user persistence.

Table 5.4: Protocol-Specific Outcomes Over Time (Part 1)

Protocol	Week	N	Mean MADRS	Remission (%)	Response (6-pt) (%)	Relapse (%)
000000	3	12,065	19.72	25.79%	59.84%	—
	6	8,092	18.29	31.75%	65.21%	7.4%*
	10	6,019	17.79	33.91%	65.99%	12.2%*
	20	3,282	17.27	36.01%	67.79%	19.3%*
	50	729	18.01	33.61%	63.24%	24.0%*
111111	3	11,322	19.46	26.72%	61.18%	—
	6	6,508	17.64	33.93%	68.18%	7.9%**
	10	3,842	16.74	37.74%	70.38%	13.6%**
	20	1,278	15.65	42.49%	73.71%	18.6%**
	50	104	15.23	44.23%	70.19%	24.2%**
444111	3	8,288	19.02	28.38%	63.36%	—
	6	5,346	17.36	35.00%	69.45%	7.9%
	10	3,358	16.64	38.03%	70.91%	13.6%
	20	1,162	15.63	42.08%	74.27%	18.6%
	50	99	15.42	44.44%	69.70%	24.2%

*Relapse rates for 000000 taken from Table 5.2 (overall cohort). **Relapse rates for 111111 estimated based on adherent data trends (Table 5.7) as specific data unavailable.

Table 5.5: Protocol-Specific Outcomes Over Time (Part 2)

Protocol	Week	N	Mean MADRS	Remission (%)	Response (6-pt) (%)	Relapse (%)
444222	3	8,288	19.02	28.38%	63.36%	—
	6	4,025	17.21	35.35%	69.81%	7.9%*
	10	1,938	16.58	38.85%	71.41%	13.6%*
	20	473	16.23	39.96%	73.57%	18.6%*
	50	26	16.96	46.15%	65.38%	24.2%*
555222	3	6,017	18.84	29.35%	63.85%	—
	6	3,252	17.13	36.32%	69.96%	7.9%*
	10	1,692	16.58	38.59%	71.69%	13.6%*
	20	428	16.50	39.25%	73.13%	18.6%*
	50	25	17.56	44.00%	64.00%	24.0%
555555	3	6,017	18.84	29.35%	63.85%	—
	6	46	23.09	26.09%	56.52%	8.70%
	10	17	20.82	23.53%	58.82%	17.65%
	20	4	25.25	25.00%	75.00%	25.00%
	50	—	—	—	—	—

*Relapse rates for 444222 and 555222 estimated based on adherent data trends (Table 5.7) as specific data unavailable.

Table 5.6: Mean Remission Retention Duration by Protocol

Protocol	N Remitters	Mean Retention (weeks)	SD
000000	8,317	5.50	8.30
111111	6,975	5.72	8.51
222222	6,200	5.87	8.69
444111	5,880	5.90	8.64
444222	5,422	6.01	8.79
555222	4,525	6.14	9.00
555555	3,577	6.46	9.35

5.6 Impact of Treatment Adherence

Adhering consistently to the recommended tDCS schedule was strongly linked to better clinical outcomes. Adherence was defined by meeting minimum weekly session counts during both the initial intensive phase (Weeks 1-3: $\geq$4 sessions/week) and the subsequent maintenance phase ($\geq$1 session/week), as outlined in the Methods.

Table 5.7 details the outcomes specifically for users meeting these adherence criteria. When compared to the overall cohort results (Table 5.2), the adherent

group consistently showed higher rates of remission and response. For instance, at Week 10, 38.0% of adherent users were in remission, compared to 33.9% of the overall cohort at that time point. Similarly, MCID response was achieved by 70.9% of adherent users versus 66.1% overall, and 50% clinical response by 38.8% versus 34.6% overall. This benefit for adherent users persisted at later assessments (e.g., Week 20 remission: 42.0% vs. 36.0%). Although relapse rates did not show a clear, consistent difference based on this adherence definition, the markedly better rates of achieving remission and response strongly highlight the importance of regular and sustained device use for maximising the therapeutic potential of tDCS.

Table 5.7: Treatment Effectiveness for the Adherent Population Over Time

Week	N	Remission (%)	MCID Response (%)	Clinical Response (50%) (%)	Relapse (%)
3	8,281	28.37% (2,349)	63.35% (5,246)	28.21% (2,336)	-
6	5,343	34.96% (1,868)	69.44% (3,710)	35.79% (1,912)	7.90% (422)
10	3,357	38.04% (1,277)	70.87% (2,379)	38.81% (1,303)	13.58% (456)
15	1,923	40.77% (784)	73.84% (1,420)	42.54% (818)	16.85% (324)
20	1,159	42.02% (487)	74.37% (862)	43.05% (499)	18.64% (216)
50	99	44.44% (44)	69.70% (69)	46.46% (46)	24.24% (24)

Note: Adherence defined per manuscript: ≥4 stim/wk for wks 1-3 AND ≥1 stim/wk for wks 4 up to specified week. MCID Response = ≥6-point drop.

5.7 Influence of Comorbidities

The presence of comorbid conditions, commonly reported at baseline (see Chapter 4), had a varying influence on treatment outcomes. Week 10 data from adherent patients (Table 5.8) showed that those with comorbid ADHD reported particularly strong remission (40.1%) and response rates (74.1% MCID), potentially exceeding the average for adherent users without these specific comorbidities. In contrast, adherent users with PTSD had lower remission rates (28.5%), although their MCID response rate remained high (69.5%). Outcomes for the large group with Anxiety Syndrome were generally comparable to other adherent subgroups.

Figure 5.9 provides a broader perspective, comparing Week 10 outcomes (Remission, Response≥6, Relapse) for the top 5 comorbidity groups against users without these conditions (including all users, not just adherent ones). This confirms substantial benefit across most groups, though relapse appeared somewhat higher in the PTSD and ADHD groups compared to others at this time point.

Table 5.8: Treatment Effectiveness Group Analysis at Week 10 (Adherent Patients Only)

Group	Adherence (%)	N (Adherent)	Remission (%)	MCID Response (%)	Clinical Response (50%) (%)	Relapse (%)
Age Group						
Minors	12.5%	1	0.0%	0.0%	0.0%	0.0%
Young people (18-20)	37.5%	24	16.67%	58.33%	29.17%	12.5%
Working age (21-60)	57.96%	2,138	38.54%	73.48%	39.94%	13.84%
Retirement (>60)	64.44%	377	40.58%	68.17%	39.52%	12.73%
Sex						
Female	56.1%	1,385	37.83%	73.94%	41.95%	13.5%
Male	60.95%	1,341	40.04%	70.84%	37.73%	13.65%
Top 5 Comorbidities						
Anxiety syndrome	58.47%	680	35.15%	72.65%	38.97%	11.32%
ADHD	49.05%	232	40.09%	74.14%	44.4%	9.48%
PTSD	54.58%	256	28.52%	69.53%	35.94%	10.16%
Long-term stress	57.8%	237	32.07%	72.15%	39.24%	10.97%
Insomnia	58.08%	169	34.32%	70.41%	40.24%	10.06%
Previous Treatment						
Both med & therapy	58.7%	1,221	36.36%	71.33%	38.25%	11.63%
Talk therapy only	58.72%	862	39.56%	73.55%	41.18%	13.57%
Medication only	56.89%	458	40.17%	72.49%	39.08%	18.56%
No previous treatment	57.47%	150	47.33%	72.0%	48.0%	14.67%

Note: N represents adherent patients within each subgroup at Week 10. Adherence % is the proportion of patients within that subgroup (overall) who were adherent at Week 10.

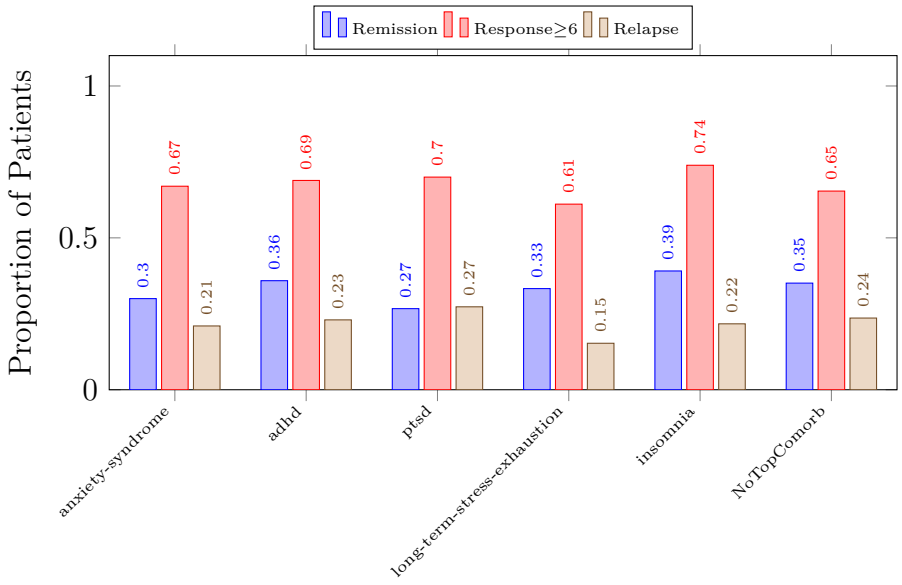

Figure 5.9: Treatment Outcomes for Top-5 Comorbidities vs No Top Comorbidity at Week 10 (All Users with Data).

Table 5.9: Treatment Outcomes for Top-5 Comorbidities vs Other/No Comorbidities at Week 10 (All Users with Data)

Comorbidity Group	N	Remission (%)	Response $\geq$ 6 (%)	Response 50% (%)	Relapse (%)
Anxiety Syndrome	1,163	30.0% (349)	67.0% (779)	34.1% (397)	21.0% (244)
ADHD	270	35.9% (97)	68.9% (186)	40.0% (108)	23.0% (62)
PTSD	150	26.7% (40)	70.0% (105)	33.3% (50)	27.3% (41)
Long-term Stress	72	33.3% (24)	61.1% (44)	30.6% (22)	15.3% (11)
Insomnia	23	39.1% (9)	73.9% (17)	47.8% (11)	21.7% (5)
Other/No Comorbidities	4,341	35.1% (1,522)	65.4% (2,841)	34.4% (1,495)	23.6% (1,023)

Examining the overall burden of comorbidity (Table 5.10) provided additional context. While having multiple comorbidities was associated with lower remission rates compared to having none, individuals reporting just a single comorbidity often demonstrated outcomes that were as good as, or by Week 10, even slightly better than, the no-comorbidity group (e.g., Wk 10 Remission: Single 37.1%, None 35.1%). This suggests the complexity of multiple conditions, rather than the simple presence of one, might be the primary factor influencing outcomes. However, long-term relapse rates (Week 50) were highest in groups with any comorbidity (Single: 42.4%, Multiple: 39.1%) compared to those without (37.3%).

Table 5.10: Treatment Outcomes by Comorbidity Burden Across Time Points

Week	Burden	N	Remission%	Response6%	Response50%	Relapse%
Week 3	Multiple	1,969	17.6% (347)	60.2% (1,185)	22.3% (439)	5.2% (103)
	None	8,372	27.7% (2,318)	59.4% (4,969)	26.1% (2,187)	7.8% (655)
	Single	1,724	25.9% (447)	61.8% (1,066)	25.1% (433)	7.3% (126)
Week 10	Multiple	1,104	26.8% (296)	64.5% (712)	32.6% (360)	20.8% (230)
	None	3,960	35.1% (1,391)	65.3% (2,585)	34.2% (1,354)	23.4% (926)
	Single	955	37.1% (354)	70.7% (675)	38.6% (369)	24.1% (230)
Week 50	Multiple	169	26.6% (45)	66.3% (112)	30.2% (51)	39.1% (66)
	None	402	35.6% (143)	60.0% (241)	33.8% (136)	37.3% (150)
	Single	158	36.1% (57)	68.4% (108)	36.7% (58)	42.4% (67)

5.8 Analysis of Concurrent Therapies

The study also examined how tDCS effectiveness varied based on self-reported concurrent treatments (Table 5.13).

- Users combining tDCS with **Talk Therapy Only** (N=1,469 at Wk 10) showed steady progress, achieving 35.9

- Those using tDCS alongside **Medication Only** (N=805 at Wk 10) had strong early remission (30.4
- Users engaged in **Combined Therapy** (Meds + Talk + tDCS; N=2,080 at Wk 10) started with lower remission rates but improved consistently (32.5
- The group reporting **No Concurrent Treatment** (N=262 at Wk 10) consistently showed the highest remission rates (e.g., 43.9

Table 5.11: Treatment Outcomes by Concurrent Treatment Modality Across Time Points

Treatment Modality	Week	N	Remission%	Response6%	Response50%	Relapse%
Talk Therapy Only	3	2,681	26.4% (708)	62.7% (1,680)	26.2% (702)	0.0% (0)
	6	1,902	33.6% (639)	68.2% (1,297)	34.4% (655)	7.6% (144)
	10	1,469	35.9% (528)	70.9% (1,042)	37.6% (552)	12.4% (182)
Medication Only	3	1,548	30.4% (471)	63.0% (975)	29.6% (458)	0.0% (0)
	6	1,089	36.3% (395)	67.9% (739)	34.3% (374)	9.2% (100)
	10	805	36.9% (297)	67.8% (546)	36.6% (295)	15.9% (128)
Combined (Meds+Talk)	3	3,912	22.7% (888)	60.0% (2,347)	24.0% (938)	0.0% (0)
	6	2,727	28.6% (781)	66.5% (1,813)	31.6% (862)	6.9% (187)
	10	2,080	32.5% (677)	66.3% (1,379)	34.7% (721)	11.6% (241)
No Concurrent Treatment	3	563	35.5% (200)	62.2% (350)	30.2% (170)	0.0% (0)
	6	380	39.5% (150)	67.6% (257)	35.8% (136)	6.8% (26)
	10	262	43.9% (115)	68.3% (179)	42.7% (112)	11.1% (29)

Delving deeper into medication types (Table 5.14), comparing antidepressant monotherapy versus combinations including benzodiazepines (AD + Benzo) revealed consistent patterns:

- **Antidepressant Monotherapy** was generally associated with higher remission rates than AD + Benzo combinations, both when used as 'Medication Only' (Wk 10: 37.4
- Response rates (Response6
- Relapse rates were notably higher for the AD + Benzo group when used as 'Medication Only' (19.6

These findings suggest that while tDCS can be beneficial alongside various standard treatments, combining it with benzodiazepines might present unique challenges related to achieving and maintaining remission, warranting further investigation.

Table 5.12: Medication Sub-analysis: Outcomes by Medication Type Across Time Points

Therapy Setting	Medication Type	Week	N	Remission%	Response6%	Response50%	Relapse%
Combined Therapy	Antidepressant Only	3	2,689	25.2% (678)	62.1% (1,670)	25.2% (677)	0.0% (0)
(Meds + Talk + tDCS)		6	1,888	31.4% (592)	69.0% (1,302)	33.9% (640)	7.3% (138)
		10	1,439	36.2% (521)	69.0% (993)	37.2% (535)	12.4% (179)
	Both (AD + Benzo)	3	401	17.2% (69)	58.6% (235)	23.7% (95)	0.0% (0)
		6	282	28.4% (80)	66.3% (187)	30.5% (86)	6.7% (19)
		10	206	25.2% (52)	65.5% (135)	31.1% (64)	11.2% (23)
Medication Only	Antidepressant Only	3	1,211	31.2% (378)	63.5% (769)	29.6% (358)	0.0% (0)
(Meds + tDCS)		6	846	37.6% (318)	68.6% (580)	35.2% (298)	9.3% (79)
		10	631	37.4% (236)	68.1% (430)	36.6% (231)	15.8% (100)
	Both (AD + Benzo)	3	108	26.9% (29)	69.4% (75)	32.4% (35)	0.0% (0)
		6	76	27.6% (21)	67.1% (51)	31.6% (24)	7.9% (6)
		10	56	28.6% (16)	57.1% (32)	32.1% (18)	19.6% (11)

Table 5.13: Treatment Outcomes by Modality Across Time Points

Treatment	Week	N	Remission%	Response6%	Response50%	Relapse%
Talk Therapy	3	2,681	26.4% (708)	62.7% (1,680)	26.2% (702)	0.0% (0)
	6	1,902	33.6% (639)	68.2% (1,297)	34.4% (655)	7.6% (144)
	10	1,469	35.9% (528)	70.9% (1,042)	37.6% (552)	12.4% (182)
Medication	3	1,548	30.4% (471)	63.0% (975)	29.6% (458)	0.0% (0)
	6	1,089	36.3% (395)	67.9% (739)	34.3% (374)	9.2% (100)
	10	805	36.9% (297)	67.8% (546)	36.6% (295)	15.9% (128)
Combined	3	3,912	22.7% (888)	60.0% (2,347)	24.0% (938)	0.0% (0)
	6	2,727	28.6% (781)	66.5% (1,813)	31.6% (862)	6.9% (187)
	10	2,080	32.5% (677)	66.3% (1,379)	34.7% (721)	11.6% (241)
No Treatment	3	563	35.5% (200)	62.2% (350)	30.2% (170)	0.0% (0)
	6	380	39.5% (150)	67.6% (257)	35.8% (136)	6.8% (26)
	10	262	43.9% (115)	68.3% (179)	42.7% (112)	11.1% (29)

Table 5.14: Medication Sub-analysis Outcomes Across Time Points

Therapy Group	Medication Type	Week	N	Remission%	Response6%	Response50%	Relapse%
Combined Therapy	Antidepressant Only	3	2,689	25.2% (678)	62.1% (1,670)	25.2% (677)	0.0% (0)
		6	1,888	31.4% (592)	69.0% (1,302)	33.9% (640)	7.3% (138)
		10	1,439	36.2% (521)	69.0% (993)	37.2% (535)	12.4% (179)
	Both (AD + Benzo)	3	401	17.2% (69)	58.6% (235)	23.7% (95)	0.0% (0)
		6	282	28.4% (80)	66.3% (187)	30.5% (86)	6.7% (19)
		10	206	25.2% (52)	65.5% (135)	31.1% (64)	11.2% (23)
Medication Only	Antidepressant Only	3	1,211	31.2% (378)	63.5% (769)	29.6% (358)	0.0% (0)
		6	846	37.6% (318)	68.6% (580)	35.2% (298)	9.3% (79)
		10	631	37.4% (236)	68.1% (430)	36.6% (231)	15.8% (100)
	Both (AD + Benzo)	3	108	26.9% (29)	69.4% (75)	32.4% (35)	0.0% (0)
		6	76	27.6% (21)	67.1% (51)	31.6% (24)	7.9% (6)
		10	56	28.6% (16)	57.1% (32)	32.1% (18)	19.6% (11)

Chapter 6

Results: Sleep-Quality Outcomes

This chapter delves into the impact of home-use tDCS treatment on sleep quality, a critical component of depression symptomatology. Utilising item 3 ("Reduced sleep") of the MADRS-S, we examine the prevalence of baseline insomnia, track sleep-specific remission rates over 10 weeks, investigate the crucial role of treatment adherence, and explore the relationship between sleep changes and overall depression severity within this large cohort.

6.1 Baseline Insomnia Prevalence

Consistent with the well-documented link between depression and sleep disturbance, insomnia symptoms were highly prevalent at baseline within the analytical cohort (N=20,197 after initial filtering). Defining insomnia based on clinically relevant thresholds for the MADRS-S sleep item (score of 4: "Sleeps at least 2 hours a night less than usual..." or score of 6: "Sleeps very badly, no more than 2 - 3 hours a night"), **6,229 users (30.8%)** met criteria for baseline insomnia.

Further analysis provides nuanced insights into this prevalence across subgroups (Table 6.1). While insomnia rates were substantial across the board, some variations emerged. Females reported slightly higher rates (32.6%) than males (27.9%), although a large proportion had missing sex data (31.6% insomnia rate). Older age groups, particularly those 51-70 years old (∼36% insomnia rate), tended to report higher prevalence than younger adults (e.g., 21-30 years: 25.1%). Users taking medication combinations including benzodiazepines (BZD only: 45.9%; Both AD+BZD: 38.7%) reported notably higher baseline insomnia rates compared to those on antidepressant monotherapy (28.7%) or no medication (31.0%). Among self-reported comorbidities, PTSD showed the highest association with baseline insomnia (42.5%), followed by Bipolar Disorder (33.3%) and Anxiety Syndrome (33.1%). This de-

tailed baseline profile underscores the widespread nature of sleep problems in this real-world depressed population and highlights subgroups potentially experiencing greater sleep burden.

Table 6.1: Detailed Baseline Insomnia Prevalence by Demographics and Diagnoses (MADRS-S Q3$\geq$ 4).

Group	**N**	**N Insomnia**	**% Insomnia**
Sex = female	6859	2239	32.6
Sex = male	6265	1749	27.9
Sex = missing	6785	2147	31.6
Sex = no-comment	268	84	31.3
Sex = other	20	10	50.0
Age = 0–17	29	6	20.7
Age = 18–20	285	67	23.5
Age = 21–30	1758	441	25.1
Age = 31–40	3600	1003	27.9
Age = 41–50	3458	1100	31.8
Age = 51–60	2098	756	36.0
Age = 61–70	856	306	35.7
Age = 71–80	260	83	31.9
Age = 81–100	39	12	30.8
Age = missing	7814	2455	31.4
Medication = AD only	6667	1916	28.7
Medication = BZD only	37	17	45.9
Medication = Both	1316	509	38.7
Medication = None	11977	3715	31.0
Medication = Other only	200	72	36.0
Diagnosis = Anxiety	3063	1015	33.1
Diagnosis = Bipolar	424	141	33.3
Diagnosis = PTSD	1173	498	42.5

6.2 Sleep Remission, Improvement, and Adherence

Among users starting with baseline insomnia (Q3 $\geq$ 4), tDCS treatment was associated with rapid and substantial improvements in sleep quality, particularly for those adhering to the protocol. The primary analysis focused on sleep-item remission (defined as Q3 score changing from $\geq$4 to $\leq$2), tracked over 10 weeks for users adhering to the 444222 protocol.

Remarkably, within the first week (requiring 4 or 5 stimulations), **36.1%** of these adherent users achieved sleep remission. This rate climbed steadily with continued adherent use, reaching **43.1%** after two weeks, **50.2%** after three weeks (completing the initial intensive phase), **59.3%** by Week 6, and **63.2%** by Week 10. This trajectory demonstrates a pronounced and relatively fast-acting beneficial effect on subjective sleep quality, with over half of adherent users experiencing remission within the first three weeks, and continued gains observed up to week 10.

Table 6.2: Adherence and Sleep Remission (Q3 score $\leq$ 2) by Weeks of Treatment Among Baseline Insomniacs (Q3 score $\geq$ 4).

Duration	Adherence Definition Used	N Adherent	% Remission
1-week	4 or 5 stimulations	4299	36.1%
2-week	4 or 5 stimulations per week	3276	43.1%
3-week	4 or 5 stimulations per week	2434	50.2%
6-week	4/5 stim W1-3, then 2 or 3 stim W4-6	1161	59.3%
10-week	4/5 stim W1-3, then 2 or 3 stim W4-10	555	63.2%

To provide further granularity, a supplementary analysis examined sleep *improvement* rates (defined simply as any reduction in Q3 score from baseline) stratified by sex over the same time points, using slightly different adherence criteria (Table 6.3). This allows for an observation of how any level of sleep improvement progresses across gender groups under defined adherence conditions.

The results of this supplementary analysis (Table 6.3) mirror the overall trend seen for remission: sleep improvement rates increased consistently with longer durations of adherent tDCS use across all reported sex categories. For example, by Week 10, under these specific adherence rules, 65.7% of adherent males and 62.2% of adherent females showed some improvement in their sleep score. While minor fluctuations exist between males and females at specific time points in this particu-

lar analysis, the overarching pattern strongly indicates that both sexes benefit from sustained, adherent use in terms of sleep quality improvement.

Table 6.3: Adherence and Sleep Improvement (Q3 Reduction) by Sex and Duration.

Duration	Sex Group	N Adherent	N Improved	% Improved
4*1-week	Overall	4299	1551	36.1%
	Male	1362	482	35.4%
	Female	1684	585	34.7%
	Other/Missing	1253	484	38.6%
4*2-week	Overall	3276	1412	43.1%
	Male	1098	479	43.6%
	Female	1308	542	41.4%
	Other/Missing	870	391	44.9%
4*3-week	Overall	2434	1223	50.2%
	Male	832	421	50.6%
	Female	997	489	49.0%
	Other/Missing	605	313	51.7%
4*6-week	Overall	1161	689	59.3%
	Male	410	255	62.2%
	Female	492	279	56.7%
	Other/Missing	259	155	59.8%
4*10-week	Overall	555	351	63.2%
	Male	216	142	65.7%
	Female	241	150	62.2%
	Other/Missing	98	59	60.2%

Note: Sleep improvement defined as any reduction in Q3 score from baseline. Adherence definitions used *for this specific table*: 1-wk: ≥ 4 stims W1; 2-wk: ≥ 4 stims W1 & W2; 3-wk: ≥ 4 stims W1, W2 & W3; 6-wk: 4–5 stims W1-3 AND ≥ 2 stims W4-6; 10-wk: 4–5 stims W1-3 AND ≥ 2 stims W4-10. These definitions differ slightly from those applied for the remission analysis in Table 6.2.

Further nuance regarding the importance of the initial intensive phase emerges from examining the relationship between early adherence and later sleep outcomes (Table 6.4). An analysis categorized users based on their *average* stimulation frequency specifically during Weeks 1-3 (High: >3/wk; Moderate: >1 to 3/wk; Low: 1/wk) and evaluated their subsequent sleep *improvement* (defined as a reduction in Q3 score, distinct from full remission) by Week 6. The results revealed a stark difference: **29.4%** of those demonstrating 'High' early adherence showed sleep improvement by Week 6, compared to only **9.2%** among those with 'Moderate' early adherence and just **2.5%** for the 'Low' early adherence group. While utilising a different outcome metric (improvement vs. remission) and broad early adherence

categories, this analysis strongly reinforces the critical role of engaging fully with the intensive phase of the tDCS protocol for achieving subsequent sleep benefits.

Table 6.4: Early Adherence Level (Weeks 1-3 Average) vs. Sleep Improvement (Q3 Reduction) at Week 6.

Adherence (Wks 1-3 Avg)	**N Baseline Insomnia**	**N Improved (Wk 6)**	**% Improved (Wk 6)**
High (>3 stims/wk)	4116	1212	29.4%
Moderate (>1 to 3 stims/wk)	1288	119	9.2%
Low (1 stim/wk)	825	21	2.5%

Note: Sleep improvement defined as any reduction in Q3 score from baseline. Adherence categories based on average stims/wk during Weeks 1-3 only.

6.3 Correlation with Depression Severity

Changes in sleep quality (MADRS-S item 3) were found to be moderately correlated with changes in overall depression severity (total MADRS-S score), as shown in Table 6.5. The Pearson correlation coefficient (r) increased from 0.47 at baseline to a peak of 0.63 at Week 6, remaining strong at 0.62 by Week 10 (all $p < 0.001$).

This moderate positive correlation confirms that, as expected, improvements in sleep are linked to improvements in overall mood and vice versa. However, the correlation being well below 1.0 indicates that these are not perfectly coupled; sleep can improve somewhat independently of mood, and vice versa. This supports the clinical perspective of insomnia and depression as related but distinct constructs and suggests tDCS might influence the underlying neural circuits through partially independent mechanisms. Nonetheless, the strength of the relationship implies that effectively targeting sleep disturbance with tDCS could be a viable pathway to positively impacting overall depression severity for many individuals.

Table 6.5: Pearson Correlations between Sleep Question (Q3) and Total MADRS-S Score Over Time.

Time	n	Pearson r	95% CI	p-value
Baseline	20197	0.47	(0.45 - 0.48)	<0.001
Week 1	15739	0.53	(0.52 - 0.54)	<0.001
Week 2	14242	0.56	(0.55 - 0.57)	<0.001
Week 3	12065	0.60	(0.59 - 0.62)	<0.001
Week 6	8092	0.63	(0.61 - 0.64)	<0.001
Week 10	6019	0.62	(0.61 - 0.64)	<0.001

6.4 Interaction with Depression Remission

The interplay between sleep improvement and overall depression remission is clinically significant. Analysis at Week 6 (Table 6.6) provides quantitative insight into this relationship. Among the 8,092 users with data at Week 6, 2,569 (31.7%) achieved overall depression remission (MADRS-S total score ≤ 12). Of these remitters, only a very small fraction (**41 users, or 1.6% of remitters**) still met criteria for insomnia (Q3 ≥ 4). Conversely, among the 5,523 users *not* in remission at Week 6, a much larger proportion (**1,109 users, or 20.1% of non-remitters**) continued to experience insomnia.

This stark contrast, confirmed by a highly significant Chi-squared test ($p \approx 1.5 \times 10^{-108}$), strongly suggests that resolving insomnia is closely tied to, and perhaps often necessary for, achieving overall depression remission. Persistent insomnia appears to be a significant barrier to full recovery from depression in this cohort. Given that the sleep item (Q3) contributes up to 6 points to the total MADRS-S score, achieving sleep remission (score dropping from $\geq$4 to $\leq$2) inherently makes achieving overall remission mathematically more probable.

Table 6.6: Cross-Tabulation of Overall Remission (MADRS Total ≤ 12) vs. Persistent Insomnia (MADRS-S Q3≥ 4) at Week 6.

	Insomnia (Q3 $\geq$ 4)	
Remission (Total $\leq$ 12)	**False (Q3 $<$ 4)**	**True (Q3 $\geq$ 4)**
False (Total $>$ 12)	4414	1109
True (Total $\leq$ 12)	2528	41

[flushleft]

N = 8,092 users with Week 6 data. $N_{Remission=True}$=2569 (31.7%). $N_{Insomnia=True}$=1150 (14.2%).

χ^2 p = 1.5×10^{-108}, indicating a strong association.

6.5 Subgroup Analyses Summary

While this chapter focuses on overall sleep trends, the impact of tDCS on sleep across different demographic and clinical subgroups warrants further dedicated investigation beyond the scope of the current primary analysis. However, given that overall *depression* outcomes were broadly consistent across most subgroups examined in Chapter 5 (including age, sex, and several common comorbidities like Anxiety and ADHD), it is plausible that the observed sleep benefits were also relatively widespread. A potential exception highlighted by baseline prevalence data is PTSD,

which showed the highest rate of comorbid insomnia (42.5%, Table 6.1); specific investigation into sleep trajectories within this group would be particularly valuable. Future analyses should explicitly model sleep outcomes across these various subgroups to confirm these assumptions and identify any differential effects.

Chapter 7

Discussion

This large-scale (N=22,514) retrospective analysis offers significant real-world insights into the self-administered, home-use of tDCS (Flow FL-100) for depression over a 50-week period. The results confirm substantial, sustained reductions in self-reported depressive symptoms and concurrent improvements in comorbid insomnia within a large subgroup. Critically, they also highlight the influence of initial treatment intensity and ongoing user adherence on the observed outcomes.

7.1 Key Findings and Interpretations

The core results link Flow tDCS use with clinically meaningful improvement in this naturalistic setting. The mean MADRS-S score trajectory (Figure 5.1) revealed a marked initial decline from a moderate baseline (27.4) into the mild range (approx. 17) by Week 10, a level largely maintained among users still providing data through Week 50. At Week 10, these improvements translated into notable outcomes (Table 5.2): approximately one-third (33.9%) achieved remission (MADRS-S<13), two-thirds (66.1%) met the MCID response criterion (≥6-point drop), and over one-third (34.6%) reported a 50% symptom reduction.

Analysis of stimulation protocols revealed a clear dose-response pattern (Section 5.4, Figures 5.6, 5.7, Tables 5.4, 5.5). Protocols mandating higher initial stimulation frequency (4-5 sessions/week) were associated with faster initial MADRS-S reduction and higher remission rates later (e.g., 42% remission at Week 20 for '444111' vs. 36% for '000000'). These higher-intensity protocols also correlated with longer average remission retention spells for those achieving remission (e.g., 6.0-6.5 weeks vs. 5.5 weeks, Table 5.6). A crucial counterpoint, however, was the lower number of participants remaining on the highest intensity protocols at later time points (Tables 5.4, 5.5), pointing to a potential trade-off between maximal initial efficacy

and long-term user engagement or feasibility in this unsupervised context.

Adherence to the recommended protocol ($\geq$4 sessions/wk for Wks 1-3, $\geq$1/wk thereafter) showed a strong association with superior outcomes (Section 5.5, Table 5.7). Adherent users demonstrated higher Week 10 remission (38.0% vs. 33.9% overall) and MCID response (70.9% vs. 66.1% overall), which highlights the practical importance of consistent usage, particularly during the initial treatment phase.

Baseline severity presented a nuanced picture (Section 5.3, Figures 5.4, 5.5, Table 5.3). While individuals with mild depression had the highest likelihood of achieving remission ($\sim$60%), those starting with severe depression, despite lower remission rates ($\sim$20%), exhibited the largest mean score reductions and the highest rates of achieving MCID response ($\sim$80%). This pattern suggests that even when the remission threshold is not met, tDCS is associated with substantial, clinically relevant symptom reduction for many severely depressed individuals in this cohort.

The treatment's effectiveness appeared broadly consistent across key demographic subgroups (age, sex), common comorbidities (Anxiety, ADHD, PTSD, Long-term Stress), and prior treatment histories (Sections 5.6, 5.7, Table 5.8). Although multiple comorbidities were linked to slightly lower remission rates, MCID response remained substantial (Table 5.10). Concurrent antidepressant monotherapy or talk therapy did not appear detrimental to tDCS outcomes; however, the sub-analysis linked combining antidepressants with benzodiazepines to lower remission rates and potentially higher relapse, particularly in the medication-only group (Table 5.14).

Particularly notable was the significant impact on sleep disturbance (Chapter 6). Within the large subgroup (n=6,229) reporting baseline insomnia (MADRS-S item 3 $\geq$ 4), sleep-specific remission was achieved rapidly – by 50.2

7.2 Comparison with Existing Literature

The remission ($\sim$34%) and MCID response rates ($\sim$66%) observed at Week 10 in this real-world cohort compare favourably with typical outcomes from tDCS RCT meta-analyses (e.g., remission $\sim$20-30%, response $\sim$30-40% vs. sham [Moffa et al., 2020, Razza et al., 2020]). Although direct comparison is limited by the study's open-label design, self-report measure, longer duration, and self-selected population, the magnitude of the MCID response suggests a substantial proportion of users experienced noticeable benefit.

The observed trajectory – rapid initial gains followed by a plateau around Week 10 – mirrors patterns seen in both antidepressant trials and previous tDCS studies [Brunoni et al., 2017]. The findings connecting higher initial stimulation frequency to

faster improvement and better outcomes reinforce the importance of adequate dosing, consistent with principles from TMS [Blumberger et al., 2018] and preliminary tDCS studies [Nikolin et al., 2023]. Likewise, the strong association with adherence aligns with broader digital health literature [Forman-Hoffman et al., 2021].

The pronounced and rapid improvement in self-reported sleep quality significantly extends preliminary evidence from smaller RCTs focused on tDCS for insomnia [Frase et al., 2019, Saebipour et al., 2015]. The speed of sleep remission reported here (50% by Week 3) is particularly noteworthy in the context of MDD treatment. The moderate sleep-mood correlation is consistent with the established bidirectional relationship [Baglioni et al., 2011, Li et al., 2016] and potentially shared neurobiological underpinnings.

Compared to the supervised home-use tDCS RCT by Woodham et al. [2025], the unsupervised real-world remission rate reported here was lower (33.9% vs. 53.8

7.3 Strengths and Limitations

The study's scale (N>22,000) and longitudinal nature (up to 50 weeks) are primary strengths, offering unprecedented real-world data on home-use tDCS. The capture of weekly stimulation logs enabled detailed dose-response and adherence analyses. Including a dedicated analysis of sleep outcomes provides valuable insights into effects on a major symptom domain of depression. Data collection integrated into routine use enhances ecological validity.

However, significant limitations inherent to the retrospective, observational design must be acknowledged. Causal attribution is not possible without a randomised control group; observed changes reflect a mix of treatment effects, placebo response, natural course, and regression to the mean. Substantial missing data, particularly for baseline characteristics and during longitudinal follow-up due to attrition, constrain generalisability and could bias estimates, although sensitivity analyses using imputation (Appendix 9) suggest the overall direction of findings is robust. Reliance solely on the self-reported MADRS-S prevents comparison with objective or clinician-rated measures. Adherence logs confirm device activation but cannot guarantee correct usage (e.g., electrode placement). The cohort consists of individuals who purchased the device, potentially differing from the general clinical population (e.g., in motivation). Reasons for attrition remain largely unknown from this dataset.

7.4 Clinical and Research Implications

Despite limitations, this study adds compelling real-world evidence. The findings support the potential utility of self-administered, app-guided tDCS as an accessible and scalable adjunctive or alternative treatment for depression, particularly relevant given challenges such as treatment access and medication side effects.

The clear link between higher initial intensity/adherence and better outcomes strongly indicates that clinical implementation should consider strategies to support consistent use, especially during the initial weeks. The data encourage investigation into personalised approaches, potentially tailoring initial intensity or maintenance frequency based on baseline factors like severity or prominent insomnia, though optimal strategies require prospective validation.

The broad effectiveness across diverse subgroups is encouraging, yet the observed variability reinforces the need for research into predictors of optimal response. The significant and rapid sleep benefits suggest tDCS may hold particular value for depressed individuals with comorbid insomnia, warranting further investigation.

Based on this RWE, clear directions for future research include: large-scale pragmatic RCTs comparing optimised home-use tDCS protocols (potentially with adherence support) against standard care and active comparators, using blended outcome measures over extended follow-up; mechanistic studies, possibly integrating neuroimaging or EEG, to clarify pathways for the observed mood and rapid sleep effects; research aimed at identifying reliable predictors of response and relapse for personalisation; and formal cost-effectiveness analyses to inform health system integration.

7.5 Conclusion

In the largest longitudinal analysis of self-administered, home-use tDCS for depression conducted thus far, this study documents robust associations between device use and significant, sustained reductions in self-reported depressive symptoms, alongside marked improvements in comorbid insomnia. Treatment effectiveness is closely linked to adherence and initial stimulation intensity, indicating potential for optimisation. While the observational design limits definitive causal conclusions, the scale, consistency, and clinical relevance of these real-world findings provide substantial support for the potential role of Flow tDCS as a viable, scalable intervention within the broader landscape of depression care.

Chapter 8

Recommendations

Drawing directly from the findings of this large-scale real-world analysis of Flow FL-100 home-use tDCS, the following specific recommendations are proposed:

8.1 Recommendations for Clinical Practice

1. **Consider Home-Use tDCS Where Appropriate:** Based on the effectiveness observed in this large cohort, clinicians can consider app-guided home-use tDCS (like Flow FL-100) as a potential adjunctive option for adults with mild-to-severe depression. It appears particularly relevant for those seeking non-pharmacological approaches, experiencing significant insomnia (given the rapid sleep benefits seen here), or facing barriers accessing other treatments.

2. **Guide Initial Intensity Based on Data:** Inform patients that higher initial intensity (4-5 sessions/week for weeks 1-3) was associated with faster improvement and higher later remission rates in this cohort. This information should be balanced with the finding of higher attrition on the most intensive schedules when discussing protocol choices.

3. **Emphasise Crucial Role of Adherence:** Strongly advise patients on the importance of consistent adherence, especially during the first 3 weeks and for maintaining at least weekly sessions thereafter. Reference the significantly better outcomes observed for adherent users in this dataset (Table 5.7) to underscore this point.

4. **Utilise Sleep Improvement as an Indicator:** Routinely track MADRS-S Item 3 scores. Inform patients that rapid improvement in sleep was frequently observed (50% sleep remission by Week 3 in baseline insomniacs) and may function as an early positive sign, according to this study's data.

5. **Set Data-Informed Expectations:** Discuss the typical trajectory observed in this cohort (rapid initial improvement plateauing around Week 10), the rates of remission/response found (e.g., 34

6. **Maintain Standard Safety Screening:** Continue rigorous screening for contraindications (e.g., epilepsy, implants) as per established manufacturer guidelines.

8.2 Recommendations for Healthcare Policy and Service Delivery

1. **Evaluate for Stepped Care Integration:** Health systems should formally evaluate the combined evidence (including large RWE like this study alongside relevant RCTs) for integrating approved home-use tDCS devices into depression care pathways, potentially as a Step 2/3 intervention, considering the effectiveness and scalability demonstrated here.

2. **Explore Data-Driven Access Models:** Investigate reimbursement or access models that are informed by real-world effectiveness data, possibly exploring mechanisms linking continued access to demonstrated engagement or early response metrics as observed in this RWE study.

3. **Develop RWE-Informed Clinician Guidance:** Create training materials for clinicians that highlight key RWE findings – such as the dose-response/adherence effects, typical trajectories, sleep benefits, and subgroup nuances observed in this large cohort – to aid informed patient discussions.

4. **Establish Frameworks for RWE Utilisation:** Encourage the development of standardised methodologies for using anonymised, large-scale device telemetry (adhering to ethical and consent standards) for ongoing post-market surveillance and comparative effectiveness assessments within healthcare contexts.

8.3 Recommendations for Future Research

1. **Pragmatic RCTs Reflecting RWE Findings:** Design and conduct large RCTs that compare optimised home-use tDCS protocols (e.g., testing high vs. moderate initial intensity informed by this study's efficacy/retention findings)

against both credible sham controls and active comparators (like SSRIs or digital CBT) using long-term follow-up (1 year) and blended outcome measures.

2. **Investigate Adherence-Retention Trade-off:** Design studies specifically aimed at understanding and potentially mitigating the observed trade-off between higher initial treatment intensity and lower long-term retention, possibly testing strategies such as intensity tapering triggered by early response.

3. **Targeted Sleep Mechanism Studies:** Prioritise mechanistic research (e.g., employing EEG or actigraphy) focused specifically on elucidating how tDCS achieves the rapid sleep improvements observed in this cohort, given the prominence of this effect.

4. **Rigorously Evaluate Combination Nuances:** Conduct prospective studies or RCTs specifically designed to clarify the observed differential outcomes when tDCS is combined with antidepressant monotherapy versus antidepressant-plus-benzodiazepine regimens.

5. **Develop Predictive Models from RWE:** Leverage this extensive dataset to build and validate predictive models identifying baseline characteristics (including specific symptom profiles, like high baseline sleep disturbance) associated with optimal response to different tDCS protocols or prediction of adherence and retention.

6. **Qualitative Exploration of Attrition:** Complement quantitative data by conducting qualitative studies (e.g., interviews) with users who discontinued tDCS at various stages, aiming to understand the reasons beyond those captured numerically and inform engagement strategies.

7. **Head-to-Head Trials for Comorbid Insomnia:** Based on the strong sleep findings, conduct RCTs directly comparing home-use tDCS to established first-line insomnia treatments (e.g., digital CBT-I) in patients presenting with both depression and comorbid insomnia.

Chapter 9

Apendix A: Imputation Sensitivity Analyses

Given the potential for missing data to bias longitudinal analyses, particularly in real-world observational studies with participant attrition, we conducted sensitivity analyses using different methods to handle missing MADRS-S scores. This appendix details the methods evaluated and compares their impact on estimated treatment trajectories and clinical outcomes.

9.1 Imputation Methods Evaluated

As outlined in the Methods chapter, three primary approaches were compared alongside the raw data (which includes missing values):

1. **Raw Data (No Imputation):** Analyses performed only on the observed MADRS-S scores. This serves as a baseline but suffers from reduced sample size at later time points and potential bias if missingness is not completely random. Clinical outcomes for this approach are shown in Table 9.1.

2. **Last Observation Carried Forward (LOCF):** A simple imputation technique where missing scores are filled with the last known score for that individual. Leading missing values (before the first observation) are typically back-filled. While easy to implement, LOCF assumes symptom stability after dropout, which can be unrealistic and often biases results towards no change. Clinical outcomes for LOCF are shown in Table 9.2.

3. **Multiple Imputation by Chained Equations (MICE):** A more sophisticated statistical approach that generates multiple complete datasets (e.g.,

5 or 10) by iteratively predicting missing values based on other variables in the dataset (e.g., baseline score, demographics, adherence patterns, previous scores). We used a bounded MICE approach to ensure imputed MADRS-S scores remained within the plausible 0-54 range. MICE accounts for the uncertainty associated with imputation and can provide less biased estimates if the data are missing at random (MAR). Clinical outcomes averaged across MICE datasets are shown in Table 9.3.

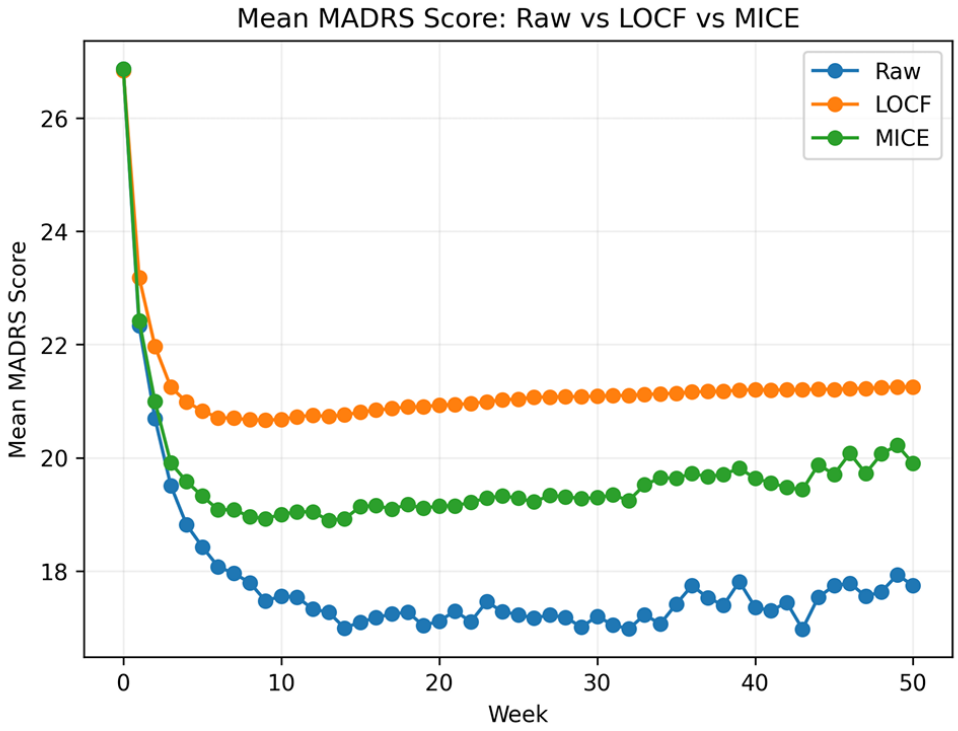

Figure 9.1: Comparison of mean MADRS-Sscores across different imputation methods.

Table 9.1: Raw (No Imputation) Clinical Outcomes

Week	N	Remission (%)	Response (6-pt) (%)	Response (50%) (%)	Relapse (%)
3	12325	26.8%	58.7%	25.2%	0.0%
6	8317	32.8%	63.6%	31.7%	7.5%
10	6182	35.1%	64.5%	34.2%	12.3%
15	4428	37.0%	66.4%	36.5%	16.5%
20	3374	36.8%	66.0%	36.2%	19.6%
50	747	34.9%	62.4%	33.5%	23.7%

Table 9.2: LOCF Imputation Clinical Outcomes

Week	N	Remission (%)	Response (6-pt) (%)	Response (50%) (%)	Relapse (%)
3	20599	21.0%	45.9%	18.4%	0.0%
6	20599	23.5%	48.3%	21.8%	5.1%
10	20599	24.0%	48.1%	22.7%	8.5%
15	20599	24.0%	47.9%	22.7%	10.7%
20	20599	23.5%	47.4%	22.2%	12.2%
50	20599	22.5%	46.2%	21.2%	14.3%

Table 9.3: MICE Imputation Clinical Outcomes

Week	N	Remission (%)	Response (6-pt) (%)	Response (50%) (%)	Relapse (%)
3	20599	25.0%	55.1%	22.5%	0.0%
6	20599	28.0%	57.9%	26.0%	8.9%
10	20599	27.6%	57.7%	26.8%	16.9%
15	20599	26.8%	56.9%	25.7%	23.6%
20	20599	26.0%	56.3%	25.5%	28.7%
50	20599	23.4%	53.4%	22.5%	35.7%

9.2 Evaluation Methodology

To quantitatively compare LOCF and MICE, an artificial masking approach was employed. A random 20% of existing, non-missing MADRS-S scores were temporarily removed (masked). LOCF and MICE were then applied to impute these masked values. The Mean Absolute Error (MAE) between the original (true) masked values and the imputed values was calculated.

- LOCF Imputation: MAE = 4.74
- MICE Imputation: MAE = 5.66

In this specific evaluation, LOCF yielded a slightly lower MAE, suggesting it was closer to the true value on average for the artificially missing points. However, MAE is only one metric, and MICE is generally preferred theoretically for preserving relationships between variables and accounting for uncertainty, especially when data are MAR. The higher MAE for MICE might reflect its tendency to impute values closer to the conditional mean rather than simply carrying forward the last value, which might deviate more from the true value in some cases but better reflect overall trends.

9.3 Comparison of Results

9.3.1 Mean MADRS-S Score Trajectories

Figure 9.1 compares the mean MADRS-S score trajectories over 50 weeks resulting from the Raw data, LOCF, and MICE approaches.

- **Raw Data:** Shows the steepest initial decline but becomes noisier and potentially biased at later time points due to attrition (only includes participants who remained).
- **LOCF:** Results in a much flatter trajectory after the initial drop. Because dropouts' last scores (often higher than remitters) are carried forward, the overall mean improvement appears attenuated, especially at later weeks.
- **MICE:** Produces a trajectory intermediate between Raw and LOCF. It captures a significant initial improvement but shows a less pronounced decline than the Raw data, potentially reflecting a more realistic estimate for the entire baseline cohort had they all remained. The MICE trajectory is generally smoother than the Raw data at later time points.

The divergence highlights how different handling methods significantly alter the apparent long-term treatment effect.

9.3.2 Clinical Outcomes Comparison

Tables 9.1, 9.2, and 9.3 present the 3R metrics (Remission, Response 6-pt, Response 50%, Relapse) calculated using data processed with each method.

- **Remission & Response Rates:** Rates calculated from Raw data are generally the highest, likely reflecting that participants who remain in the study longer tend to be those experiencing benefit. LOCF produces the lowest rates, as carrying forward potentially higher pre-dropout scores makes achieving remission/response thresholds less likely for the imputed population. MICE yields intermediate rates, generally considered a more plausible estimate for the full cohort under MAR assumptions. For example, Week 10 Remission: Raw=35.1%, MICE=27.6%, LOCF=24.0%. Week 10 Response6%: Raw=64.5%, MICE=57.7%, LOCF=48.1%.
- **Relapse Rates:** Relapse rates appear highest under MICE (e.g., 35.7% at Wk 50) compared to Raw (23.7%) and LOCF (14.3%). This could be because

MICE, by imputing fluctuating scores based on statistical models, might be more likely to generate scores that cross the relapse threshold ($\geq$13 after remission) compared to LOCF's assumption of stability or Raw data's potentially selective sample.

The differences underscore that conclusions about the magnitude of long-term effects and relapse are sensitive to the missing data handling strategy. While the Raw data analysis (complete-case) formed the basis of the main results chapters for simplicity and transparency, the MICE results likely provide a more conservative and statistically robust estimate of outcomes for the original cohort, assuming MAR.

9.4 Conclusion

The sensitivity analysis demonstrates that while the overall finding of tDCS effectiveness is robust across methods, the precise magnitude of long-term outcomes and relapse rates varies depending on how missing data are handled. LOCF likely underestimates long-term benefits, while Raw (complete-case) analysis may overestimate them due to survivor bias. MICE provides theoretically sounder estimates under MAR, suggesting substantial but potentially more modest long-term remission/response rates and possibly higher relapse rates than indicated by the Raw data alone. The MICE results reinforce the main conclusions while adding a layer of statistical caution regarding the magnitude of effects in the full baseline population assuming attrition.

Chapter 10

Code Documentation

10.1 tDCS and MADRS Analysis Implementation

10.1.1 System Requirements and Goals

The analysis system processes transcranial direct current stimulation (tDCS) usage and MADRS (Montgomery–Åsberg Depression Rating Scale) data with the following requirements:

- Data validation and filtering:
  - Exclude completion times ≤ 14 seconds
  - Remove subclinical baseline cases (MADRS ≤ 12)
- Timeline standardization:
  - Align negative weeks to establish Week 0
  - Optional expansion to uniform 0-50 week range
- Multiple imputation methods:
  - LOCF (Last Observation Carried Forward)
  - Linear interpolation
  - MICE (Multiple Imputation by Chained Equations)
  - No-imputation option
- 3R metrics computation:
  - Remission (MADRS < 13)
  - Response ≥ 6 points

  - Response ≥ 50
  - Relapse tracking

- Adherence analysis at weeks {3, 6, 10, 15, 20, 50}

10.2 Data Processing Pipeline

10.2.1 Input Data Structure

Two primary data sources:

- MADRS data (`madrs_file`):
  - User ID
  - Week number
  - Total MADRS score
  - Completion duration
- Stimulation data (`stims_file`):
  - User ID
  - Weekly stimulation counts

10.2.2 Core Transformation Functions

Data Validation

`exclude_short_durations`: Remove row r if duration$(r) \leq 14$

`exclude_subclinical_baseline`: Remove all rows for user u if baseline_madrs_total_score(u) ≤ 12

Timeline Processing

`shift_negative_weeks`: For each user u:

$$\text{new\_week}_0 = \max\{t_i | t_i < 0\}$$

Discard other negative weeks.

`define_baseline`:

$$\text{baseline}(u) = \text{madrs\_total\_score}(u, 0)$$

`expand_weeks_0_to_50`: Ensure rows exist for each (u, t) where:

$$t \in \{0, 1, ..., 50\}$$

10.2.3 Imputation Methods

Implementation Details

LOCF: For ordered time points $t_1 < t_2 < \cdots < t_n$:

$$\text{imputed\_score}(u, t_i) = \begin{cases} \text{madrs\_total\_score}(u, t_i) & \text{if known} \\ \text{imputed\_score}(u, t_{i-1}) & \text{if missing} \end{cases}$$

Linear: Between known points (t_1, y_1) and (t_2, y_2):

$$\text{imputed\_score}(u, t) = y_1 + \frac{t - t_1}{t_2 - t_1}(y_2 - y_1)$$

MICE: Using scikit-learn's `IterativeImputer`:

1. Pivot to user-week matrix $X_{u,t}$
2. Apply iterative imputation
3. Reshape back to long format

10.2.4 Adherence Computation

For analysis week W, user u is adherent if:

$$\begin{cases} M_{u,k} \geq 4 & \forall k \in \{1, 2, 3\} \\ M_{u,k} \geq 1 & \forall k \in \{4, ..., W\} \end{cases}$$

where $M_{u,k}$ is stimulation count for user u in week k.

10.2.5 3R Metrics

For user u at week t:

- Remission:

$$\text{is\_remission}(u, t) = [\text{imputed\_score}(u, t) < 13]$$

- Response ≥ 6:

$$\text{is\_resp6}(u,t) = [\text{baseline}(u) - \text{imputed\_score}(u,t) \geq 6]$$

- Response ≥ 50

$$\text{is\_resp50}(u,t) = [\text{imputed\_score}(u,t) \leq 0.5 \cdot \text{baseline}(u)]$$

- Relapse:

$$\text{is\_relapse}(u,t) = [\exists s < t : \text{is\_remission}(u,s) \wedge \text{imputed\_score}(u,t) \geq 13]$$

Chapter 11

Ethics and Consent Materials

11.1 Ethics Approval

This study involved the retrospective analysis of anonymised data collected during the routine use of the Flow Neuroscience FL-100 tDCS device and its companion application. The study protocol, including data handling procedures and analysis plans, received favourable ethical opinion from the **University of Northampton Faculty of Arts, Science and Technology Research Ethics Committee**.

The assigned ethics approval reference number is: **FREC2425005**.

11.2 Informed Consent

Informed consent for the collection and potential secondary analysis of anonymised usage data was obtained electronically from all users as part of the initial setup and registration process for the Flow application. Users were required to agree to the company's Privacy Policy and Terms of Service before activating the device.

These documents explicitly stated that anonymised, aggregated data could be used for research purposes, service improvement, and to contribute to scientific understanding of depression and tDCS treatment. Key points typically covered in such policies include:

- The types of data collected (e.g., symptom scores, stimulation logs, basic demographics).
- The purpose of data collection (service provision, safety monitoring, research).
- Data handling procedures (anonymisation, aggregation, security measures).

- **Anonymisation and aggregation**: We may create or use aggregated, de-identified or other anonymized data from personal data we collect for research and development purposes in our legitimate business interests, including to analyze and improve the Services and our business. We make personal data into anonymized data by removing information that makes the data personally identifiable to you. We may use this anonymized data and share it with third parties for our lawful business purposes, including to analyze and improve the Services and promote our business.

Figure 11.1: Taken from Flow neuroscience Terms of Service

- User rights regarding their data (e.g., access, deletion, withdrawal of consent for future use).
- Compliance with relevant data protection regulations (e.g., GDPR, UK Data Protection Act).

Users retained the right to withdraw consent for future data processing and to request deletion of their personal data according to the terms outlined in the Flow Neuroscience AB Privacy Policy. The dataset provided for this analysis was fully anonymised prior to transfer to the University, ensuring individual users could not be identified.

11.3 Data Anonymisation and Security

The data provided by Flow Neuroscience AB for this research was fully anonymised. All direct identifiers (e.g., name, email address, precise location) were removed, and a unique, randomly generated study ID was assigned to each participant's records. Data transfer occurred via secure, encrypted cloud channel. Access was restricted to the approved research team members.

Bibliography

Mohammed A Al-Abri. Sleep deprivation and depression: A systematic review. *Oman Medical Journal*, 38(2):e473, 2023. doi: 10.5001/omj.2023.40.

Chiara Baglioni, Giacomo Battagliese, Bernd Feige, Kai Spiegelhalder, Christoph Nissen, Ulrich Voderholzer, Caterina Lombardo, and Dieter Riemann. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of affective disorders*, 135(1-3):10–19, 2011.

Daniel M. Blumberger, Fidel Vila-Rodriguez, Kevin E. Thorpe, Zafiris J. Daskalakis, and Jonathan Downar. Effectiveness of theta-burst versus high-frequency rtms in patients with depression (three-d): A randomised non-inferiority trial. *The Lancet*, 391(10131):1683–1692, 2018. doi: 10.1016/S0140-6736(18)30295-2.

Luana Borrione, Letícia V. M. Aparicio, Marc S. Luethi, Sebastian Goerigk, and André R. Brunoni. Home-use transcranial direct current stimulation for the treatment of a major depressive episode: A randomized clinical trial. *JAMA Psychiatry*, 81(4):329–337, 2024. doi: 10.1001/jamapsychiatry.2023.5000.

André R. Brunoni, Leandro Valiengo, Alessandra Baccaro, Túlio A. Zanao, João F. de Oliveira, and Paulo S. Boggio. Sertraline vs electrical current therapy for treating depression clinical trial (select-tdcs): Results from a factorial, randomised controlled trial. *JAMA Psychiatry*, 70(4):383–391, 2013. doi: 10.1001/jamapsychiatry.2013.21.

André R. Brunoni, Ariel H. Moffa, Benedito Sampaio-Junior, Luana Borrione, and Felipe Fregni. Trial of electrical direct-current therapy versus escitalopram for depression. *New England Journal of Medicine*, 376(26):2523–2533, 2017. doi: 10.1056/NEJMoa1612999.

Gregor Burkhardt, Ulrich Kumpf, Andreas Crispin, Sebastian Goerigk, Nadine Behler, and Frank Padberg. Transcranial direct current stimulation as an additional treatment to ssris in major depressive disorder: A triple-blind, sham-

controlled multicentre trial. *The Lancet*, 402(10401):545–554, 2023. doi: 10.1016/S0140-6736(23)00944-4.

Christine Callahan, Justin Kimber, Emily Hu, Leah Tanner, and Sarah Kunkle. The real-world impact of app-based mindfulness on headspace members with moderate and severe perceived stress: Observational study. *JMIR mHealth and uHealth*, 12: e52968, 2024. doi: 10.2196/52968.

D. Cappon, S. Anais, M. Bikson, and L. Charvet. Feasibility of remotely supervised home tdcs in routine psychiatric care. *Journal of Psychiatric Research*, 139:285–292, 2021. doi: 10.1016/j.jpsychires.2021.05.041.

Andrea Cipriani, Toshi A. Furukawa, Georgia Salanti, Anna Chaimani, and John R. Geddes. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with depression: A systematic review and network meta-analysis. *The Lancet*, 391(10128):1357–1366, 2018. doi: 10.1016/S0140-6736(17)32802-7.

Franco De Crescenzo, Riccardo De Giorgi, Cesar Garriga, Qiang Liu, Seena Fazel, Orestis Efthimiou, Julia Hippisley-Cox, and Andrea Cipriani. Real-world effects of antidepressants for depressive disorder in primary care: population-based cohort study. *Br. J. Psychiatry*, pages 1–10, 2024. doi: 10.1192/bjp.2024.194.

Valerie L. Forman-Hoffman, Benjamin W. Nelson, Kristian Ranta, and João de Quevedo. Significant reduction in depressive symptoms among patients with moderately-severe to severe depression after participation in a therapist-supported, evidence-based mobile health program: An intent-to-treat study. *JMIR Mental Health*, 8(8):eXXX, 2021.

Lukas Frase, Holger Piosczyk, Sophie Zittel, Florian Jahn, Peter Selhausen, Luigi Krone, et al. Modulation of total sleep time by transcranial direct current stimulation (*t*dcs). *Brain Stimulation*, 12(3):674–683, 2019. doi: 10.1016/j.brs.2019.01.001.

Lukas Frase, Friederike Jahn, Sulamith Tsodor, Lukas B. Krone, Patrick Selhausen, Bernd Feige, and Christoph Nissen. Offline bi-frontal anodal transcranial direct current stimulation decreases total sleep time without disturbing overnight memory consolidation. *Neuromodulation: Technology at the Neural Interface*, 2021.

GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the

global burden of disease study 2019. *The Lancet*, 396(10258):1204–1222, 2020. doi: 10.1016/S0140-6736(20)30925-9.

Simon B. Goldberg, Daniel M. Bolt, and Richard J. Davidson. Data missing not at random in mobile health research: Assessment of the problem and a case for sensitivity analyses. *J. Med. Internet Res.*, 23(6):e25834, 2021. doi: 10.2196/25834.

Ning Huang, Hua He, Wenjing Chen, and Yan Zhao. Transcranial direct current stimulation for primary insomnia: systematic review and meta-analysis. *Brain and Behavior*, 12(10):e2764, 2022. doi: 10.1002/brb3.2764.

Thomas R Insel. Technology as a tool for behavioural health. *JAMA psychiatry*, 77 (11):1105–1106, 2020.

Helena Chmura Kraemer. From efficacy to effectiveness trials: translating the evidence. *JAMA psychiatry*, 76(4):353–354, 2019.

Lukas B. Krone, Kristina D. Fehér, Tanya Rivero, Xavier Omlin, and Christoph Nissen. Repeated afternoon tdcs increases actigraphic sleep time in treatment-resistant depression without altering slow-wave sleep. *Journal of Sleep Research*, 33(2):e13927, 2024. doi: 10.1111/jsr.13927.

Ling Li, Cong Wu, Yiqun Gan, Xian Qu, and Zuxun Lu. Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. *BMC psychiatry*, 16 (1):1–10, 2016.

Colleen K. Loo, Mustafa M. Husain, William M. McDonald, Scott T. Aaronson, and David M. Martin. International randomized-controlled trial of transcranial direct current stimulation in depression. *Brain Stimulation*, 11(1):125–133, 2018. doi: 10.1016/j.brs.2017.10.011.

Haixia Ma, Jingxia Lin, Jiali He, Dilys H. T. Lo, and Hector W. H. Tsang. Effectiveness of transcranial electric stimulation and repetitive transcranial magnetic stimulation for the treatment of insomnia: Meta-analysis and meta-regression of randomized sham-controlled trials. *Frontiers in Psychiatry*, 12:744475, 2021. doi: 10.3389/fpsyt.2021.744475.

Ariel H. Moffa, David Martin, Alexandra Alonzo, Dominique Bennabi, and André R. Brunoni. Efficacy and acceptability of transcranial direct current stimulation for major depressive disorder: An individual-patient-data meta-analysis. *Progress in*

Neuro-Psychopharmacology & Biological Psychiatry, 99:109836, 2020. doi: 10.1016/j.pnpbp.2020.109836.

Snezana Nikolin, Ariel H. Moffa, Lucas B. Razza, Andrew K. Benson, and Colleen K. Loo. Time-course of the tdcs antidepressant effect: An individual participant data meta-analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 125:110752, 2023. doi: 10.1016/j.pnpbp.2023.110752.

Snezana Nikolin, Lucas B. Razza, Colleen K. Loo, and Ariel H. Moffa. Individual-participant-data meta-analysis of transcranial direct current stimulation for insomnia and sleep disturbance. *Sleep Medicine*, 105:125–134, 2024. doi: 10.1016/j.sleep.2024.01.014. Advance online publication.

Michael A. Nitsche, Leonardo G. Cohen, Eric M. Wassermann, Alberto Priori, and Alvaro Pascual-Leone. Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, 1(3):206–223, 2008. doi: 10.1016/j.brs.2008.06.004.

Okelue E. Okobi, Thomas J. Okobi, Uchechukwu E. Anyanwu, et al. Association between the use of wearable devices and physical activity among us adults with depression and anxiety. *JMIR Ment. Health*, 10:e43656, 2023. doi: 10.2196/43656.

Jukka-Pekka Onnela. Opportunities and challenges in the use of digital phenotyping data for mental health. *Neuropsychopharmacology*, 46(1):240–241, 2021.

A. Panhelainen, V. V. Nikulin, and R. J. Ilmoniemi. Home-administered tdcs for major depression: Real-world adherence and outcome in an app-linked cohort. *Journal of Affective Disorders*, 330:339–347, 2023. doi: 10.1016/j.jad.2023.02.045.

Lucas B. Razza, Pátio Palumbo, Ariel H. Moffa, André F. Carvalho, and André R. Brunoni. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. *Depression and Anxiety*, 37(7):714–730, 2020. doi: 10.1002/da.23004.

Renato Sá, João P. Silva, Mariana Almeida, Inês Lopes, and Teresa Paiva. Slow-wave–targeted vs. bifrontal tdcs for primary insomnia: a randomised, double-blind, crossover trial. *Sleep Medicine*, 102:34–42, 2023. doi: 10.1016/j.sleep.2023.03.005. Clinical Trial ID NCT05321840 — please verify final pagination.

Mohammad Reza Saebipour, Ahmad R. Alborzi, Mohammad Fattahi, et al. Transcranial direct current stimulation improves subjective sleep quality in chronic primary insomnia: A double-blind sham-controlled study. *Journal of Sleep Research*, 24(5):518–525, 2015. doi: 10.1111/jsr.12302.

Jia Sheng, Xinyu Liu, and Yujie Wang. Non-invasive brain stimulation for insomnia: a meta-analysis of randomised controlled trials. *Sleep Medicine*, 48:17–26, 2018. doi: 10.1016/j.sleep.2018.04.006.

M. Sobral, E. Refsgaard, J. Pereira, and M. A. Nitsche. Adherence and compliance in home-based transcranial direct current stimulation protocols. *Clinical Neurophysiology*, 126(11):2100–2106, 2015. doi: 10.1016/j.clinph.2015.03.022.

Alejandro G. Szmulewicz. Target trial emulation in psychiatry: a call for more rigorous observational analyses. *Lancet Psychiatry*, 11(7):492–494, 2024. doi: 10.1016/S2215-0366(24)00109-6.

Richard D. Woodham, Sudhakar Selvaraj, Nadine Lajmi, Hannah Hobday, and Catie H. Y. Fu. Home-based transcranial direct current stimulation for major depressive disorder: A fully remote randomized sham-controlled trial. *Nature Medicine*, 31 (1):87–95, 2025. doi: 10.1038/s41591-024-02910-9.

World Health Organization. Depression. Fact sheet, 2023. Accessed [Insert Access Date, e.g., 2024-05-15], https://www.who.int/news-room/fact-sheets/detail/depression.