International Journal of Neuropsychopharmacology, 2026, 29(4), pyag012
https://doi.org/10.1093/ijnp/pyag012
Published: 9 April 2026
Regular Research Article

OXFORD

Identifying treatment response classes to transcranial direct current stimulation from daily ecological momentary assessment patterns in patients with depression

Han Wool Jung, MS[1,2], Sehwan Park, MS[3], Kyungmi Chung, PhD[1,4], Yujin Kim, PhD[5], Daeyoung Roh, MD, PhD[6,7], Kyungun Jhung, MD, PhD[8], Woo Jung Kim, MD, PhD[1,4], Jin Young Park, MD, PhD[1,4,9], Jaesub Park, MD, PhD[1,4,*]

[1]Department of Psychiatry, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea
[2]Department of Integrative Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[3]Medical Research Team, Digital Medic Co., Ltd., Seoul, Republic of Korea
[4]Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[5]Graduate School of Public Administration, Seoul National University, Seoul, Republic of Korea
[6]Department of Psychiatry, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea
[7]Clinical Emotion and Cognition Research Laboratory, Inje University College of Medicine, Goyang, Republic of Korea
[8]Department of Psychiatry, Catholic Kwandong University International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Republic of Korea
[9]Center for Digital Health, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea

*Corresponding author: Jaesub Park, MD, PhD, Department of Psychiatry, Yongin Severance Hospital, Yonsei University College of Medicine, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do, Yongin, 16995, Republic of Korea (seob0115@gmail.com)

Abstract

Importance: Transcranial direct current stimulation (tDCS) is known to be promising for depression, but heterogeneity across studies highlights the need for strategies to optimize treatment effectiveness. Identifying distinct response patterns based on ecological momentary assessment (EMA) may enhance therapeutic outcomes and support the development of personalized and precision psychiatry.

Objective: To identify distinct EMA-derived response profiles to tDCS in patients with depression and examine how the identified subtypes differentially predict treatment responses and symptom return following treatment termination.

Design: A secondary analysis of a double-blind, multicenter randomized clinical trial investigating the effects of tDCS on depression. Daily EMA data on mood and sleep duration during the intervention period were processed using time-series feature extraction and clustered via Gaussian Mixture Modeling.

Participants: One hundred and ninety-seven participants (original study) and 147 participants (current study) diagnosed with mild-to-moderate depression.

Interventions or Exposures: Six-week active tDCS vs 3-week active and 3-week sham tDCS.

Main Outcomes and Measures: Beck Depression Inventory-II (BDI-II) and Montgomery–Åsberg Depression Rating Scale (MADRS) measured at baseline (V1), post-treatment (V3), and 6-week follow-up (V4).

Results: Clustering analysis identified 3 response types: (1) stable improvement (gradual mood reduction, stable sleep duration, moderate treatment effect with no symptom return), (2) persistent high-symptom (consistently elevated depressive mood, sleep disturbance, low-to-moderate treatment effect without symptom return), and (3) volatile symptom (large day-to-day variability in mood and sleep, marked acute improvement but high symptom return). The linear mixed model identified significant interaction effects between clusters and treatment efficacy (V1, V3)/symptom return (V3, V4) intervals.

Conclusions and Relevance: Clustering of daily EMA data identified 3 distinct tDCS response profiles associated with different clinical characteristics and relapse risks. These patterns may reflect underlying subtypes of depression and highlight the value of individualized treatment planning. Future studies can fully characterize the subtypes of response profiles and the unique response patterns of individuals that may facilitate data-driven decision-making and support precision psychiatry by enabling tailored tDCS protocols based on patient-specific response characteristics.

Keywords digital phenotyping, time-series clustering, machine learning analysis, home-based brain stimulation, treatment-resistant depression

Received: September 23, 2025. **Revision received:** January 26, 2026. **Accepted:** March 16, 2026.

Significance statement

The deployment of tDCS for depression does not yield equal benefits for all patients, due to their clinical and biological profiles across depressive subtypes. The current study employed smartphone-based daily EMA records of mood and sleep during tDCS administration to identify distinct response patterns. Through cluster analysis of mood and sleep trajectories, we identified 3 distinct types of response profiles, ie, steady improvement, persistent high-symptoms, and volatile, highly fluctuating symptoms, which may reflect underlying differences in depressive subtypes. Understanding distinct response patterns across patients can help clinicians optimize treatment protocols and reduce unnecessary costs such as extra visits due to the limited treatment effectiveness. Moreover, this approach could potentially contribute to the advancement of more personalized, data-driven neuromodulation and precision psychiatry.

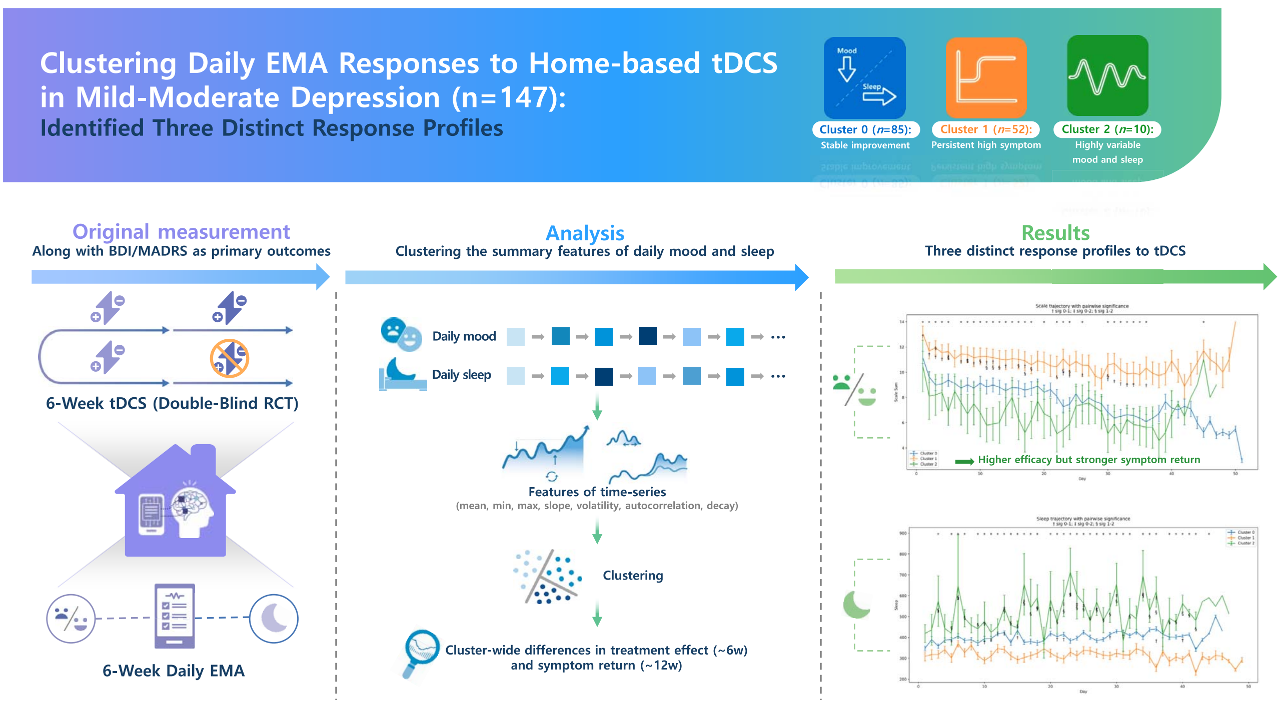
Significant outcomes

- Optimizing tDCS may require personalization based on patients' heterogeneous depression profiles.
- EMA clustering of daily mood and sleep identified 3 response classes to tDCS.
- The identified classes differed in tDCS treatment efficacy and symptom return after termination.

Limitations

- The current results should be interpreted as preliminary, given the limited sample size and the absence of full-time series modeling.
- Missing data and the imputation strategy may have affected the stability of the results.
- Future studies with larger samples and longitudinal clustering approaches may identify additional tDCS-relevant response classes.

Graphical abstract



Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that applies weak direct electrical currents to modulate activity in the cerebral cortex.[1] By placing anodal and cathodal electrodes over targeted brain regions, tDCS generates low-intensity electric fields that alter neuronal excitability and influence synaptic plasticity.[1,2] This modulation process has been shown to alleviate depressive symptoms and potentially improve various forms of psychiatric and cognitive dysfunction.[2–4] Despite ongoing concerns about the lack of standardized protocols and clinical guidelines,[2,3] tDCS is now expected to see broader adoption in clinical practice, as the United States Food and Drug Administration recently approved at-home tDCS device for moderate-to-severe depression.[5] However, recent systematic reviews and meta-analyses indicate that the effect of tDCS on depression is still not solid, even though depression is a common disorder that is prevalent among approximately 8% of men and 15% of women over the lifetime and associated with physical complications, disability, and elevated suicide risk.[6] For instance, Ren et al. (2025) reported that although tDCS led to significant improvements in depression among patients with comorbid psychiatric and medical symptoms, its effect on patients with pure depression was not significant.[3] Yachou et al. (2025) concluded that the effects of tDCS on depression exhibit significant heterogeneity, primarily depending on the target regions or electric field distribution.[2] These reviews underscore the need for careful modulation and optimization strategies to improve tDCS treatment efficacy on depression.

Optimization of tDCS may involve adjusting stimulation protocols or field strength/electrode placement,[2] but understanding patients' response patterns to tDCS derived from their unique individual characteristics can also be beneficial. There are diverse subtypes of depression with different physiological and genetic characteristics,[6,7] and such discrepancies may contribute to variability in treatment responses and effects in tDCS as well. It is known that melancholic depression is associated with a high level of cortisol secretion as reflected in adrenocorticotropin levels and the hypothalamic–pituitary–adrenal (HPA) axis,[8,9] and such a relationship is also observed in depression with comorbid psychosis.[10] In contrast, atypical depression is associated with relatively low HPA-axis activity but elevated inflammatory markers,[9] which has also been suggested in depression with mixed features, that is characterized by agitation, mood lability, or frequent, rapidly shifting manic episodes.[11] Regarding neurological differences, the evidence for structural or functional variability among subtypes is less obvious; however, it is known that melancholic depression is associated with decreased functional connectivity primarily in frontoparietal regions of the brain,[12,13] whereas atypical depression exhibits increased functional connectivity in the orbitofrontal cortex.[14] On the contrary, depression with mixed features demonstrates increased connectivity in the default mode network,[15] and bipolar depression exhibits variable connectivity across both orbitofrontal and default mode network areas,[16] suggesting aberrant synchronization in functional brain network dynamics.

Studies suggest considerable inconsistencies in the effects of tDCS based on the different types and clinical stages of depression. It is known that patients with moderate-to-severe depression, chronic depression, or depression with bipolar symptoms are more resistant to tDCS treatment.[17–19] Treatment-resistant depression may lead to higher relapse rates following the termination of tDCS, even when their immediate treatment responses are favorable.[18,20] Therefore, studies need to clearly identify which patients are most likely to exhibit treatment resistance to tDCS. Considering the heterogeneous and transdiagnostic nature of depression, it is beneficial to adopt data-driven approaches for identifying the treatment-resistant subtypes of depression. Moreover, evaluation of the effects of tDCS should include follow-up assessments to monitor the recurrence of depressive symptoms. Since depressive symptoms may relapse 6-12 weeks after the acute phase of tDCS ends,[20] assessing the long-term efficacy of tDCS is required for identifying robust response patterns of patients.

The current study aims to explore the response patterns exhibited by patients with depression in response to tDCS treatment, using daily ecological momentary assessment (EMA) data obtained during the tDCS treatment period. EMA can minimize recall bias in traditional retrospective assessments and enhance the ecological validity of the responses, as it captures patients' responses immediately upon symptom occurrence.[21] Subtyping depression using EMA data was previously explored by van Genugten et al. (2022).[22] They applied cluster analysis to derive 4 types of EMA response profiles classified based on the average levels and variability of daily mood during a clinical trial of cognitive behavioral therapy. Similarly, Paul et al. (2019)[23] identified response patterns in the treatment of major depressive disorder by clustering sociodemographic, physical health, personality, and treatment-related variables, highlighting the clinical relevance of the derived response classes. Building on previous studies, the current study aims to identify how the subtype profiles identified by cluster analysis may differentially predict treatment responses to tDCS, as well as the return of symptoms following treatment termination. For this purpose, this study extracted several summary features capturing participants' response patterns over the intervention period and identified distinct response classes that reflect heterogeneous response profiles to tDCS, which may contribute to differences in treatment efficacy and the occurrence of symptom return.

Methods

Original study design

The study analyzed data derived from a double-blind, multicenter clinical trial[24] to evaluate the real-world effects of tDCS on depression. Participants were recruited from 5 centers across South Korea. Participants with a primary diagnosis of mild-to-moderate depression based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) were included in the clinical trial, confirmed by the Mini International Neuropsychiatric Interview (MINI).[25] Individuals with (1) a diagnosis of bipolar or psychotic disorders, post-traumatic stress disorder, or obsessive-compulsive disorder, (2) significant suicide risk, and (3) any scalp or neurological conditions that could interfere with the application of tDCS were excluded. Eligible participants were randomly assigned through a computerized sequence into 2 groups: the 6-week active stimulation group (6WA; $n = 108$) or the 3-week active stimulation group (3WA; $n = 89$). Simple randomization (1:1) was implemented using a pre-generated randomization list linked to sequential study IDs, with allocation concealed via sealed allocation codes.

At Visit 1 (V1), participants' baseline depression levels were assessed using the Beck Depression Inventory-II (BDI-II)[26] and the Montgomery–Åsberg Depression Rating Scale (MADRS).[27] Following the baseline assessments, participants began administering tDCS at home using a portable device (MINDD STIM+, Ybrain Inc., Republic of Korea), with the anode positioned over the left forehead and the cathode over the right forehead, targeting each side of the dorsolateral prefrontal cortex (DLPFC). All participants received active tDCS (1.5-2 mA of current for 30 minutes per day) for the first 3 weeks. After this period (Visit 2, V2), the 3WA group switched to sham stimulation, which consisted of a 30-minute daily session without active current, except for an initial 1-minute low-intensity stimulation to mimic the sensation of active treatment. In contrast, the 6WA group continued receiving active tDCS throughout the entire stimulation period.

The intervention concluded 6 weeks after baseline (Visit 3, V3), at which point post-treatment BDI and MADRS scores were collected to evaluate changes in depression severity following the intervention. Follow-up assessments were conducted 6 weeks after the end of the stimulation period (Visit 4, V4), during which BDI and MADRS scores were reassessed to examine the persistence of treatment effects after the discontinuation of tDCS. The trial was prospectively registered at ClinicalTrials.gov (Identifier: NCT05539131), and a detailed flow diagram of the study is available in the Supplementary Material. For more information about the methodology and results of this trial, see Park et al. (2025).[24]

EMA recording

During the treatment period (V1-V3), all participants enrolled were asked to record their daily mood and the previous night's sleep duration using a smartphone app. Mood was assessed with the 20-item Center for Epidemiologic Studies Depression Scale – Revised

(CESD-R),[28] but the response format was adapted to a binary scale (1 = symptom present, 0 = symptom absent) because the original scale was designed to measure the frequency of symptom occurrence over the past week (eg, not at all, 1-2 days, 3-4 days, 5-7 days, nearly every day), not for daily monitoring. The binary responses to the 20 items were aggregated to generate a daily measure of mood (range: 0-20), with higher scores indicating greater depressive symptom burden. This method was developed and evaluated in a previous study.[29]

The participants were also asked to report the total duration of their previous night's sleep (in minutes), constituting the daily measure of sleep duration. The app automatically estimated the total duration of the previous night's sleep through internal smartphone sensors, and participants edited and confirmed their daily sleep duration on the next day. The app was programmed to collect their mood and sleep duration for 2 weeks, repeated 3 times across the intervention phase. Participants received daily notifications at a preset time that could be adjusted to their preference, reminding them to complete their entries by the end of the same day. The EMA app was developed by Digital Medic Co., Ltd. (Seoul, Republic of Korea).

Outcome measures and covariates

The main outcome measures of this study were BDI and MADRS, which were also the primary outcomes in the original clinical trial. In particular, this study used the individual changes in BDI and MADRS over the timeline of V1, V3, and V4. In addition to the main outcomes, the following covariates were included: sex, age, years of education, household income, randomized tDCS group (6WA vs 3WA), occurrence of adverse events during tDCS administration, concomitant use of psychotropic medications, presence of comorbid mental disorders, and smoking and drinking status. The tDCS adverse events, concomitant psychotropics, comorbid mental disorders, smoking, and drinking were binary coded (present = 1, absent = 0).

Statistical analysis

EMA preprocessing and feature extraction

The raw EMA records were reorganized into a tabular dataset with participants as rows and days as columns. For each participant, the first entry was designated as Day 1, and subsequent entries were numbered sequentially as *(recorded date – first record date + 1)*. Participants with no records for 14 or more consecutive days after their first entry, or with a total of 4 or fewer recorded days, were excluded from the study. For all participants, records dated more than 50 days after the first entry were excluded from the analysis. Additionally, data from the participants with low baseline depression levels ($\leq$13 on BDI or $\leq$6 on MADRS) were excluded from the analysis. This process finally selected 147 out of 197 original participants.

For each participant's daily mood and sleep data, missing values were imputed using an iterative imputation method with all covariates included. The imputed daily mood and sleep data were treated as time series, from which the following 7 features were extracted: mean value, minimum and maximum values, slope of individual changes, volatility (sum of daily absolute changes), autocorrelation (correlation between each value and the value from the previous day), and decay, calculated using an exponentially weighted moving average. As 7 features were extracted separately for mood and sleep, a total of 14 features were used to cluster the EMA profiles. For some feature cells where values could not be extracted, missing entries were further imputed using the multivariate imputation by chained equations algorithm without covariates.

Clustering of EMA profiles

Clustering of participants' response patterns to tDCS was conducted using a Gaussian Mixture Model (GMM) based on 14 features extracted (7 derived from mood and 7 from sleep). All feature values were standardized before clustering. To determine the optimal number of clusters (k), candidate models with k ranging from 1 to 10 were evaluated using 2 criteria: the Bayesian Information Criterion (BIC; lower values indicate better fit) and the mean log-likelihood estimated via 5-fold cross-validation (CV; higher values indicate better fit). The optimal k was selected based on these criteria, and participants were assigned to clusters according to their maximum a posteriori (MAP) membership under the selected GMM. Models were implemented using the GaussianMixture function in scikit-learn,[30] with 10 random initializations (n_init = 10) and otherwise default settings. Random seeds were fixed at 42 for the preprocessing and main clustering stages.

Main analysis

For the primary analysis, Time × Cluster interaction effects on BDI and MADRS were tested using likelihood ratio tests (LRTs) comparing a full linear mixed model (LMM) including the interaction with a reduced LMM excluding the interaction term. Linear mixed models were fit using maximum likelihood estimation, and the limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) optimizer was used by default with full BFGS as a fallback when L-BFGS failed to converge. Interaction effects were tested for the full timeline (V1, V3, V4) as well as separately for the treatment interval (V1, V3) and the symptom return interval (V3, V4).

To supplement the primary tests, cluster-level (cross-sectional) differences in BDI and MADRS scores were examined across each assessment point (V1, V3, V4), as well as for treatment effects (V3-V1) and symptom return (V4-V3), using analysis of covariance (ANCOVA) and Tukey's Honest Significant Difference (HSD) post hoc comparisons of estimated marginal means. For both LMM LRTs and ANCOVA, all 10 covariates were included in the primary analysis. Missing values in BDI and MADRS due to participant attrition were handled via rowwise listwise deletion for LMMs and pairwise deletion for ANCOVA. In addition, daily trajectories of mood and sleep were analyzed and visualized by cluster to better characterize the temporal response patterns of each group.

Sensitivity analysis

The sensitivity analyses aim to evaluate the robustness of the main findings against (1) covariate specification and (2) stochasticity derived from the missing value imputation and clustering procedures. First, 10 additional LMM interaction tests in which covariates were entered one at a time were conducted for the LMM interaction effects (ie, each model included a single covariate in addition to the main effects and the Time × Cluster interaction) to examine whether the significance of the interaction depended on any specific covariate. The retention rate of the significance and the covariates associated with changes in significance were identified.

To assess the robustness of the findings against potential statistical artifacts arising from missing value imputation and clustering model variability, a seed-based sensitivity analysis was conducted. In addition to the main analysis performed with a fixed random seed

(seed = 42), 20 independent iterations of the imputation and clustering were run using seeds ranging from 0 to 19, allowing for evaluation of the influence of stochastic elements in the imputation process and the potential risk of overfitting in GMM clustering. The number of clusters was held constant, matching the value selected in the main analysis. Clustering consistency was evaluated by computing the Adjusted Rand Index (ARI) between each seed-based solution and the main clustering. To assess the reproducibility of inferential results, the primary LMM interaction tests with all covariates included for the entire timeline, treatment effect, and symptom return intervals, and the supplementary cross-sectional ANCOVA for treatment effects (V3-V1) and symptom return (V4-V3) were repeated for each iteration. All data analyses and visualization were performed using custom Python code with assistance from ChatGPT (OpenAI, CA, United States).

Results

Participants and sample characteristics

Of the 197 participants of the original study, 147 participants were included in the EMA analysis, after excluding individuals with no records for 14 or more consecutive days after their first entry, with a total of 4 or fewer recorded days, and with low baseline depression levels (≤13 on BDI or ≤6 on MADRS). Among the 147 participants included, 30 participants dropped out at V3, and 12 dropped out at V4, resulting in 105 participants who completed the final study phase, corresponding to a completion rate of 71.4%. Detailed information on participant numbers and attrition by group and study phase is provided in the Supplementary Material.

The common reasons for dropout include withdrawal of consent, medical issues, protocol violations, and loss to follow-up. The attrition at V3 and V4 was mostly not significantly associated with baseline depression levels (BDI and MADRS) or covariates, but they were significantly related to the occurrence of adverse events during tDCS (Ps < .004). Logistic regression models including baseline BDI/MADRS and covariates predicted attrition at V3 (P = .030, Nagelkerke R^2 = .275) but not at V4 (P = .218). When tDCS adverse events were excluded, the models became insignificant for both V3 and V4 (Ps > .158), indicating the limited effects of attrition without the adverse events during tDCS.

Missing data analysis

For the daily EMA data, the proportion of missing cells for mood and sleep data was 34.6% during the first 30 days following the initial entry. Across all 51 days, only Days 16, 20, and 41 rejected the missing completely at random (MCAR) hypothesis in Little's MCAR test (Ps < .05), indicating that the missing data can generally be considered random. However, across the 51-day EMA period, missing data of mood and sleep items tended to be associated with tDCS-related adverse events on 23 and 19 days, respectively. Additionally, higher years of education were also linked to lower response rates for sleep items, particularly after the third week (12 days). The logistic regression models, including baseline BDI/MADRS and covariates, significantly predicted missingness for mood on 20 days and for sleep on 17 days (Ps < .05), suggesting potential systematic bias in missing data. Nevertheless, the number of significant models considerably dropped after excluding tDCS adverse events (Ps < .05 for 8 and 6 days, respectively), indicating that the effects of other factors than tDCS adverse events are minimal, and the risk of bias due to missing data may be limited if the impact of tDCS adverse events is adequately controlled.

Descriptive and demographic profiles of GMM-derived clusters

Clustering was conducted using GMM based on the features (mean, min, max, slope, volatility, autocorrelation, and decay) extracted from the imputed daily mood and sleep data. To determine the optimal number of clusters (k) for GMM, BIC, and 5-fold CV, log-likelihood was computed for values of k ranging from 1 to 10. The BIC reached its minimum at k = 3, whereas the mean CV log-likelihood was highest at k = 1. Considering both criteria and visual inspection of the BIC and CV curves (Figure 1), a 3-cluster solution was selected to balance model complexity and generalization performance.

Each participant was assigned to clusters based on their MAP probability under the selected 3-cluster GMM solution. Of the 147 analyzed participants, 85 participants were assigned to Cluster 0, followed by 52 to Cluster 1 and 10 to Cluster 2. There were no significant differences across clusters in any covariates, including demographic characteristics, tDCS-related factors, or mental/physical health factors, although years of education and comorbid mental disorders exhibited marginally significant differences between clusters (Table 1). Notably, the EMA completion and dropout rates significantly differed between clusters, indicating that missingness was not evenly distributed across clusters.

Feature profiles

Table 2 presents the differences in the distribution of extracted feature values across clusters. Cluster 0 exhibited the lowest variability in both mood and sleep, reflecting the most stable response patterns to tDCS. Cluster 1 showed the highest levels of daily depressive mood along with the shortest sleep durations, indicating that this cluster is showing the highest depressive symptoms accompanied by sleep disturbance. In contrast, Cluster 2 showed highly variable sleep durations as well as depressive mood, indicating pronounced fluctuations in emotional and behavioral states.

To identify detailed feature profiles based on daily trajectories, cluster-specific response patterns were examined and illustrated using the raw daily EMA data for mood and sleep (Figure 2). Cluster 0, representing the most common response pattern to tDCS, showed gradually decreasing depressive mood scores over time alongside stable sleep durations. In contrast, Cluster 1 maintained persistently high depressive mood and short sleep durations across the treatment period. Cluster 2 exhibited marked daily fluctuations in both mood and sleep, possibly suggesting volatile response patterns.

Cluster-wide changes in BDI and MADRS

In the primary analysis with all covariates included, the Time × Cluster interaction effects for the entire timeline identified by LRTs of LMM were significant for BDI and marginally significant for MADRS, $\chi^2(4) = 13.48$, P = .009, $\chi^2(4) = 9.17$, P = .057, respectively. Looking at the treatment and symptom return timelines separately, the interaction effect during the treatment interval (V1, V3) with all covariates included was significant for BDI and marginally significant for MADRS [$\chi^2(2) = 10.24$, P = .006 and $\chi^2(2) = 4.64$, P = .098, respectively]. The interaction effect during the symptom return interval (V3, V4) was

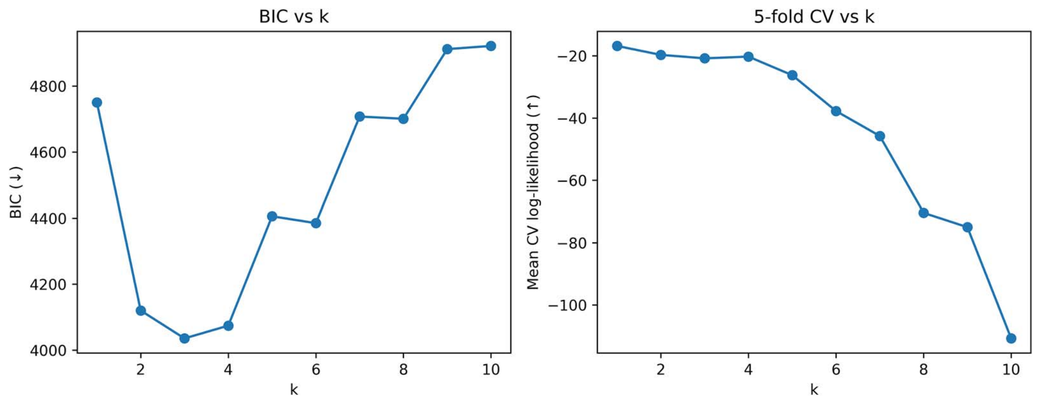


Figure 1 Bayesian Information Criterion and 5-fold cross-validation scores by the number of clusters (*k*).

Table 1 Demographics and covariates across clusters.

	Cluster 0 (*n* = 85)	**Cluster 1 (*n* = 52)**	**Cluster 2 (*n* = 10)**	***p*** **(χ^2 or ANOVA)**
Demographics				
Sex (female, %)	57 (67%)	33 (63%)	7 (70%)	.887
Age	39.2 ± 13.0	38.6 ± 13.6	34.6 ± 13.4	.590
Years of education	14.8 ± 2.2	14.1 ± 2.5	13.2 ± 2.7	.068[b]
Household income (1 m Korean won)	<2: 19 (22%) 2-3.99: 23 (27%) 4-5.99: 24 (28%) 6+: 16 (19%)	<2: 13 (25%) 2-3.99: 17 (33%) 4-5.99: 12 (23%) 6+: 9 (17%)	<2: 3 (30%) 2-3.99: 3 (30%) 4-5.99: 1 (10%) 6+: 3 (30%)	.917
tDCS factors				
Group (6WA, %)	43 (51%)	31 (60%)	6 (60%)	.550
tDCS adverse events (%)	42 (49%)	18 (35%)	3 (30%)	.165
Mental/physical health factors				
Concomitant psychotropics (%)	77 (91%)	47 (90%)	8 (80%)	.570
Comorbid mental disorders (%)	35 (41%)	12 (23%)	4 (40%)	.091[b]
Smoking (%)	17 (20%)	13 (25%)	5 (50%)	.105
Drinking (%)	32 (38%)	18 (35%)	5 (50%)	.653
Missingness/dropout				
Missing EMA % (first 30 days)	46.2	20.1	10.8	.000[a]
Dropout, V3 (%)	25 (29%)	5 (10%)	0 (0%)	.005[a]
Dropout, V4 (%)	33 (39%)	9 (17%)	0 (0%)	.003[a]

Note: [a]$P < .05$, [b]$P < .10$. For household income, 3 in Cluster 0 and one in Cluster 1 provided no answer, which were coded 0. Abbreviations: tDCS, transcranial direct current stimulation; ANOVA, analysis of variance; 6WA, 6-week active; EMA, ecological momentary assessment.

significant both BDI and MADRS [$\chi^2(2) = 9.56$, $p = .008$ and $\chi^2(2) = 7.46$, $P = .024$, respectively].

Table 3 summarizes the distribution of BDI and MADRS scores across each time point and the treatment effect and symptom return based on the score changes, as well as the results of between-cluster ANCOVA assessed for each time point. Consistent with the feature profiles, Cluster 1 exhibited the highest BDI and MADRS scores at V1, V3, and V4. The immediate treatment efficacy assessed at the end of tDCS administration was most pronounced in Cluster 2, although the difference reached statistical significance for BDI but not for MADRS. Notably, Cluster 2 also demonstrated a return of symptoms in both BDI and MADRS at 12 weeks post-treatment, indicating a higher return rate than other clusters.

Sensitivity analysis

The Time × Cluster interaction effects in the single-covariate LMMs for the full timeline, which were significant for BDI and marginally significant for MADRS in the primary analysis, remained significant across all 10 covariates entered independently for BDI ($Ps < .009$). For MADRS, 5 of the 10 single-covariate models were significant at $P < .05$. Covariates associated with significant interaction effects when entered independently included sex, age, years of education, tDCS group (6WA vs 3WA), and drinking, whereas the remaining covariates yielded trend-level interaction effects consistent with the primary analysis ($Ps < .054$). For the treatment interval (V1, V3), all single-covariate models were significant for BDI ($Ps < .007$) and marginally significant for MADRS ($Ps < .094$), indicating no changes in inference relative to the primary analysis. For the symptom return interval (V3, V4), the single-covariate interaction effects were significant across all covariates for both BDI ($Ps < .009$) and MADRS ($Ps < .024$).

To assess the influence of potential statistical artifacts arising from missing value imputation of the EMA features and clustering model variability, a seed-based sensitivity analysis was performed by repeating the imputation and clustering 20 times using seeds ranging from 0 to 19 in addition to the main seed of 42. Across 18 of the 20 runs,

Table 2 Cluster-level profiles of mood and sleep features.

	Cluster 0 (n = 85)	Cluster 1 (n = 52)	Cluster 2 (n = 10)	P
Mood features				
Mean	8.0 ± 2.6^{a}	10.1 ± 3.5^{b}	5.8 ± 3.7^{a}	<.001*
Min	0.4 ± 3.7^{c}	-4.0 ± 8.3^{b}	-21.4 ± 23.5^{a}	<.001*
Max	15.1 ± 3.2^{a}	22.4 ± 9.0^{b}	26.3 ± 27.4^{b}	<.001*
Slope	-0.07 ± 0.10	-0.08 ± 0.16	-0.12 ± 0.27	.518
Volatility	1.9 ± 0.8^{a}	2.7 ± 0.9^{b}	4.1 ± 1.8^{c}	<.001*
Autocorrelation	0.47 ± 0.28	0.46 ± 0.22	0.48 ± 0.18	.894
Decay	9.1 ± 4.1^{a}	11.1 ± 4.5^{b}	6.9 ± 3.9^{a}	.004*
Sleep features				
Mean	372.7 ± 38.2^{b}	318.1 ± 73.0^{a}	491.2 ± 91.0^{c}	<.001*
Min	222.5 ± 28.1^{b}	75.2 ± 73.2^{a}	41.8 ± 111.2^{a}	<.001*
Max	478.8 ± 80.4^{a}	556.0 ± 137.4^{b}	1284.0 ± 598.0^{c}	<.001*
Slope	-0.50 ± 0.65	-0.30 ± 1.51	-0.68 ± 3.22	.563
Volatility	51.0 ± 26.8^{a}	95.6 ± 26.0^{b}	183.5 ± 88.6^{c}	<.001*
Autocorrelation	0.16 ± 0.15^{b}	0.03 ± 0.20^{a}	0.11 ± 0.22^{ab}	<.001*
Decay	383.4 ± 70.6^{b}	303.9 ± 95.7^{a}	508.1 ± 120.9^{c}	<.001*

*$P < .05$. P-values are based on between-group one-way ANOVA with imputed data. Grouping letters are based on Tukey HSD post-hoc tests: clusters sharing at least one common letter indicate no significant differences (adjusted $P \geq .05$), whereas clusters sharing no letters in common indicate significant differences (adjusted $P < .05$). For example, the letter "ab" indicates no significant differences from both "a" and "b," although the "a" and "b" are significantly different from each other. Mood features are based on the Center for Epidemiologic Studies Depression Scale – Revised (CESD-R) items (higher scores indicate depressive symptoms). Sleep features are based on the self-reported sleep duration in minutes.

the mean ARI score relative to the reference seed solution was 0.80 (SD = 0.04), with 2 seeds (7 and 18) yielding markedly low agreement (ARI = 0.28 and 0.19). For the interaction effects that were significant in the main analysis—specifically, the entire timeline (BDI), treatment efficacy (BDI), and symptom return (BDI, MADRS)—LRTs of LMMs revealed that 53.8% of the corresponding tests remained significant across all 20 seeds and 58.3% remained significant when excluding the 2 low-agreement seeds. The supplementary cross-sectional ANCOVA for the significant between-cluster effects of treatment efficacy (BDI) and symptom return (BDI, MADRS) revealed that 73.3% and 81.5% of the corresponding tests remained significant across all seeds and 18 high-agreement seeds, respectively. The results suggest that although the current findings are generally robust to covariate specification and the stochastic characteristics of the imputation and clustering procedures, the instability observed in a minority of iterations and moderate sensitivity of statistical significance to cluster assignment variability underscore the potential for unstable clustering solutions under some variations.

Discussion

This study presents a pioneering approach that integrates EMA-based daily assessments of mood and sleep with tDCS to typologize response patterns across distinct patient characteristics, highlighting differences in tDCS efficacy and the degree of symptom recurrence following treatment discontinuation. Using GMM clustering on summary features derived from daily EMA trajectories, 3 distinct response types were identified: (1) a stable improvement type, characterized by stable (low-volatility) depressive mood and sleep duration; (2) a persistent high-symptom type, marked by consistently elevated depressive mood and restricted sleep duration, as shown in its mean scores; and (3) a volatile symptom type, exhibiting pronounced fluctuations (volatility) in both mood and sleep over time along with high overall (mean) sleep duration. The volatile symptom type, relative to the others, demonstrated substantial initial treatment effects but also a significant return of symptoms during follow-up, a pattern broadly consistent with previous reports in treatment-resistant and bipolar depression.[17,18,20] The clustering results remained generally robust to covariate specification and the stochasticity in the imputation and clustering processes, although some instability was observed in the sensitivity analysis.

This study employed real-world, data-driven analysis to explore patient response profiles to tDCS, laying the groundwork for tailored treatment protocols within a patient-centered, transdiagnostic framework. If treatment-response trajectories to tDCS can be fully characterized based on our findings, this could enable optimized stimulation settings, including decisions on continuation, supplementation, or integration of parallel interventions, based on predicted outcomes. This can facilitate a closed-loop neuromodulation system that dynamically monitors patient status and adjusts treatment parameters without continuous therapist input.[31–33] The integrated framework, combining tDCS, mobile EMA, and machine learning, serves as a prototype for precision psychiatry, offering a scalable model for the collection, analysis, and application of behavioral and physiological data.[34,35] The same architecture can be extended to other modalities, such as psychopharmacology and psychotherapy, to build comprehensive, personalized treatment portfolios in the future.

Among the identified response types in this study, stable improvement was the most common tDCS response pattern, comprising more than half of the participants. This cluster appears to reflect uncomplicated unipolar depression without prominent melancholic, atypical, or bipolar features. Characterized by relatively mild-to-moderate symptoms and robust clinical gains with tDCS, this group is known to have the most favorable treatment effects of tDCS.[18,19,36] The second type showed persistent high symptoms throughout the treatment period despite ongoing tDCS, which accounted for approximately 35% of the sample. This cluster resembles treatment-resistant, relatively more symptomatic depression, a profile that typically shows reduced responsiveness to tDCS.[18,19] This group may also include the melancholic subtype of depression, as sleep disturbances are known to be

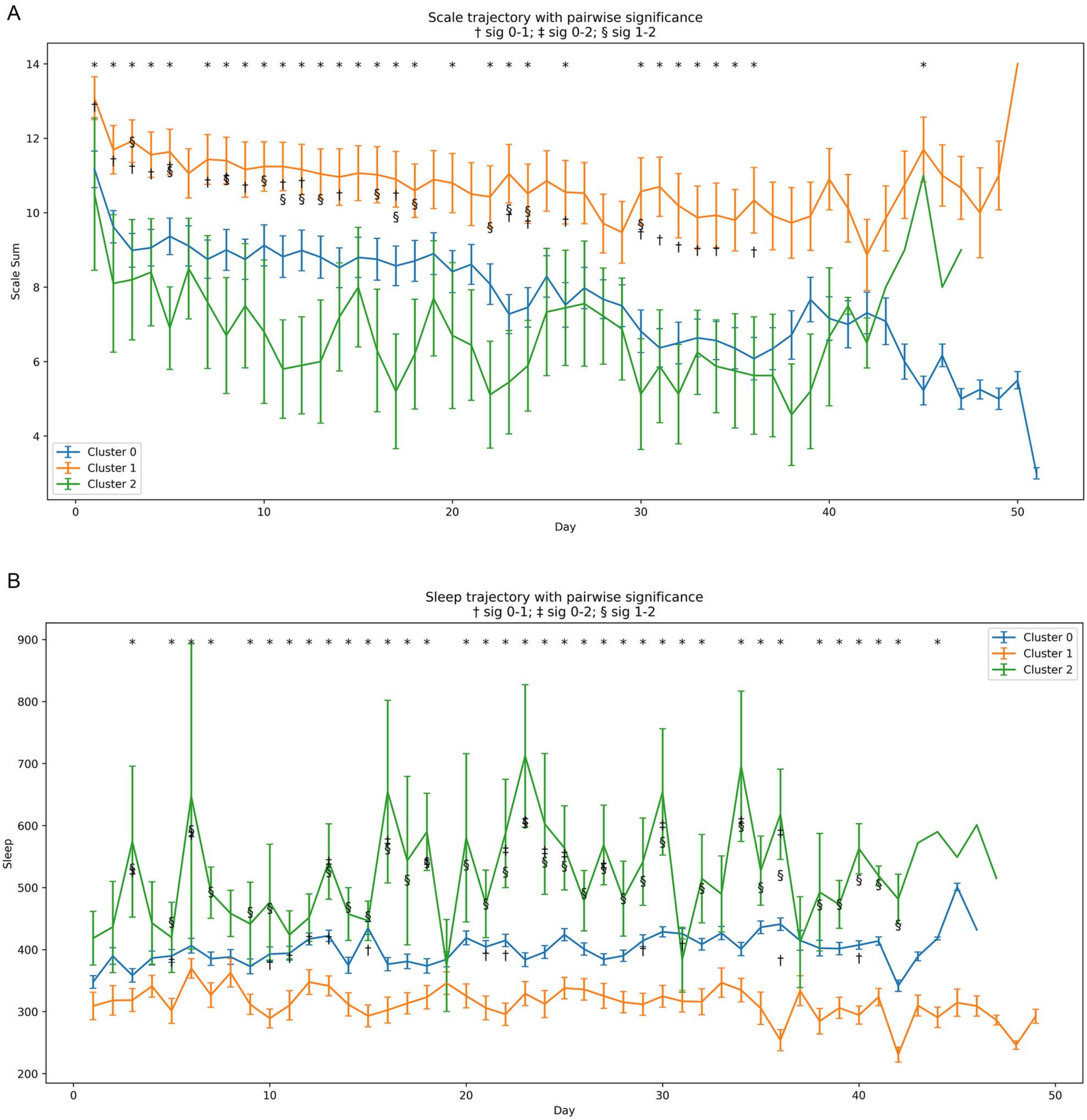


Figure 2 Daily trajectories of depressive mood scale and sleep duration across clusters. Based on raw (non-imputed) daily ecological momentary assessment scores with participants assigned to their respective clusters. Solid lines denote the cluster-specific daily means, and vertical bars indicate ± 1 standard error of the mean. The asterisks (*) at the top indicate significant between-group differences for each day based on one-way analysis of variance. Daggers (†), double daggers (‡), and section signs (§) denote significant pairwise differences in Tukey Honest Significant Difference post-hoc tests for Clusters 0 vs 1, 0 vs 2, and 1 vs 2, respectively.

one of the common symptoms of this subtype.[37] Also, in the current study, this cluster showed the highest V1 scores across clusters on items indicating melancholic profiles such as BDI-4 (loss of pleasure; 2.21 ± 0.93 vs 1.88 ± 0.76 in Cluster 0 and 1.90 ± 0.88 in Cluster 2), MADRS-8 (inability to feel; 3.12 ± 1.49 vs 2.87 ± 1.53 in Cluster 0 and 2.50 ± 1.65 in Cluster 2), and MADRS-1 (apparent sadness; 3.27 ± 1.01 vs 2.85 ± 1.11 in Cluster 0 and 2.70 ± 1.16 in Cluster 2), although most between-cluster differences did not reach statistical significance with the exception of BDI-4 (P = .047). This subtype may have difficulty responding to tDCS, as impaired plasticity in the DLPFC and rigid high-beta connectivity system may hinder the effects of the stimulation.[38,39] Nevertheless, in this study, the persistent high-symptom group did derive benefit from tDCS and did not show symptom recurrence during the follow-up period.

The final type represents a volatile symptom profile, which was also observed among 5%-15% of the participants in a previous study that clustered treatment response trajectories for depression using sociodemographic, physical health, personality, and treatment-related

Table 3 Cluster-level differences in depressive symptomatology (BDI and MADRS) across time points

	Cluster 0 ($n = 85$ on V1)	Cluster 1 ($n = 52$ on V1)	Cluster 2 ($n = 10$ on V1)	*P*
BDI scores at timeline				
V1	29.9 ± 9.2^{a}	37.4 ± 9.4^{b}	37.2 ± 13.1^{ab}	<.001*
V3	22.4 ± 12.6^{a}	30.4 ± 14.0^{b}	18.5 ± 12.0^{a}	.005*
V4	19.7 ± 12.4^{a}	29.1 ± 15.4^{b}	26.8 ± 17.0^{ab}	.006*
V3-V1 (efficacy)	-7.8 ± 10.7^{a}	-6.9 ± 9.9^{a}	-18.7 ± 15.8^{b}	.006*
V4-V3 (return)	-2.1 ± 9.4^{a}	-1.3 ± 7.2^{a}	8.3 ± 18.6^{b}	.002*
MADRS scores at timeline				
V1	25.6 ± 7.3^{a}	28.8 ± 6.6^{b}	25.0 ± 8.2^{ab}	.017*
V3	18.3 ± 9.8^{a}	24.2 ± 9.4^{b}	13.8 ± 7.2^{a}	.001*
V4	19.7 ± 12.4^{a}	29.1 ± 15.4^{b}	26.8 ± 17.0^{ab}	.043*
V3-V1 (efficacy)	-7.2 ± 9.4	-4.6 ± 9.5	-11.2 ± 10.4	.203
V4-V3 (return)	-0.9 ± 8.8^{a}	-0.4 ± 8.1^{a}	7.2 ± 10.2^{b}	.016*

Note: *$P < .05$. *P*-values are based on between-group one-way ANCOVA for each timeline. Grouping letters are based on Tukey HSD post-hoc tests: clusters sharing at least one common letter indicate no significant differences (adjusted $P \geq .05$), whereas clusters sharing no letters in common indicate significant differences (adjusted $P < .05$). For example, the letter "ab" indicates no significant differences from both "a" and "b," although the "a" and "b" are significantly different from each other. Missing values for BDI and MADRS were handled by pairwise deletion. *Covariates*: sex, age, year of education, household income, tDCS group, tDCS adverse events, concomitant psychotropics, comorbid mental disorders, smoking, drinking. Abbreviations: BDI, Beck Depression Inventory; MADRS, Montgomery–Åsberg Depression Rating Scale.

characteristics.[23] This type also likely corresponds to depression with mixed features, characterized by an agitated mood and the co-occurrence of depressive and (hypo)manic symptoms.[11] The current study also supports this type's potential link to mixed features, as this cluster showed the highest V1 scores on BDI-11 (agitation; 1.70 ± 0.95 vs 1.09 ± 0.93 in Cluster 0 and 1.46 ± 0.91 in Cluster 1) and BDI-17 (irritability; 1.90 ± 0.99 vs 1.07 ± 0.83 in Cluster 0 and 1.62 ± 0.99 in Cluster 1); $Ps < .029$. Research suggests that approximately 7.5% of all depression cases are classified as the mixed features type under DSM-5 criteria, which aligns with the proportion observed in the current sample, although this figure increases to 29% when using the Research-Based Diagnostic Criteria.[40] Because of their marked mood and sleep lability and bipolar-spectrum traits,[11,41,42] this group may exhibit reduced and less durable responses to tDCS, with an elevated risk of symptom relapse.[17,43] The symptom return shown in this cluster may reflect instability within cortico-limbic and default-mode network circuits: lower phase synchronization across brain regions has been associated with poorer remission after tDCS.[44] In addition, evidence of impaired synaptic plasticity in bipolar disorder could blunt the neuroplasticity-dependent effects of tDCS, which can also explain the limited long-term benefit in this subtype.[45]

The current results, if confirmed by future studies, are expected to contribute to the advancement of precision psychiatry, which aims to deploy guidelines and tools for diagnosis, treatment selection, and prognosis by leveraging individual, data-driven profiles.[34] The response profiles identified here could be translated into a clinical decision-support system for psychiatrists and tDCS clinical staff, providing actionable information on patients' response trajectories and anticipated treatment effectiveness and/or relapse risk, thereby supporting ongoing monitoring and optimized treatment decisions.[46–48] Ultimately, this framework could be extended toward a closed-loop neuromodulation system that adaptively adjusts stimulation parameters based on patient states and biomarkers.[32,33,49] Although most current closed-loop neuromodulation approaches rely primarily on biological signals,[32] incorporating longitudinal symptom-response data into closed-loop tDCS may further enhance the clinical utility of precision neuromodulation.

Despite these implications, this study also has several limitations. First, the clustering relied on summary features of longitudinal response trajectories rather than modeling the time series directly. Applying longitudinal clustering methods, such as Growth Mixture Modeling, could help address this limitation. Also, the sample size is relatively small to adequately detect the full range of tDCS response patterns in cases of depression. Although a previous study identifying treatment response patterns by clustering data from patients with depression yielded 7 distinct clusters across multiple datasets comprising 1826 participants,[23] the current study extracted 3 clusters with only 147 participants. Notably, the volatile symptom type included only 10 participants, a number likely insufficient to reliably extract stable EMA-based response features. Larger samples are needed to validate these findings and to identify additional response subtypes that may not have emerged due to limited statistical power.

Second, the impact of missing values warrants caution. The EMA dataset had a substantial proportion of missing values, exceeding 30%, which were handled using imputation algorithms based on multiple assumptions. Moreover, the rate of missing EMA cells differed across clusters, indicating that the impact of missingness may affect differentially across clusters. Although various tests and adjustments were employed to minimize bias, imputation may nonetheless have distorted the results, as shown in the sensitivity analysis with seed alteration. Indeed, many participants (particularly in Clusters 1 and 2) exhibited negative min values on the mood scale post-imputation, which are not possible in the original scoring system. Nevertheless, the distinct response patterns identified in this study may remain valid, as distinct response patterns were also observed in the non-imputed daily trajectory data.

Finally, this study did not differentiate between the randomized groups (6WA vs 3WA) in the main analysis. We pooled all participant data for the analyses regardless of intervention assignment, as no significant differences were observed in the overall treatment effects of tDCS between groups [$n = 147$; BDI V3–V1: -7.31 ± 12.19 vs -9.76 ± 9.74, $P = .248$; MADRS V3–V1: -6.87 ± 9.44 vs -5.92 ± 9.98, $P = .601$], the distribution of participants across clusters did not differ by group, and randomization status was included as a covariate in the main analysis. However, aggregating the intervention groups may still result in missing subtle group-specific effects, particularly given the limited sample size and statistical power. Therefore, further studies should account for potential heterogeneity in the response patterns to tDCS, which may include individual time-series or dose–response trajectories or interaction terms between stimulation parameters and participant characteristics. Future research with larger datasets and refined analytical approaches is necessary to precisely characterize individual treatment responses, which will advance the personalized, data-driven neuromodulation strategies for precision medicine.

Acknowledgments

The authors acknowledge Ms. Seoyun Hong for the assistance with image design and formatting of the graphical abstract.

Author contributions

Han Jung (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Methodology [equal], Visualization [equal], Writing—original draft [equal]), Sehwan Park (Data curation [equal], Investigation [equal], Resources [equal], Software [equal]), Kyungmi Chung (Resources [equal], Software [equal]), Yujin Kim (Investigation [equal], Validation [equal]), Daeyoung Roh (Project administration [equal], Supervision [equal]), Kyungun Jhung (Project administration [equal], Supervision [equal]), Woo Jung Kim (Conceptualization [equal], Funding acquisition [equal], Project administration [equal], Supervision [equal]), Jin Young Park (Project administration [equal], Supervision [equal]), and Jaesub Park (Conceptualization [equal], Funding acquisition [equal], Methodology [equal], Project administration [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal])

Supplementary material

Supplementary material are available at *International Journal of Neuropsychopharmacology* online.

Funding

This research was supported by 2 grants from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant No. 1: RS-2023-KH134964 and Grant No. 2: RS-2024-00439193).

Conflicts of interest

None declared.

Data availability

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical restrictions, but are available from the corresponding author on reasonable request.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Yongin Severance Hospital.

Trial registration

ClinicalTrials.gov (NCT05539131).

References

1. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul*. 2008;1:206-223. https://doi.org/10.1016/j.brs.2008.06.004
2. Yachou Y, Bouaziz N, Makdah G, et al. Transcranial direct current stimulation in patients with depression: an electric field modeling meta-analysis. *J Affect Disord*. 2025;374:540-552. https://doi.org/10.1016/j.jad.2025.01.001
3. Ren C, Pagali SR, Wang Z, et al. Transcranial electrical stimulation in treatment of depression: a systematic review and meta-analysis. *JAMA Netw Open*. 2025;8:e2516459. https://doi.org/10.1001/jamanetworkopen.2025.16459
4. Zheng EZ, Wong NML, Yang ASY, Lee TMC. Evaluating the effects of tDCS on depressive and anxiety symptoms from a transdiagnostic perspective: a systematic review and meta-analysis of randomized controlled trials. *Transl. Psychiatry*. 2024;14:295. https://doi.org/10.1038/s41398-024-03003-w
5. U.S. Food and Drug Administration (FDA). *Summary of Safety and Effectiveness Data (SSED): Flow FL-100. Premarket Approval (PMA) P230024. Silver Spring (MD): FDA*2025. Dec 8 [cited 2025 Dec 31]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230024B.pdf
6. Gold PW, Machado-Vieira R, Pavlatou MG. Clinical and biochemical manifestations of depression: relation to the neurobiology of stress. *Neural Plast*. 2015;2015:1-11. https://doi.org/10.1155/2015/581976
7. Łojko D, Rybakowski J. Atypical depression: current perspectives. *Neuropsychiatr Dis Treat*. 2017;13:2447-2456. https://doi.org/10.2147/ndt.s147317
8. Carroll BJ, Cassidy F, Naftolowitz D, et al. Pathophysiology of hypercortisolism in depression. *Acta Psychiatr Scand*. 2007;115:90-103. https://doi.org/10.1111/j.1600-0447.2007.00967.x
9. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman ATF, Penninx BWJH. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol Psychiatry*. 2012;18:692-699. https://doi.org/10.1038/mp.2012.144
10. Keller J, Gomez R, Williams G, et al. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. *Mol Psychiatry*. 2016;22:527-536. https://doi.org/10.1038/mp.2016.120
11. Pini S, Raia A, Amatori G, et al. A reevaluation of mixed depressive states from the DSM-5- TR perspective: a series of prototypical cases. *Arch Clin Cases*. 2024;11:22-28. https://doi.org/10.22551/2024.42.1101.10282
12. Hyett MP, Breakspear MJ, Friston KJ, Guo CC, Parker GB. Disrupted effective connectivity of cortical systems supporting attention and Interoception in melancholia. *JAMA Psychiatry*. 2015;72:350. https://doi.org/10.1001/jamapsychiatry.2014.2490
13. Shan X, Cui X, Liu F, et al. Shared and distinct homotopic connectivity changes in melancholic and non-melancholic depression. *J Affect Disord*. 2021;287:268-275. https://doi.org/10.1016/j.jad.2021.03.038

14. Guo ZP, Chen L, Tang LR, et al. The differential orbitofrontal activity and connectivity between atypical and typical major depressive disorder. *NeuroImage Clin*. 2024;45:103717. https://doi.org/10.1016/j.nicl.2024.103717
15. Liu R, Qi H, Guan L, et al. Functional connectivity of the default mode network subsystems in patients with major depressive episodes with mixed features. *Gen Psychiatry*. 2022;35:e100929-e100929. https://doi.org/10.1136/gpsych-2022-100929
16. Pastrnak M, Klirova M, Bares M, Novak T. Distinct connectivity patterns in bipolar and unipolar depression: a functional connectivity multivariate pattern analysis study. *BMC Neurosci*. 2024;25:46. https://doi.org/10.1186/s12868-024-00895-8
17. Loo CK, Husain MM, McDonald WM, et al. International randomized-controlled trial of transcranial direct current stimulation in depression. *Brain Stimul*. 2018;11:125-133. https://doi.org/10.1016/j.brs.2017.10.011
18. Nikolin S, Moffa A, Razza L, et al. Time-course of the tDCS antidepressant effect: an individual participant data meta-analysis. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2023;125:110752. https://doi.org/10.1016/j.pnpbp.2023.110752
19. Palm U, Hasan A, Strube W, Padberg F. tDCS for the treatment of depression: a comprehensive review. *Eur Arch Psychiatry Clin Neurosci*. 2016;266:681-694. https://doi.org/10.1007/s00406-016-0674-91
20. Valiengo L, Benseñor IM, Goulart AC, et al. The sertraline versus electrical current therapy for treating depression clinical study (SELECT-tDCS): results of the crossover and follow-up phases. *Depress Anxiety*. 2013;30:646-653. https://doi.org/10.1002/da.22079
21. Moskowitz DS, Young SN. Ecological momentary assessment: what it is and why it is a method of the future in clinical psychopharmacology. *J Psychiatry Neurosci*. 2006;31:13-20.
22. van Genugten CR, Schuurmans J, Hoogendoorn AW, et al. A data-driven clustering method for discovering profiles in the dynamics of major depressive disorder using a smartphone-based ecological momentary assessment of mood. *Front Psychiatry*. 2022;13:755809. https://doi.org/10.3389/fpsyt.2022.755809
23. Paul R, TillFM A, Czamara D, et al. Treatment response classes in major depressive disorder identified by model-based clustering and validated by clinical prediction models. *Transl Psychiatry*. 2019;9:187. https://doi.org/10.1038/s41398-019-0524-4
24. Park HY, Park J, Roh D, et al. Real-world effects of home-based transcranial direct current stimulation in depression: a randomized controlled trial of 3-week versus 6-week protocols. *Brain Behav*. 2025;15:e71119. https://doi.org/10.1002/brb3.71119
25. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The MINI-international neuropsychiatric interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59:22-33.
26. Beck AT, Steer RA, Brwon G. Beck depression inventory–II (BDI-II) [database record]. *Psychol Assess*. 1996. https://doi.org/10.1037/t00742-000
27. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389. https://doi.org/10.1192/bjp.134.4.382
28. Van Dam NT, Earleywine M. Validation of the Center for Epidemiologic Studies Depression Scale—Revised (CESD-R): pragmatic depression assessment in the general population. *Psychiatry Res*. 2011;186:128-132. https://doi.org/10.1016/j.psychres.2010.08.018
29. Chung K, Jeon MJ, Park J, et al. Development and evaluation of a mobile-optimized daily self-rating depression screening app: a preliminary study. *PLoS One*. 2018;13:e0199118. https://doi.org/10.1371/journal.pone.0199118
30. Pedregosa F, Varoquaux G, Gramfort A, et al. Scikit-learn: machine learning in python. *J Mach Learn Res*. 2011;12:2825-2830. https://doi.org/10.5555/1953048.2078195
31. Scangos KW, Khambhati AN, Daly PM, et al. Closed-loop neuromodulation in an individual with treatment-resistant depression. *Nat Med*. 2021;27:1-5. https://doi.org/10.1038/s41591-021-01480-w
32. Stanslaski S, Afshar P, Cong P, et al. Design and validation of a fully implantable, chronic, closed-loop neuromodulation device with concurrent sensing and stimulation. *IEEE Trans Neural Syst Rehabil Eng*. 2012;20:410-421. https://doi.org/10.1109/tnsre.2012.2183617
33. Lo MC, Widge AS. Closed-loop neuromodulation systems: next-generation treatments for psychiatric illness. *Int Rev Psychiatry*. 2017;29:191-204. https://doi.org/10.1080/09540261.2017.1282438
34. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of "precision psychiatry.". *BMC Med*. 2017;15:80. https://doi.org/10.1186/s12916-017-0849-x
35. Bzdok D, Meyer-Lindenberg A. Machine learning for precision psychiatry: opportunities and challenges. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3:223-230. https://doi.org/10.1016/j.bpsc.2017.11.007
36. Oh J, Jeon S, Ha TH, et al. Effect of home-based self-administered transcranial direct stimulation in patients with mild to moderate major depressive disorder: a single-arm, multicentral trial. *Clin Psychopharmacol Neurosci*. 2023;21:271-278. https://doi.org/10.9758/cpn.2023.21.2.271
37. Murphy MJ, Peterson MJ. Sleep disturbances in depression. *Sleep Med Clin*. 2015;10:17-23. https://doi.org/10.1016/j.jsmc.2014.11.009
38. Kaneko N, Wada M, Nakajima S, et al. Neuroplasticity of the left dorsolateral prefrontal cortex in patients with treatment-resistant depression as indexed with paired associative stimulation: a TMS–EEG study. *Cereb Cortex*. 2024;34:bhad515. https://doi.org/10.1093/cercor/bhad515
39. Zhang Q, Du Y, Bao C, et al. Aberrant high-beta band functional connectivity during reward processing in melancholic major depressive disorder: an MEG study. *Neuroimage Clin*. 2024;43:103666-103666. https://doi.org/10.1016/j.nicl.2024.103666
40. Perugi G, Angst J, Azorin JM, et al. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J Clin Psychiatry*. 2015;76:e351-e358. https://doi.org/10.4088/JCP.14m09092
41. Wu X, Wang S, Niu Z, et al. Bipolar disorder at mixed states and major depressive disorder with mixed features differ in peripheral biochemical parameters. *BMC Psychiatry*. 2025;25:362. https://doi.org/10.1186/s12888-025-06800-9
42. Harvey AG, Talbot LS, Gershon A. Sleep disturbance in bipolar disorder across the lifespan. *Clin Psychol Sci Pract*. 2009;16:256-277. https://doi.org/10.1111/j.1468-2850.2009.01164.x
43. Dondé C, Neufeld NH, Geoffroy PA. The impact of transcranial direct current stimulation (tDCS) on bipolar depression, mania, and euthymia: a systematic review of preliminary data. *Psychiatr Q*. 2018;89:855-867. https://doi.org/10.1007/s11126-018-9584-5
44. Xiao W, Moncy JC, Ghazi-Noori AR, et al. Enhanced network synchronization connectivity following transcranial direct current stimulation (tDCS) in bipolar depression: effects on EEG oscillations and deep learning-based predictors of clinical remission. *J Affect Disord*. 2024;369:576-587. https://doi.org/10.1016/j.jad.2024.09.054
45. Elvsåshagen T, Moberget T, Bøen E, et al. Evidence for impaired neocortical synaptic plasticity in bipolar II disorder. *Biol*

Psychiatry. 2012;71:68-74. https://doi.org/10.1016/j.biopsych.2011.09.026

46. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. *NPJ Digit Med*. 2020;3:17. https://doi.org/10.1038/s41746-020-0221-y
47. Wansbrough K, Tan J, Vallence AM, Fujiyama H. Recent advancements in optimising transcranial electrical stimulation: reducing response variability through individualised stimulation. *Curr Opin Behav Sci*. 2024;56:101360. https://doi.org/10.1016/j.cobeha.2024.101360
48. Bhattacharjee S, Sivakumar PT, Venkatasubramanian G, et al. Personalized transcranial direct current stimulation for behavioral and neurophysiologic outcomes. *JAMA Netw Open*. 2025;8:e2526148. https://doi.org/10.1001/jamanetworkopen.2025.26148
49. Zrenner C, Ziemann U. Closed-loop brain stimulation. *Biol Psychiatry*. 2024;95:545-552. https://doi.org/10.1016/j.biopsych.2023.09.014

International Journal of Neuropsychopharmacology, 2026, **29**, 1–12
https://doi.org/10.1093/ijnp/pyag012
Regular Research Article