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Research Report

An Exploration of the Therapeutic Potential of Targeted tDCS in Alzheimer's-Associated Agitation & Aggression

Sofia Penttila

Research Advisor: Dr. Sanjeev Kumar

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I. Introduction

Alzheimer's Overview

Alzheimer's disease (AD) is a complex neurodegenerative disorder influenced by a combination of genetic, environmental, and lifestyle factors[1]. While an ageing brain is a normal part of human development, AD is characterized by significant cognitive, behavioral, and functional decline that can profoundly affect an individual's personality, independence, and quality of life[2].

Neuropathologically, AD is associated with the accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. These pathological changes are implicated with synaptic dysfunction, neuronal loss, and progressive brain atrophy, particularly in regions involved in learning and memory[1].

While most AD develops on a seemingly sporadic basis, mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) can cause a rare familial form of AD with symptoms typically developing between the ages of 30 to 50[1]. These mutations alter the production or processing of amyloid-β peptides, promoting plaque formation and accelerating disease progression. The much more common form of late onset AD occurs typically after the age of 65 and is likely caused by a complex interaction between genetic and environmental factors[1]. Genetics plays a significant role in susceptibility to late-onset AD, particularly through variations in the apolipoprotein E (APOE) gene, with the APOE ε4 allele representing the strongest known genetic risk factor[1].

An estimated 57 million people worldwide live with dementia, a number that is set to triple by 2050[3]. Alzheimer's Disease is the most common form of dementia globally[1], affecting far more than just those diagnosed. Patients, caregivers, families, and broader society all suffer from the profound emotional, social, and economic consequences of AD[4]. Much of the growth in dementia cases in the coming years is expected to occur in low to middle income countries[5], where healthcare systems are already overburdened and ill-equip to respond to current rates of the disease, let alone the looming dementia crisis that awaits. Given this, finding affordable and scalable Alzheimer's treatments is more important than ever if we want to ensure global healthcare infrastructures are ready to respond to the uptick in dementia cases.

Cortical Dysregulation in Alzheimer's Disease

In AD, the accumulation of amyloid-β and tau pathology impairs synaptic function and alters communication between regions of the brain[6]. These changes can result in widespread cortical dysregulation, particularly in neural circuits relevant to AD such as memory, attention, and executive function[6]. A key feature of the neural dysregulation characteristic of AD is the disruption of the balance between excitatory glutamatergic and inhibitory GABAergic signalling[6]. In healthy individuals, excitation and inhibition are tightly regulated to ensure stable neural activity, support information processing, and maintain normal cognitive function. In Alzheimer's disease, synaptic dysfunction and selective vulnerability of inhibitory interneurons can shift this balance toward cortical hyperexcitability, resulting in abnormal neuronal firing and impaired network synchronization[6]. Evidence from electrophysiological and neuroimaging studies suggests that this altered excitability contributes to cognitive decline and may underlie many of the neuropsychiatric symptoms observed in AD[6].

Cortical dysregulation has emerged as a promising target for AD therapies due to the importance of excitation-inhibition balance in AD pathology[6]. Neuromodulation techniques such

as transcranial direct current stimulation therefore have large therapeutic potential due to their ability to modify cortical excitability and improve cognitive and behavioral function[7].

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technique that uses low-intensity electrical currents to alter cortical excitability and neural activity[8]. tDCS can restore excitation and inhibition balance in the brain by altering GABA and glutamate activity[9]. tDCS is part of a broader effort in psychiatric and neurological research to evaluate the therapeutic potential of noninvasive brain stimulation techniques for a range of neuropsychiatric disorders. In tDCS electrical stimulation is delivered at a constant current of 1 to 2 mA through cathodal and anodal electrodes applied to the scalp, driven by a small battery[8]. Cathodal stimulation decreases neural excitability by hyperpolarizing neuronal membranes in targeted areas while anodal stimulation increases the spontaneous firing rate of neurons[8].

tDCS has shown promising effects in treating symptoms of depression[10], stroke[11], schizophrenia[12], anxiety[13], PTSD[14], and overall cognition[15]. A recent area of focus has been the application of tDCS to neurodegenerative conditions such as Alzheimer's disease[15]. tDCS has been used in several studies on patients with AD. Most of these studies target the Dorsolateral Prefrontal Cortex (DLPFC) and temporal lobe regions of the brain. The efficacy of tDCS as a treatment for Alzheimer's remains unclear as studies have produced mixed results on the performance of the treatment[16]. Another key area of tDCS research is whether the effects of the treatment can be retained post-treatment[8]. Whether the effects of treatment are sustained following active treatment is important in understanding the long-term treatment potential of tDCS[16].

We aim to understand how treatment with tDCS influences neuropsychiatric symptoms of Alzheimer's disease compared to sham treatment and whether these effects are sustained in a two week follow up.

tTED Study

All data for this analysis comes from the Targeting Brain Physiology to Treat Neuropsychiatric Symptoms of Dementia Using TMS-EEG and tDCS (tTED) study conducted at the Centre for Addiction and Mental Health in Toronto, Canada. The study used single and paired pulse transcranial magnetic stimulation (TMS) paradigms such as long interval cortical inhibition (LICI) and short interval intracortical inhibition (SICI) paired with electroencephalography (EEG) to assess cortical excitation/inhibition balance in the dorsolateral prefrontal cortex (DLPFC) of participants with AD with and without agitation/aggression symptoms and age matched healthy comparators. The study examined whether applying tDCS to the frontal brain regions to target deficits in inhibition could improve neuropsychiatric symptoms of AD such as agitation and aggression.

Clinical assessments, cognitive function testing, and baseline cortical inhibition measured using TMS-EEG were conducted before study initiation to characterize participants at baseline. Participants with AD and agitation received a two week course of active/sham cathodal tDCS to the frontal brain region in a double blind 1:1 randomized control design. Cathodal tDCS is designed to decrease neural excitability by hyperpolarizing neuronal membranes, ultimately helping with improving clinical symptoms linked to cortical hyperexcitability in Alzheimer's disease such as positive symptoms like agitation and aggression. By applying this stimulation to

frontal brain regions (FPz), the study specifically aimed to address deficits in inhibition that manifest as agitated or aggressive behaviors.

Assessments of cortical inhibition using measures identical to baseline were done at the end of the tDCS course. Clinical and cognitive assessments were also completed following tDCS and 2 week follow up. The treatment effects on clinical symptoms, cortical inhibition, and the rate of adverse events were compared between the active and sham tDCS groups.

II. Methods

tDCS and Sham Treatments

Active transcranial direct current stimulation (tDCS) was delivered using a Soterix tDCS device with two 5 x 5 cm saline-soaked sponge electrodes. Cathodal stimulation was applied over the frontal region (FPz), with the anode positioned at CPz according to the international 10-10 EEG system. Stimulation was delivered at an intensity of 2 mA for 30 minutes per session, 5 days per week for 2 weeks (10 sessions total). Participants randomized to the sham condition underwent the same electrode placement and treatment procedures; however, the device automatically turned off stimulation after 30 seconds while maintaining identical setup procedures to preserve blinding. Both active and sham interventions could be administered either onsite or at home under remote supervision following caregiver training.

TMS-EEG

Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) was used to assess cortical excitation-inhibition balance in the dorsolateral prefrontal cortex (DLPFC) and motor cortex. Single and paired-pulse TMS paradigms were used to measure long-interval cortical inhibition (LICI) and short-interval intracortical inhibition (SICI). LICI was assessed using paired suprathreshold stimuli separated by a 100 ms interstimulus interval, while SICI was measured using a subthreshold conditioning stimulus (80% resting motor threshold) delivered 2 ms before a suprathreshold test stimulus. Stimuli were delivered using a figure-of-eight coil at an intensity sufficient to evoke a mean 1 mV motor evoked potential. EEG activity was recorded simultaneously using a 64-channel SynAmps 2 EEG system with DC recording, a 100 Hz low-pass filter, and a sampling rate of 20 kHz. Resting-state EEG (eyes open and eyes closed) was recorded before TMS testing. To minimize auditory artifacts from the TMS coil discharge, participants wore headphones delivering continuous white noise during stimulation.

Clinical Measures

NPI-C, CMAI, CGIC, and CGI-S were selected as clinical rating scales to measure changes in neuropsychiatric clinical symptoms following tDCS and sham treatment. The tDCS intervention targeted the frontal cortex using cathodal stimulation, with the aim of modulating cortical excitability and potentially improving symptoms associated with disrupted excitation-inhibition balance, particularly agitation and aggression. Although agitation and aggression represented the primary behavioral targets of the intervention, all NPI-C domains were assessed to provide a comprehensive evaluation of the potential effects of tDCS across the broader range of neuropsychiatric symptoms associated with Alzheimer's disease.

Neuropsychiatric Inventory-Clinician (NPI-C)

The Neuropsychiatric Inventory-Clinician (NPI-C) is a validated, clinician-rated measure used to assess the presence and severity of neuropsychiatric symptoms in individuals with dementia. The NPI-C incorporates clinician judgment based on information obtained from both the patient and caregiver, allowing for a comprehensive and reliable assessment of behavioral and psychological symptoms. Subdomain-level ratings are summed to generate domain scores, enabling detailed evaluation of symptom severity and monitoring of changes over time[17]. The NPI-C evaluates 14 neuropsychiatric domains, including delusions, hallucinations, agitation, aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, aberrant motor behavior, sleep disturbances, appetite and eating disorders, and aberrant vocalizations. Domain scores were calculated by summing clinician-rated item scores within each neuropsychiatric domain. An overall NPI-C total score was calculated as the sum of all domain scores. Higher scores indicate greater neuropsychiatric symptom severity.

Cohen-Mansfield Agitation Inventory (CMAI)

The Cohen-Mansfield Agitation Inventory (CMAI) is a validated caregiver-rated measure designed to assess the frequency of agitated behaviors in individuals with dementia. The scale consists of 29 items representing physically aggressive, physically non-aggressive, verbally aggressive, and verbally non-aggressive behaviors. Each behavior is rated on a 7-point scale according to its frequency during the preceding two weeks, with higher total scores indicating greater agitation severity. The CMAI is widely used in clinical trials evaluating interventions for agitation in dementia due to its strong reliability, validity, and sensitivity to treatment-related changes[18].

Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Change (CGIC)

The Clinical Global Impression scales were used to evaluate overall illness severity and clinical change throughout the study. The Clinical Global Impression-Severity (CGI-S) assesses the clinician's impression of the participant's current illness severity using a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The Clinical Global Impression-Change (CGIC), also referred to as the Clinical Global Impression-Improvement (CGI-I), evaluates change in clinical status relative to baseline using a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Both measures provide global assessments of treatment response based on clinician judgment and are widely used in dementia and neuropsychiatric clinical trials[19].

Statistical Analysis

Statistical analysis was conducted to evaluate clinical changes following active tDCS compared with sham stimulation and to investigate whether baseline cortical inhibition is predictive of clinical response following tDCS or sham treatment. Analysis incorporated clinical assessments collected at baseline (T0), immediately following the two-week intervention (T1), and at the two-week follow-up (T2). All statistical analysis and graphical visualization were performed in R.

Baseline Demographics Analysis

Demographic factors such as age, gender, and race were assessed to understand whether there were any clear demographic differences between the tDCS treatment and sham groups

(Figure I). Mean baseline scores for clinical symptoms were also calculated to determine whether there was a significant difference between the baseline clinical ratings of the tDCS and sham groups (Figure II).

Clinical Data

Clinical symptoms were assessed at T0, T1, and T2 and compared between tDCS and sham treatment. Our analysis focused on the NPI-C subscales and CMAI total, and clinical ratings. For each clinical measure, a linear mixed-effects model was fitted with treatment group (tDCS vs sham), time (T0, T1, and T2), and their interaction as fixed effects, with a random intercept for participant to account for repeated measurements within individuals.

Type III analysis of variance (ANOVA) was used to assess the main effects of treatment group and time, as well as the group × time interaction, with degrees of freedom calculated using the Satterthwaite method. Estimated marginal means were subsequently calculated to examine between-group differences at each timepoint, using Kenward-Roger degrees of freedom and 95% confidence intervals. For measures with observations at T1 and T2 only, the same modelling approach was applied using the available timepoints. Missing observations were excluded from the corresponding analysis.

Baseline Global LICI & NPI-C Trajectory

Finally, an exploratory analysis was conducted on whether baseline global LICI levels predicted changes in NPI-C clinical symptoms following tDCS or sham treatment. For each NPI-C subscale, change scores were calculated from baseline to T1 (T0 - T1) and T2 (T0 - T2), such that positive values represented a reduction in NPI-C scores over time, indicating an improvement in symptoms.

Separate linear regression models were fitted for each NPI-C subscale and timepoint, with baseline LICI Global Average, treatment group (tDCS vs sham), and the baseline LICI × treatment group interaction included as predictors. The interaction term was used to determine whether the association between baseline LICI and subsequent NPI-C change differed between the tDCS and sham groups.

III. Results

Participant Characteristics

A total of 22 participants with Alzheimer's disease and clinically significant agitation and/or aggression were included in the intervention analysis. Participants were randomly assigned in a double-blind 1:1 design to receive either active cathodal tDCS (n=10) or sham stimulation (n=12).

Participant Demographics

At baseline, the tDCS group (n=10) had a higher mean age than the sham group (n=12), with mean ages of 78.8 ± 9.23 years and 71.67 ± 7.90 years, respectively (Figure I). The tDCS group included 7 females and 3 males, while the sham group included 6 females and 6 males (Figure I). Racial composition also differed between groups. The tDCS group included White (n=1), South Asian (n=3), Black (n=2), Latin American (n=2), Korean (n=1), and Japanese (n=1) participants, whereas the sham group included White (n=8), Black (n=1), Latin American (n=2), and Arab (n=1) participants (Figure I). The groups showed descriptive differences in age, gender

distribution, and racial composition at baseline. Given the small sample size, these demographic characteristics were primarily examined descriptively rather than interpreted as evidence of systematic group differences.

Baseline Clinical Measures

Baseline clinical ratings were also compared descriptively between treatment groups. Mean NPI-C total scores were 59.4 ± 39.62 in the tDCS group and 48.92 ± 36.89 in the sham group. Several NPI-C subdomains showed higher mean baseline scores in the tDCS group, particularly agitation (13.9 ± 6.71 vs. 9.0 ± 6.8), aggression (3.9 ± 3.76 vs. 0.42 ± 1.16), and disinhibition (5.4 ± 8.6 vs. 2.3 ± 4.68) (Figure II). Conversely, the sham group had higher mean scores for dysphoria (7.3 ± 6.47 vs. 5.2 ± 6.32), anxiety (7.08 ± 8.25 vs. 5.1 ± 4.84), and apathy/indifference (6.25 ± 8.27 vs. 4.3 ± 8.69) compared with the tDCS group (Figure II). Elation/euphoria had a mean score of zero in both groups, as clinician assessment did not find any symptoms of elation/euphoria in participants.

CMAI measures were generally comparable between groups, although some measures showed notable differences. For example, mean CMAI total frequency was 51.6 ± 7.92 in the tDCS group and 53.58 ± 11.90 in the sham group, while the corrected physical non-aggressive severity scores were 1.8 ± 1.03 and 2.4 ± 1.0, respectively (Figure II). The CGI-S ratings were also similar between groups, with mean baseline ratings of 4.70 ± 0.67 for tDCS and 4.55 ± 0.69 for sham (Figure II).

These findings indicate that some baseline clinical differences were present between the treatment groups, particularly across individual NPI-C symptom domains, while several CMAI and CGI-S measures were relatively similar. The baseline differences were considered when interpreting subsequent changes in clinical symptoms following treatment.

Clinical Data

Clinical outcomes were assessed across T0, T1, and T2 time intervals. Overall, most NPI-C subscales and CMAI measures did not show significant group × time interactions, indicating that changes in clinical symptoms over time generally did not differ significantly between the tDCS and sham groups. Similarly, CGI-S severity ratings showed no significant group × time interaction ($F(2, 35.81) = 1.36$, $p = 0.270$), with estimated mean ratings remaining relatively similar between groups across T0, T1, and T2 (Figure III).

A significant group × time interaction was observed for the NPI-C aggression subscale ($F(2, 40) = 4.74$, $p = 0.014$) (Figure IV). At baseline, aggression scores were higher in the tDCS group than in the sham group (3.90 ± 0.88 vs. 0.42 ± 0.81), although this between-group difference was no longer significant at T1 or T2. At T1, estimated mean aggression scores were 1.20 in the tDCS group and 1.25 in the sham group, while at T2 they were 3.00 and 1.42, respectively.

A significant group × time interaction was also observed for CMAI physical non-aggressive severity (corrected) ($F(2, 40) = 6.05$, $p = 0.005$) (Figure V). The tDCS group had a lower estimated mean score at baseline than the sham group (1.80 vs. 2.42), but this pattern reversed following treatment, with the tDCS group showing higher scores at T1 (2.70 vs. 1.92) and T2 (2.60 vs. 1.50).

In contrast, CMAI total frequency did not demonstrate a significant group × time interaction ($F(2, 40) = 0.80$, $p = 0.456$) (Figure VI). Estimated mean scores were 51.6 and 53.6 at T0, 60.0 and 54.7 at T1, and 58.2 and 52.4 at T2 for the tDCS and sham groups, respectively.

Several NPI-C subscales demonstrated favorable symptom trajectories in the tDCS group that may warrant further investigation. NPI-C agitation decreased from an estimated mean of 3.50 at T0 to 2.10 at T2 in the tDCS group, although the group × time interaction was not significant ($F(2, 40) = 0.98$, $p = 0.382$) (Figure VII). NPI-C apathy/indifference also showed a notable reduction in the tDCS group, decreasing from 4.30 at T0 to 0.80 at T2, compared with a decrease from 6.25 to 2.92 in the sham group; however, the group × time interaction was not significant (Figure VIII). NPI-C anxiety similarly demonstrated a favorable trajectory in the tDCS group (Figure IX).

Taken together with the significant NPI-C aggression findings, this may suggest that agitation, apathy/indifference, and anxiety warrant further investigation as potential symptom domains responsive to tDCS, while the significant interaction for aggression provides stronger evidence of a differential clinical trajectory between treatment groups.

Baseline Global LICI & NPI-C Trajectory

An exploratory analysis was conducted to determine whether baseline global LICI was associated with subsequent changes in NPI-C symptoms at T1 and T2. Overall, baseline LICI was not significantly associated with NPI-C improvement for most subscales. However, significant LICI × treatment group interactions were observed for several symptom domains. For NPI-C aberrant motor disturbance at T1, the interaction was significant ($\beta = 2.62$, $p = 0.003$, $R^2 = 0.804$), indicating that the association between baseline LICI and change in aberrant motor disturbance differed between the tDCS and sham groups (Figure X). A significant interaction was also observed for NPI-C dysphoria at T1 ($\beta = 4.39$, $p = 0.021$, $R^2 = 0.568$) (Figure XI). At T2, the NPI-C irritability interaction was significant ($\beta = 8.78$, $p = 0.045$, $R^2 = 0.459$) (Figure XII).

Additionally, baseline LICI showed a significant main association with change in NPI-C aggression at T1 ($\beta = -0.178$, $p = 0.039$), although the LICI × treatment interaction was not significant ($\beta = 0.765$, $p = 0.129$) (Figure XIII). Several other interactions approached but did not reach statistical significance, including aberrant motor disturbance at T2 ($p = 0.055$) (Figure XIV), disinhibition at T1 ($p = 0.067$) (Figure XV), and irritability at T1 ($p = 0.070$) (Figure XVI).

Taken together, these exploratory findings suggest that baseline cortical inhibition, as measured by global LICI, may be differentially associated with subsequent NPI-C symptom trajectories across treatment groups, particularly for aberrant motor disturbance, dysphoria, and irritability. Given the small sample ($N = 11$), these findings should be considered preliminary.

IV. Discussion

This study examined the effects of tDCS on neuropsychiatric symptoms in individuals with agitation/aggression associated with Alzheimer's disease, with a particular focus on whether treatment was associated with changes in clinical NPI-C and CMAI measures and whether baseline cortical inhibition, measured by global LICI, was associated with subsequent clinical trajectories. Overall, the findings provide preliminary evidence of differential changes in specific neuropsychiatric symptoms following tDCS, while most clinical outcomes did not demonstrate significant differences between treatment groups. Significant group × time interactions were observed for NPI-C aggression and CMAI physical non-aggressive severity. Exploratory analysis additionally identified favorable trajectories in agitation, apathy/indifference, and

anxiety in the tDCS group, as well as significant interactions between baseline global LICI and subsequent changes in aberrant motor disturbance, dysphoria, and irritability.

Baseline Demographics

The treatment groups demonstrated several descriptive differences at baseline. The tDCS group was older on average than the sham group and had a different racial and gender composition. Importantly, baseline clinical symptoms also differed across several NPI-C domains, with the tDCS group demonstrating higher baseline agitation, aggression, and disinhibition, while the sham group had higher dysphoria, anxiety, and apathy/indifference. These differences are particularly relevant when interpreting longitudinal changes because participants did not begin treatment with identical levels of neuropsychiatric symptom severity.

The substantially higher baseline aggression in the tDCS group is particularly important when interpreting the significant group × time interaction observed for NPI-C aggression. The tDCS group began with considerably higher aggression scores than the sham group. The subsequent reduction in aggression following treatment may partly reflect differences in baseline symptom burden and regression toward the mean. Nevertheless, the convergence of aggression scores between groups at T1 represents a potentially meaningful clinical pattern. The later increase in the tDCS group at T2, however, suggests that this improvement may not have been sustained over the two-week follow-up period. Thus, while the significant interaction provides evidence that aggression trajectories differed between groups, it does not by itself establish a sustained therapeutic effect of tDCS.

Clinical Effects of tDCS

The primary clinical analysis demonstrated significant differential trajectories for NPI-C aggression and CMAI physical non-aggressive severity (corrected). The significant group × time interaction for NPI-C aggression indicates that the pattern of change across treatment and follow-up differed between the tDCS and sham groups. The tDCS group demonstrated a substantial reduction in aggression immediately following treatment, with estimated scores decreasing from 3.90 at baseline to 1.20 at T1. In comparison, the sham group remained relatively stable between baseline and T1. This finding is consistent with the possibility that tDCS may influence specific behavioral symptoms associated with agitation and aggression.

However, the increase in the tDCS group's aggression score to 3.00 at T2 is important. It suggests that the observed improvement immediately following treatment may not be sustained. Furthermore, because the tDCS group had considerably greater aggression at baseline, baseline imbalance must be considered when interpreting this finding. Therefore, the result is better interpreted as evidence of a differential trajectory in aggression rather than definitive evidence of a sustained anti-aggressive effect of tDCS.

The significant interaction observed for CMAI physical non-aggressive severity (corrected) was notably different in direction. The tDCS group began with lower severity than the sham group but had higher estimated scores at both T1 and T2. Thus, this measure does not provide evidence of improvement associated with tDCS. Instead, the significant interaction suggests that the treatment groups followed different trajectories, with the tDCS group showing an unfavorable change relative to sham on this particular measure. This finding highlights the importance of examining multiple behavioral domains rather than interpreting the overall clinical effect of tDCS as uniformly beneficial.

Consistent with this interpretation, CMAI total frequency and CGI-S did not demonstrate significant group × time interactions. The lack of a significant effect on overall agitation frequency or global clinical severity suggests that the effects of tDCS, if present, may be symptom-specific rather than broad improvements in overall neuropsychiatric or clinical status. This is also consistent with the observation that several individual NPI-C domains showed potentially favorable trajectories despite the absence of significant effects across most measures.

Potentially Responsive Neuropsychiatric Symptoms

Although most NPI-C measures did not demonstrate statistically significant group × time interactions, several symptom domains showed patterns that may warrant further investigation. In particular, the tDCS group showed reductions in agitation, apathy/indifference, and anxiety over the follow-up period. Agitation decreased from an estimated mean of 3.50 at baseline to 2.10 at T2, while apathy/indifference decreased from 4.30 to 0.80. These findings are potentially relevant given that agitation and other behavioral disturbances represent clinically important neuropsychiatric manifestations of Alzheimer's disease.

However, these results should be interpreted cautiously. The group × time interaction for agitation was not significant, and apathy/indifference similarly did not demonstrate a significant differential trajectory. Therefore, the data do not establish that tDCS was responsible for these improvements or that improvement was greater than that observed with sham. Instead, these findings identify potential symptom areas for future investigation.

Taken together, the pattern suggests that tDCS may have greater potential to influence specific neuropsychiatric symptoms, particularly behavioral manifestations such as aggression and agitation, rather than producing a generalized reduction in clinical severity. The significant aggression finding provides the strongest evidence for a differential treatment trajectory, while the changes observed in agitation, apathy/indifference, and anxiety provide preliminary directions for future research.

Baseline LICI and Clinical Trajectory

The exploratory analysis of baseline global LICI provides an additional perspective on the potential mechanisms underlying clinical response. Baseline LICI was not significantly associated with changes in most NPI-C domains. However, significant LICI × treatment interactions were identified for aberrant motor disturbance at T1, dysphoria at T1, and irritability at T2. These findings suggest that the relationship between baseline cortical inhibition and subsequent clinical change may differ depending on whether participants received active tDCS or sham stimulation.

The finding for aberrant motor disturbance at T1 was particularly strong, with the interaction explaining a substantial proportion of variance in the model ($R^2 = 0.804$). Similarly, the interaction for dysphoria at T1 explained approximately 57% of the variance, while the irritability interaction at T2 explained approximately 46%. These results raise the possibility that baseline cortical inhibitory function may help identify individuals whose neuropsychiatric symptoms are more responsive to neuromodulation.

Importantly, these findings are exploratory and should not be interpreted as demonstrating that baseline LICI predicts treatment response. The LICI analysis were based on only 11 participants with complete data, substantially reducing statistical power. Additionally, multiple NPI-C domains and timepoints were examined, increasing the possibility of false-

positive findings. The significant associations therefore require replication in larger samples before baseline LICI can be considered a reliable biomarker of clinical response.

Limitations

Several limitations should be considered. First, the study had a small sample size, with only 22 participants overall and 11 participants with complete data available for the LICI-NPI-C exploratory analysis. This limited statistical power and makes estimates particularly sensitive to individual participants. Second, there were descriptive baseline differences between the treatment groups, including differences in age and several NPI-C symptom domains. These differences are especially important for outcomes such as aggression, where the tDCS group had substantially greater baseline symptom severity.

Third, the exploratory analysis involved numerous NPI-C subscales and multiple timepoints. Consequently, statistically significant findings should be interpreted cautiously, particularly where analysis was not adjusted for multiple comparisons. Finally, the increase in some symptoms between T1 and T2 suggests that any immediate post-treatment effects may not necessarily persist over the longer follow-up period.

Conclusion

Overall, this study provides preliminary evidence that tDCS may differentially influence specific neuropsychiatric symptoms in Alzheimer's disease, rather than producing a generalized improvement in clinical severity. The significant group × time interaction for NPI-C aggression represents the strongest evidence of a differential clinical trajectory, although the higher baseline aggression in the tDCS group and subsequent increase at T2 warrant cautious interpretation. Favorable trajectories in agitation, apathy/indifference, and anxiety warrant future investigation. Furthermore, the exploratory association between baseline global LICI and subsequent changes in several NPI-C domains suggests that cortical inhibitory function may have potential as a biomarker for differential response to neuromodulation.

V. Future Directions

Future research should further investigate the neurophysiological mechanisms underlying clinical responses to tDCS by expanding EEG analysis beyond the global LICI measure examined in this study. Analysis of additional EEG measures, including regional and electrode-specific LICI responses, SICI, N45, N100, and global mean field power (GMFP), may provide a more comprehensive characterization of cortical excitation and inhibition and help clarify how changes in cortical activity relate to neuropsychiatric symptoms. Examining associations between these neurophysiological measures and specific NPI-C symptom domains may also help identify potential biomarkers of treatment response.

Additionally, future studies should recruit larger and more representative patient samples to increase statistical power and improve the reliability and generalizability of findings. Larger samples would allow for more robust evaluation of treatment × time effects and baseline predictors of response, while reducing the influence of baseline group differences and individual variability. Longer follow-up periods could also help determine whether changes observed immediately following tDCS are sustained over time.

Together, these approaches may help establish whether specific EEG characteristics can predict which patients are most likely to benefit from tDCS and clarify the neural mechanisms underlying their effects on neuropsychiatric symptoms.

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VIII. Figures

Demographic Factors of Treatment Groups (tDCS vs Sham)

	tDCS (n=10)	Sham (n=12)
Mean Age	78.8 ± 9.23	71.67 ± 7.9
Gender	Female: 7 Male: 3	Female: 6 Male: 6
Race	White: 1 South Asian: 3 Black: 2 Latin American: 2 Korean: 1 Japanese: 1	White: 8 Black: 1 Latin American: 2 Arab: 1

Figure I: Demographic factors such as participant age, gender, and race were collected and assessed. Participants were assigned to tDCS or sham using a double-blinded randomized methodology.

Mean Baseline Clinical Measures of Treatment Groups (tDCS vs Sham)

Mean Rating at Baseline (T0)	tDCS (n=10)	Sham (n=12)
NPI-C Delusions	3.5 ± 6.19	1.0 ± 2.0
NPI-C Hallucinations	2.1 ± 3.07	0.25 ± 0.87
NPI-C Agitation	13.9 ± 6.71	9.0 ± 6.8
NPI-C Aggression	3.9 ± 3.76	0.42 ± 1.16
NPI-C Dysphoria	5.2 ± 6.32	7.3 ± 6.47
NPI-C Anxiety	5.1 ± 4.84	7.08 ± 8.25
NPI-C Elation/Euphoria	0 ± 0	0 ± 0
NPI-C Apathy/Indifference	4.3 ± 8.69	6.25 ± 8.27
NPI-C Disinhibitions	5.4 ± 8.6	2.3 ± 4.68
NPI-C Irritability	7.5 ± 10.56	6.75 ± 8.27
NPI-C Aberrant Motor Disturbance	2.1 ± 3.18	1.92 ± 3.23

NPI-C Sleep Disorders	3.4 ± 6.02	4.42 ± 4.01
NPI-C Appetite and Eating Disorders	0.9 ± 2.23	1.17 ± 2.33
NPI-C Aberrant Vocalizations	2.0 ± 4.24	1.0 ± 1.86
NPI-C Total Score	59.4 ± 39.62	48.92 ± 36.89
CMAI Total Frequency	51.6 ± 7.92	53.58 ± 11.90
CMAI Total Disruptiveness	7.07 ± 7.07	42.17 ± 8.40
CMAI Total Frequency x Disruptiveness	120.0 ± 39.21	102.0 ± 49.25
CMAI Total Aggressive Behaviors	0.5 ± 0.71	0.58 ± 1.0
CMAI Total Aggressive Behaviors Corrected	1.17 ± 1.25	1.0 ± 1.8
CMAI Physical Non-Aggressive Severity	0.5 ± 0.97	0.75 ± 0.87
CMAI Physical Non-Aggressive Severity Corrected	1.8 ± 1.03	2.4 ± 1.0
CMAI Physical Verbally Aggressive Severity	1.3 ± 0.95	0.92 ± 1.31
CMAI Physical Verbally Aggressive Severity Corrected	3.0 ± 1.15	3.0 ± 1.48
CMAI Total Agitated Behavior Severity	5.8 ± 1.99	6.6 ± 3.0
CMAI Total Other Behavior Severity	1.0 ± 0.82	1.08 ± 1.38
Log Transformed CMAI Total Frequency Score	3.93 ± 0.17	3.96 ± 0.21
CGI-S Total Rating	4.7 ± 0.67	4.55 ± 0.69

Figure II: Mean baseline scores across various measures, including NPI-C subdomains, CMAI, and CGI-S.

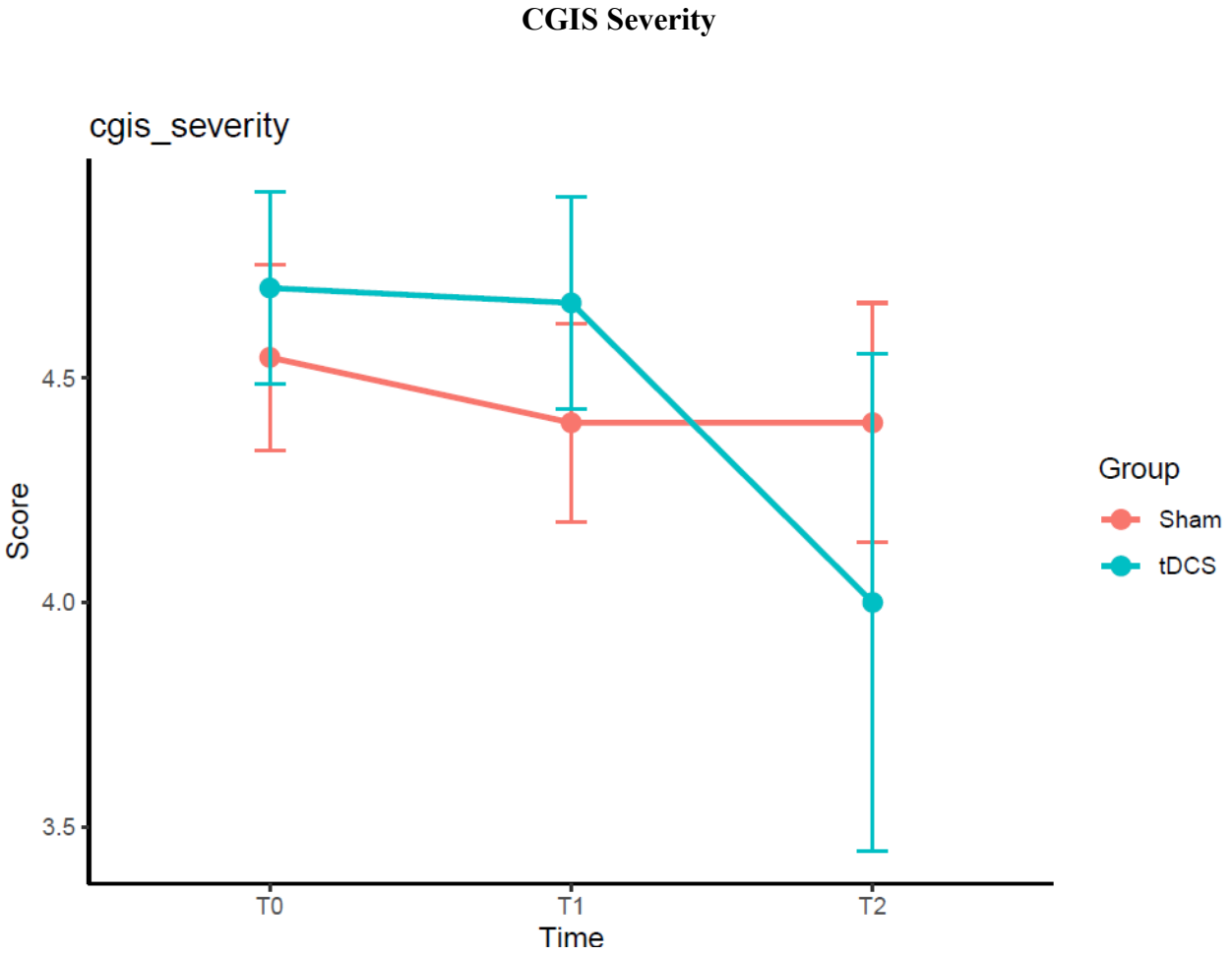

Figure III: CGI-S severity ratings across time points T0, T1, and T2 for sham and tDCS groups.

NPI-C D Aggression

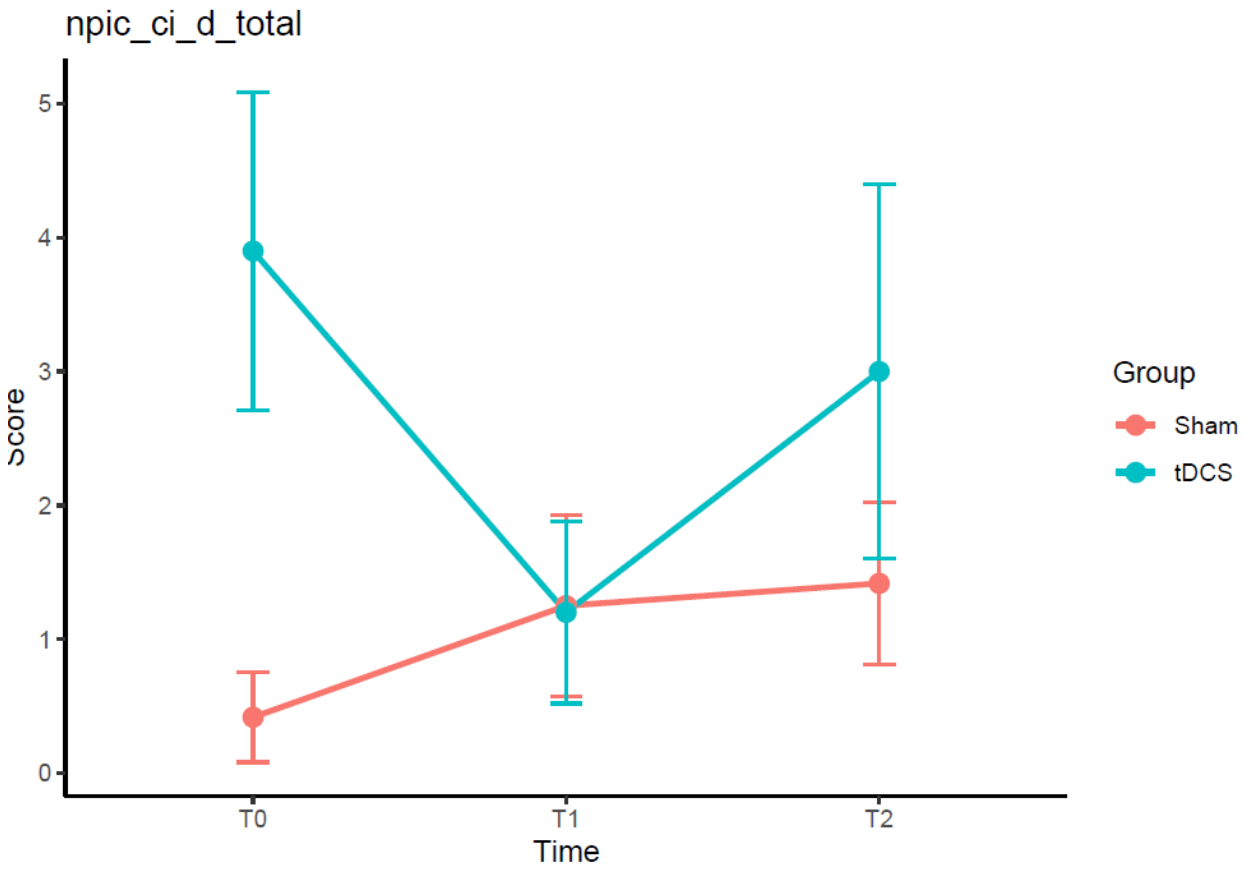

Figure IV: NPI-C Aggression rating across time points T0, T1, and T2 for sham and tDCS groups.

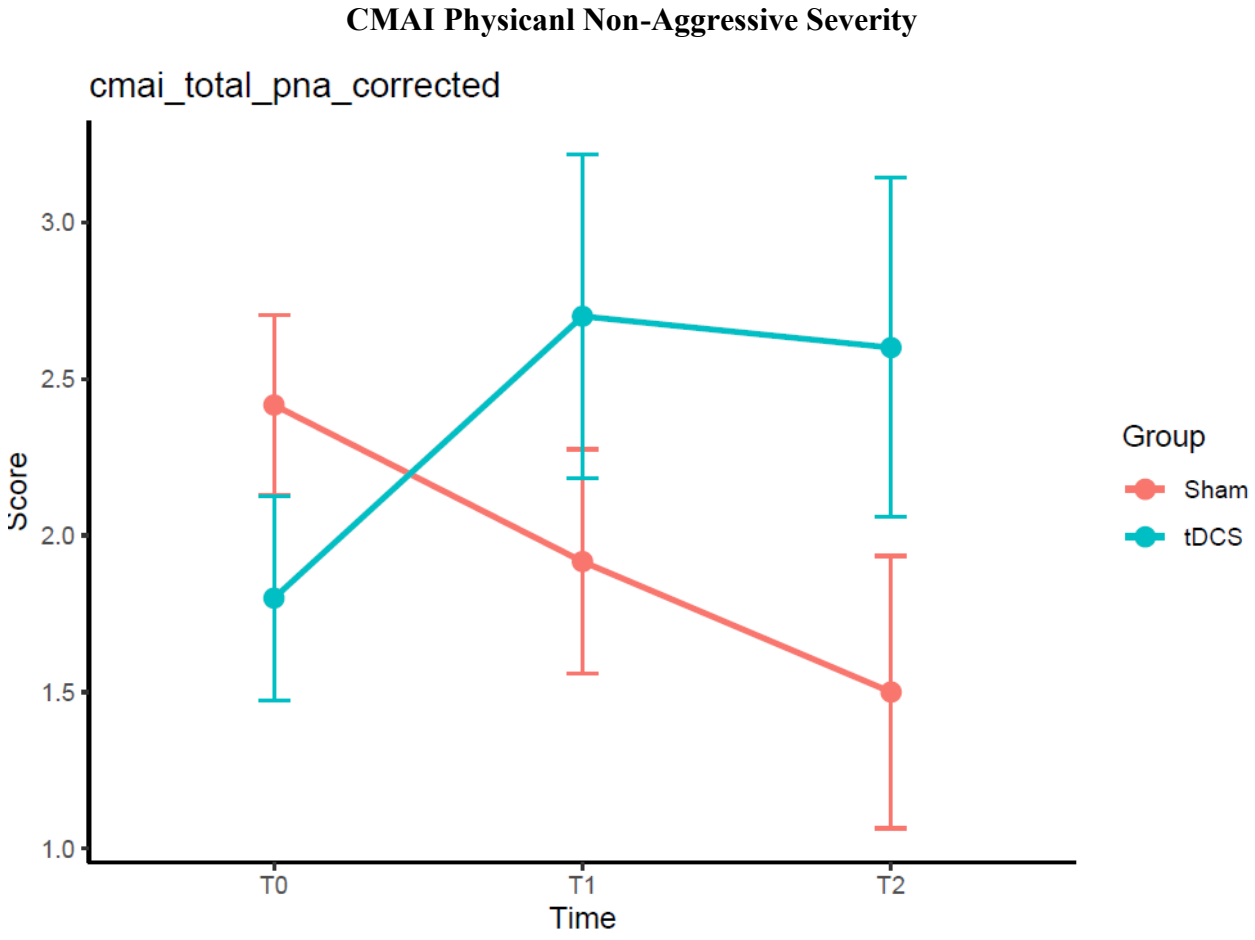

Figure V: CMAI Physical Non-Aggressive (corrected) rating across time points T0, T1, and T2 for sham and tDCS groups.

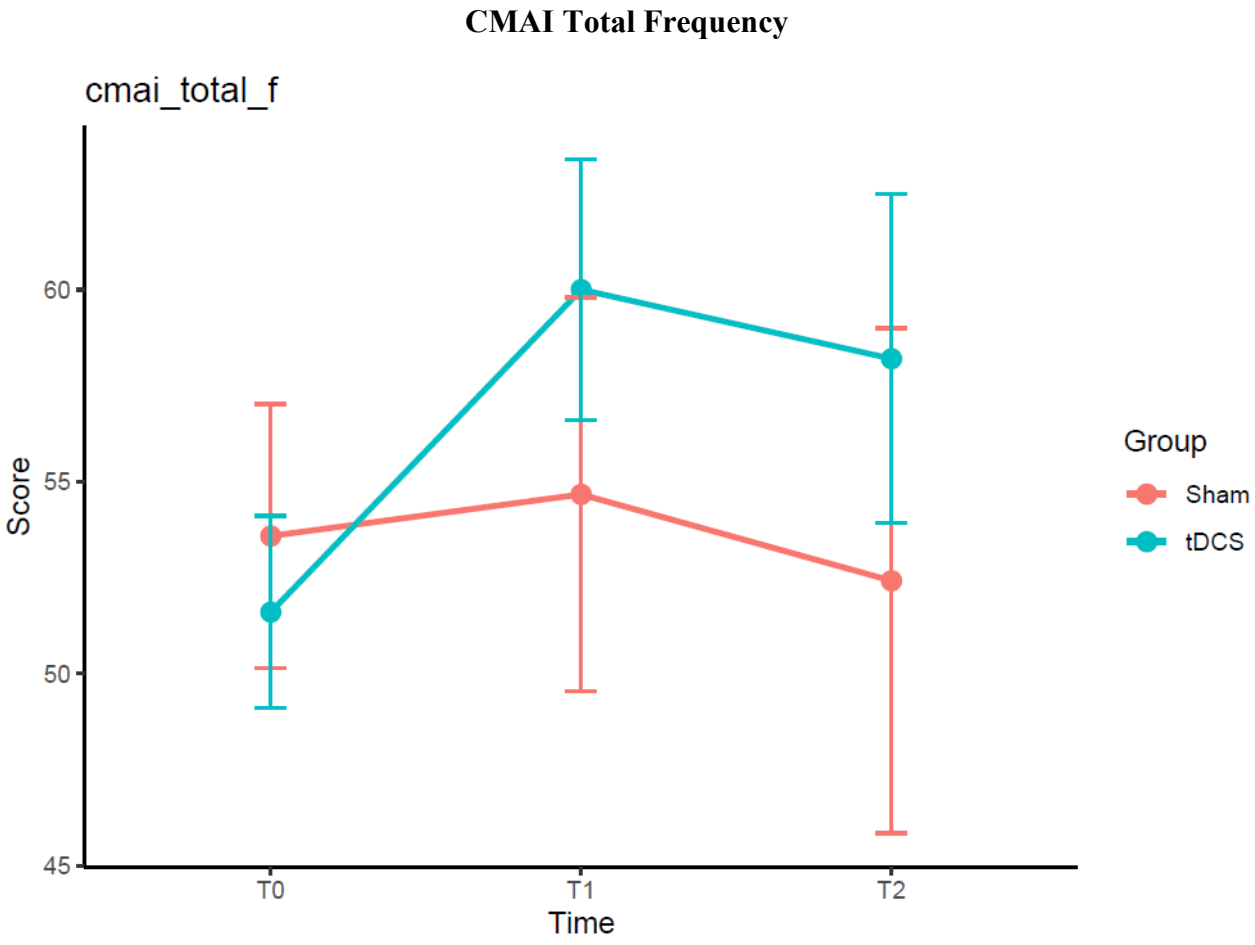

Figure VI: CMAI total frequency rating across time points T0, T1, and T2 for sham and tDCS groups

NPI-C C Agitation

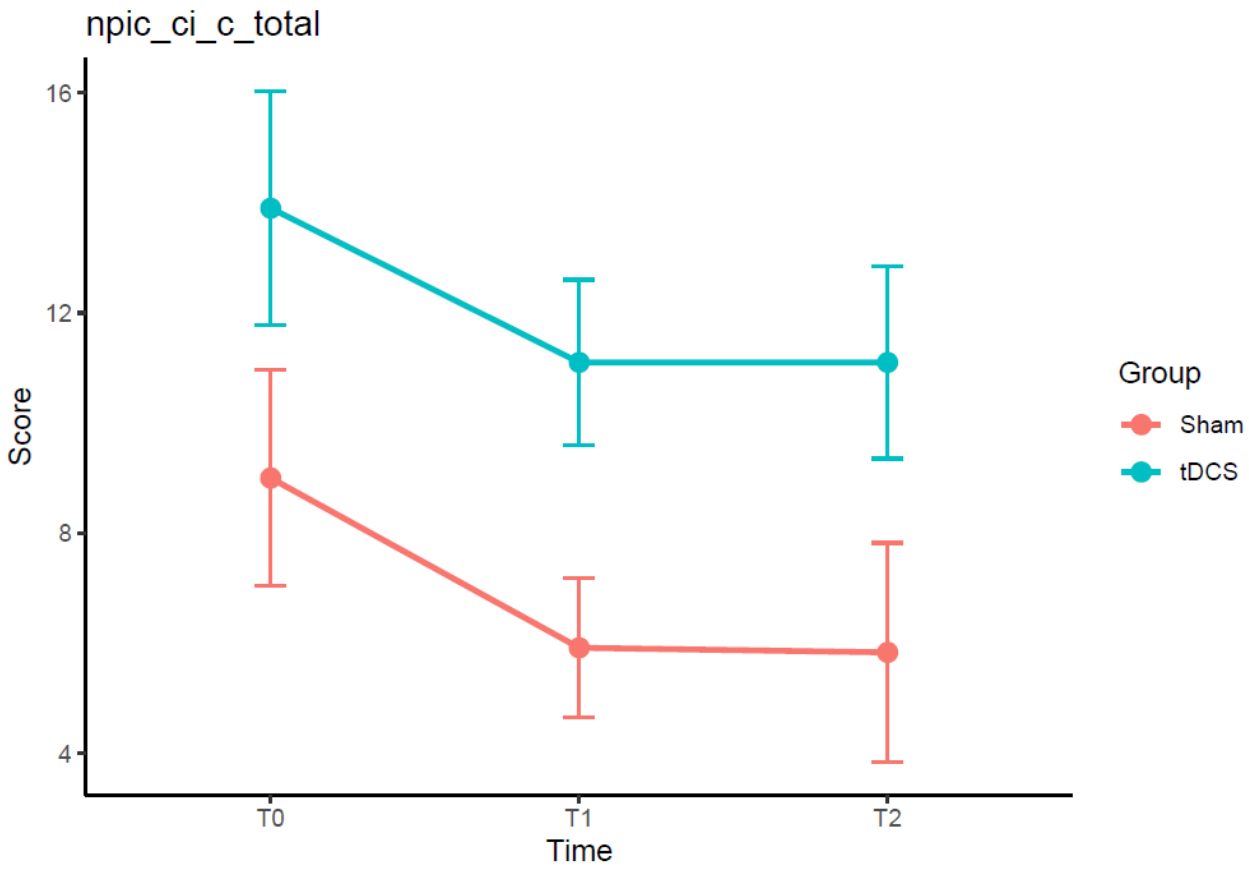

Figure VII: NPI-C Agitation rating across time points T0, T1, and T2 for sham and tDCS groups

NPI-C H Apathy/Indifference

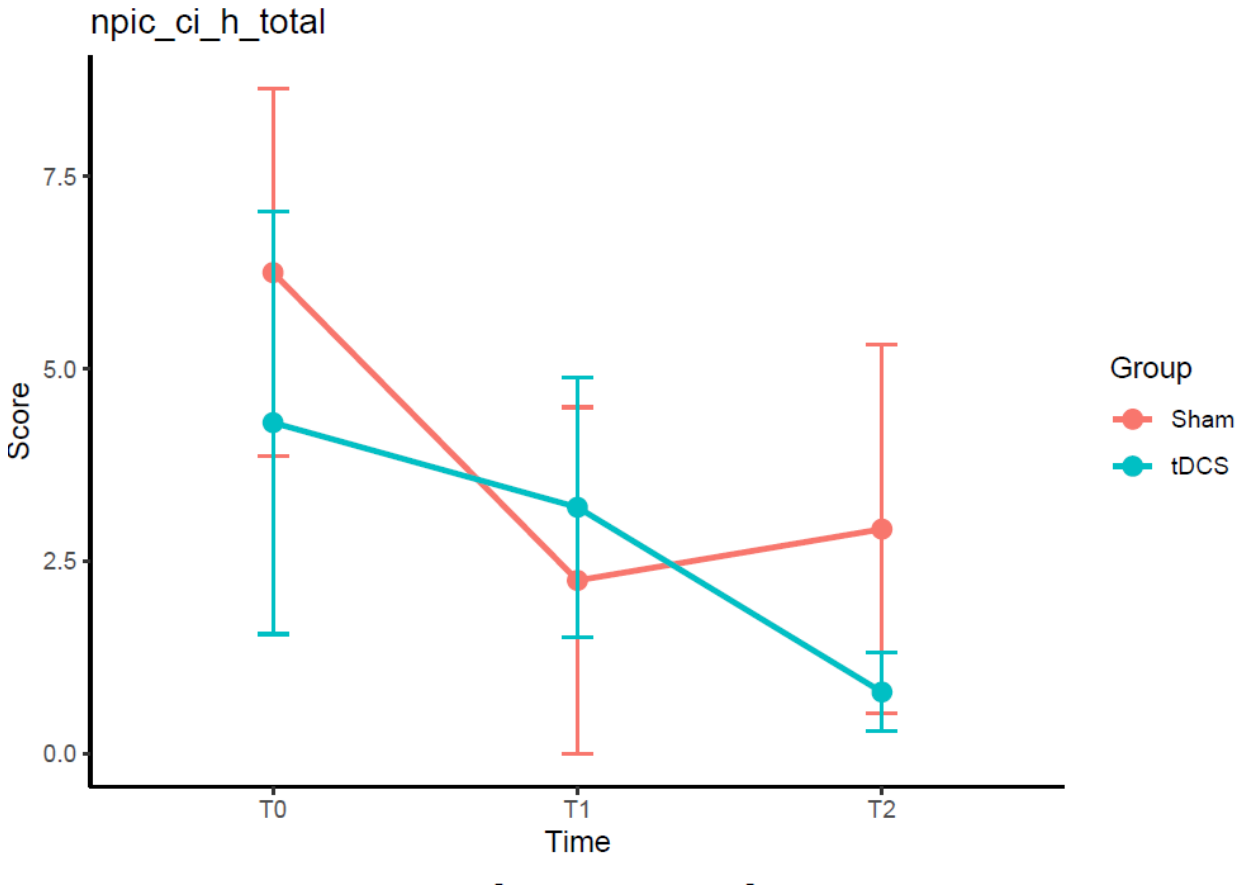

Figure VIII: NPI-C Apathy/Indifference rating across time points T0, T1, and T2 for sham and tDCS groups

NPI-C F Anxiety

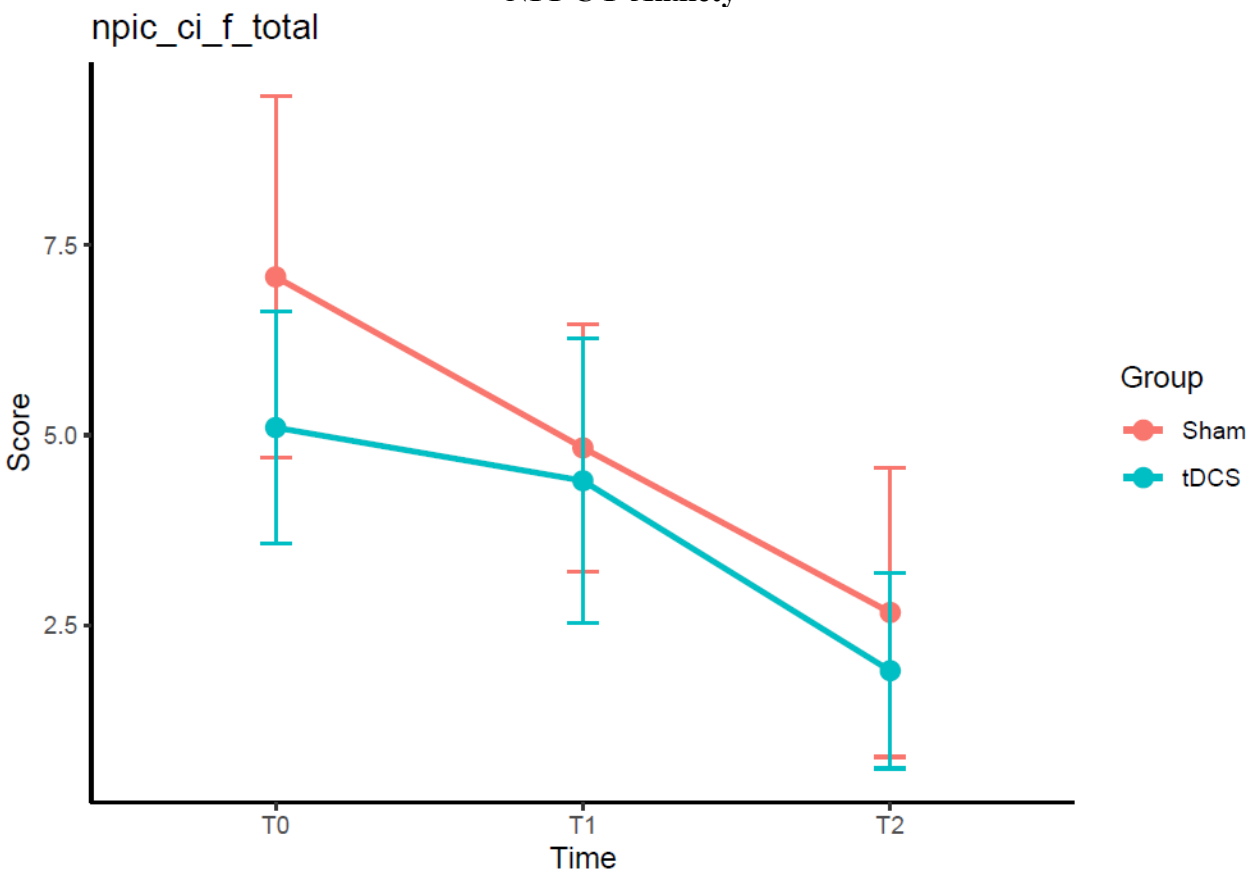

Figure IX: NPI-C Anxiety rating across time points T0, T1, and T2 for sham and tDCS groups

LICI NPI-C K Aberrant Motor Disturbance

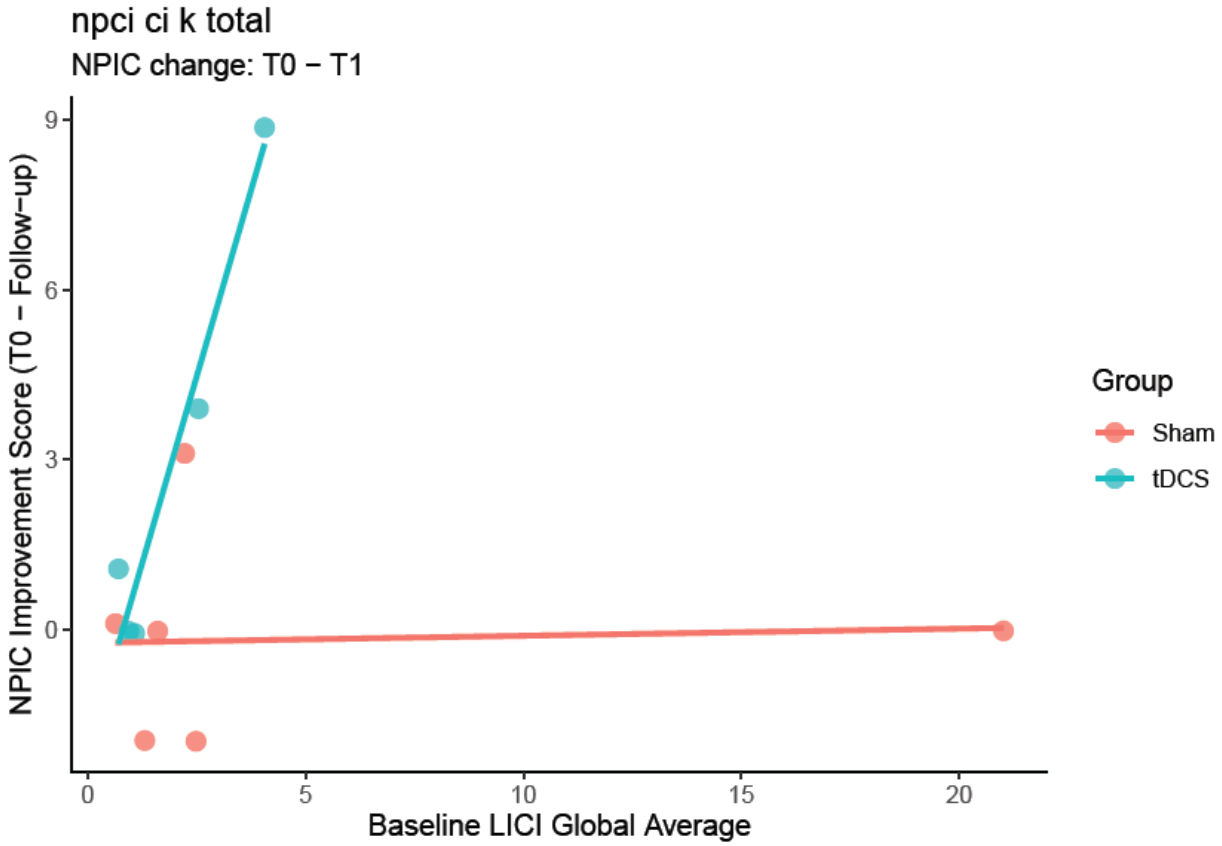

Figure X: NPI-C aberrant motor disturbance change from follow-up vs baseline LICI global averages for sham and tDCS treatment groups

LICI NPI-C E Dysphoria

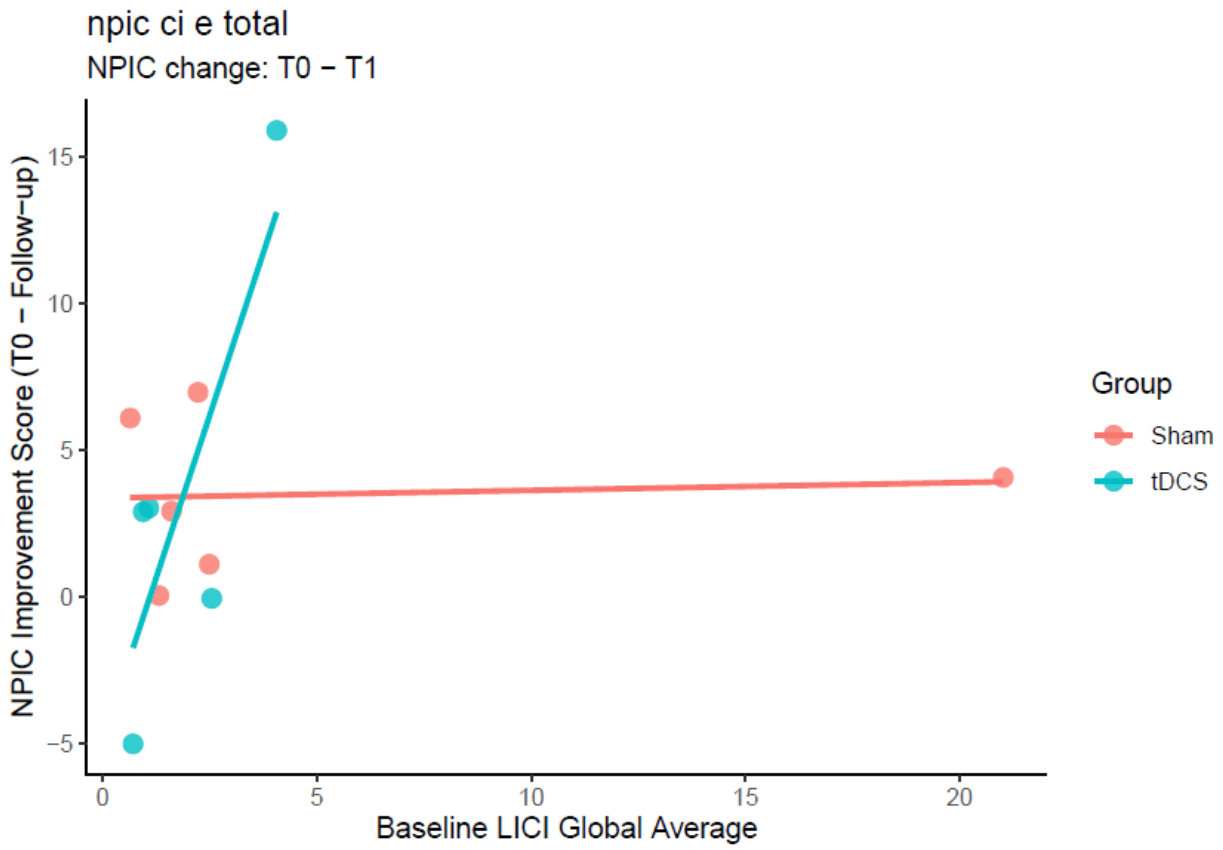

Figure XI: NPI-C dysphoria change from follow-up vs baseline LICI global averages for sham and tDCS treatment groups

LICI NPI-C J Irritability

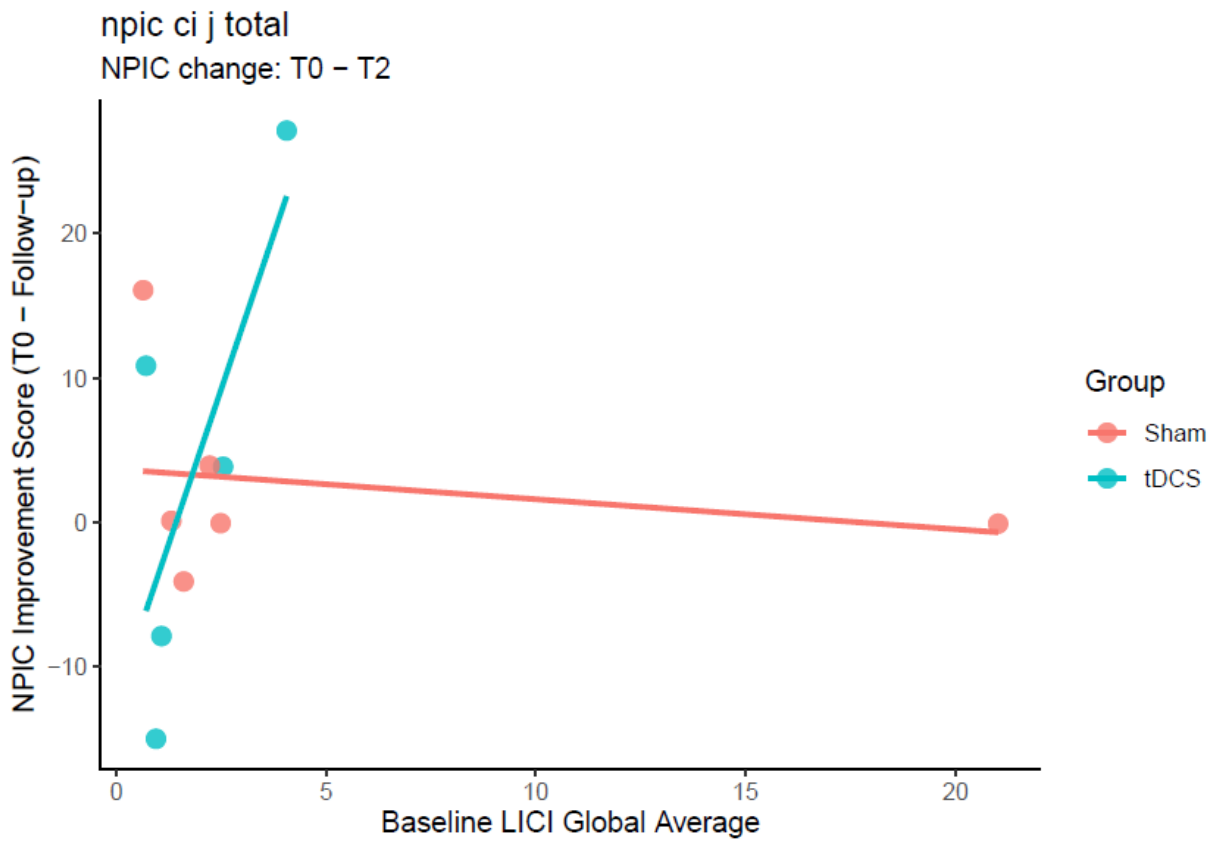

Figure XII: NPI-C irritability change from follow-up vs baseline LICI global averages for sham and tDCS treatment groups

LICI NPI-C D Aggression

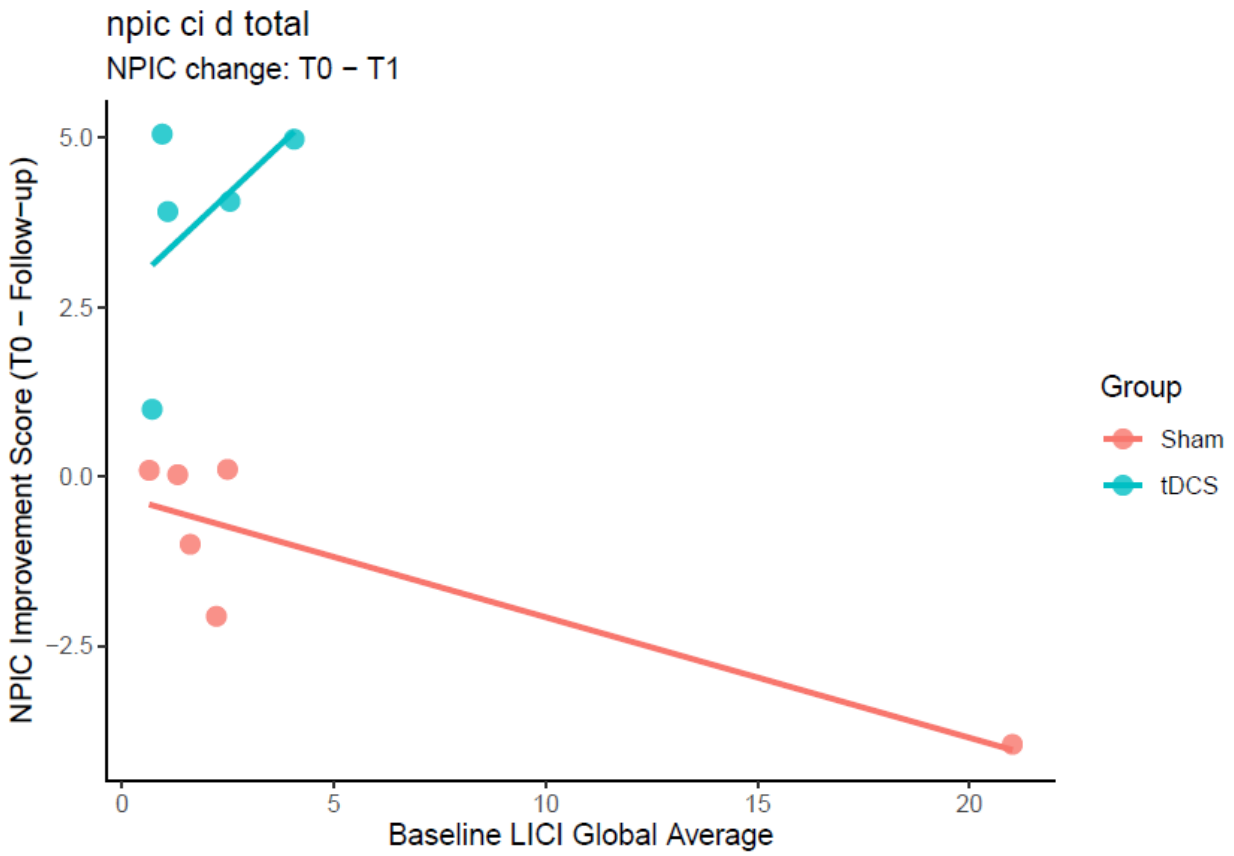

Figure XIII: NPI-C aggression change from follow-up vs baseline LICI global averages for sham and tDCS treatment groups

LICI NPI-C K Aberrant Motor Disturbance

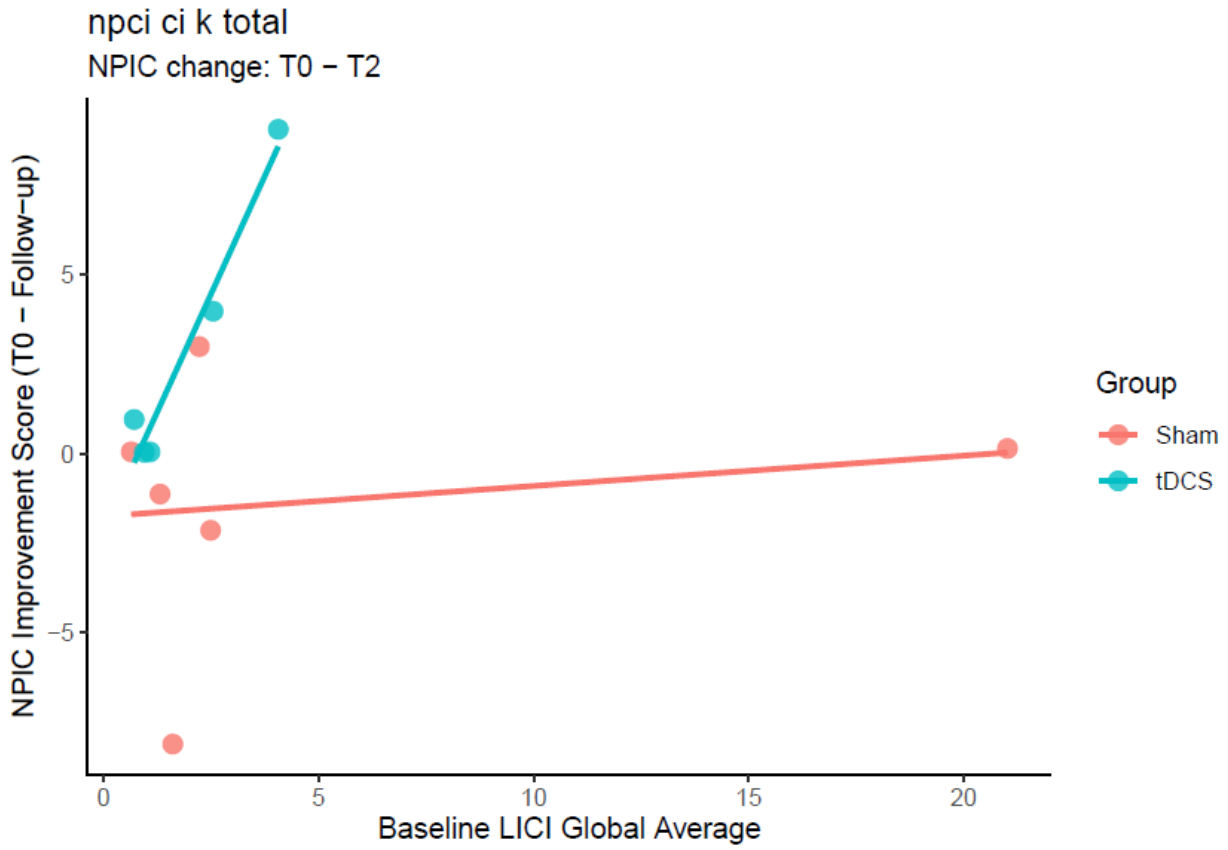

Figure XIV: NPI-C aberrant motor disturbance change from follow-up vs baseline LICI global averages for sham and tDCS treatment groups

LICI NPI-C I Disinhibition

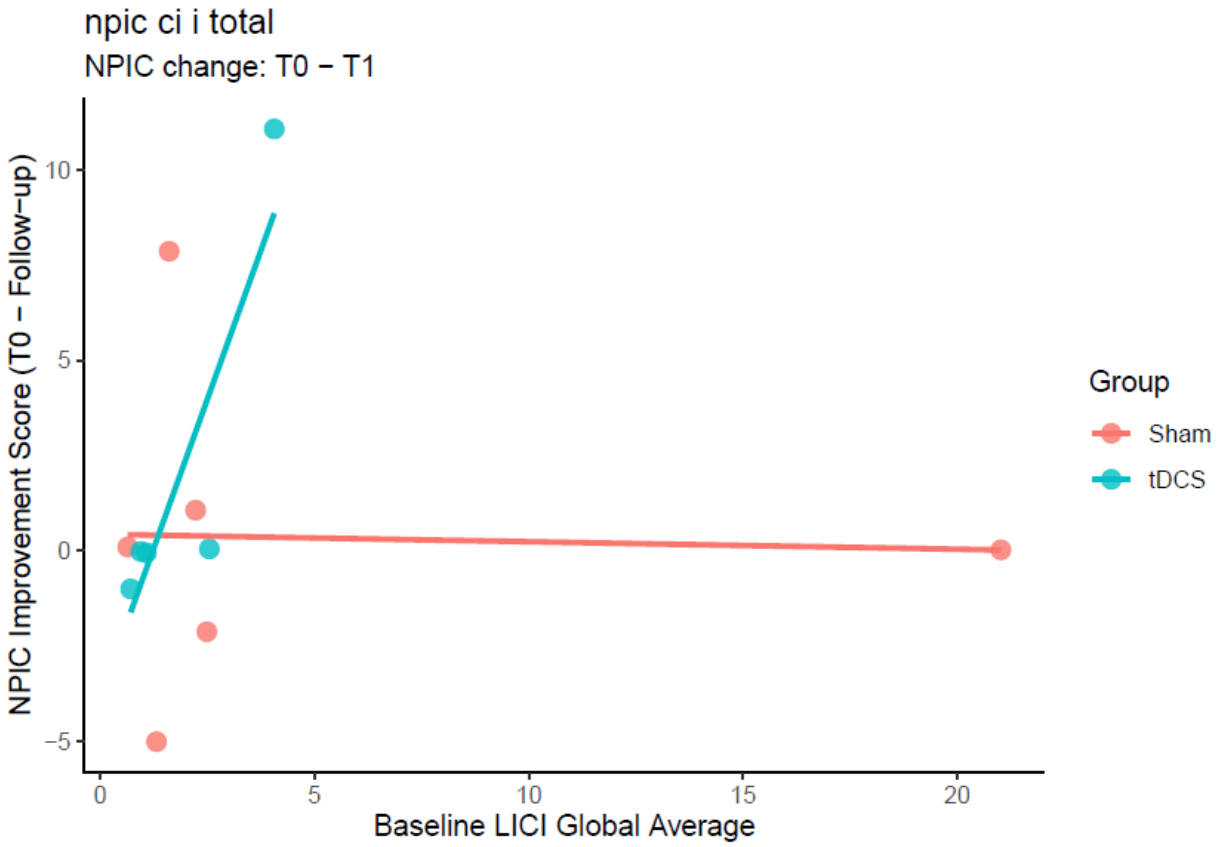

Figure XV: NPI-C disinhibition change from follow-up vs baseline LICI global averages for sham and tDCS treatment groups

LICI NPI-C J Irritability

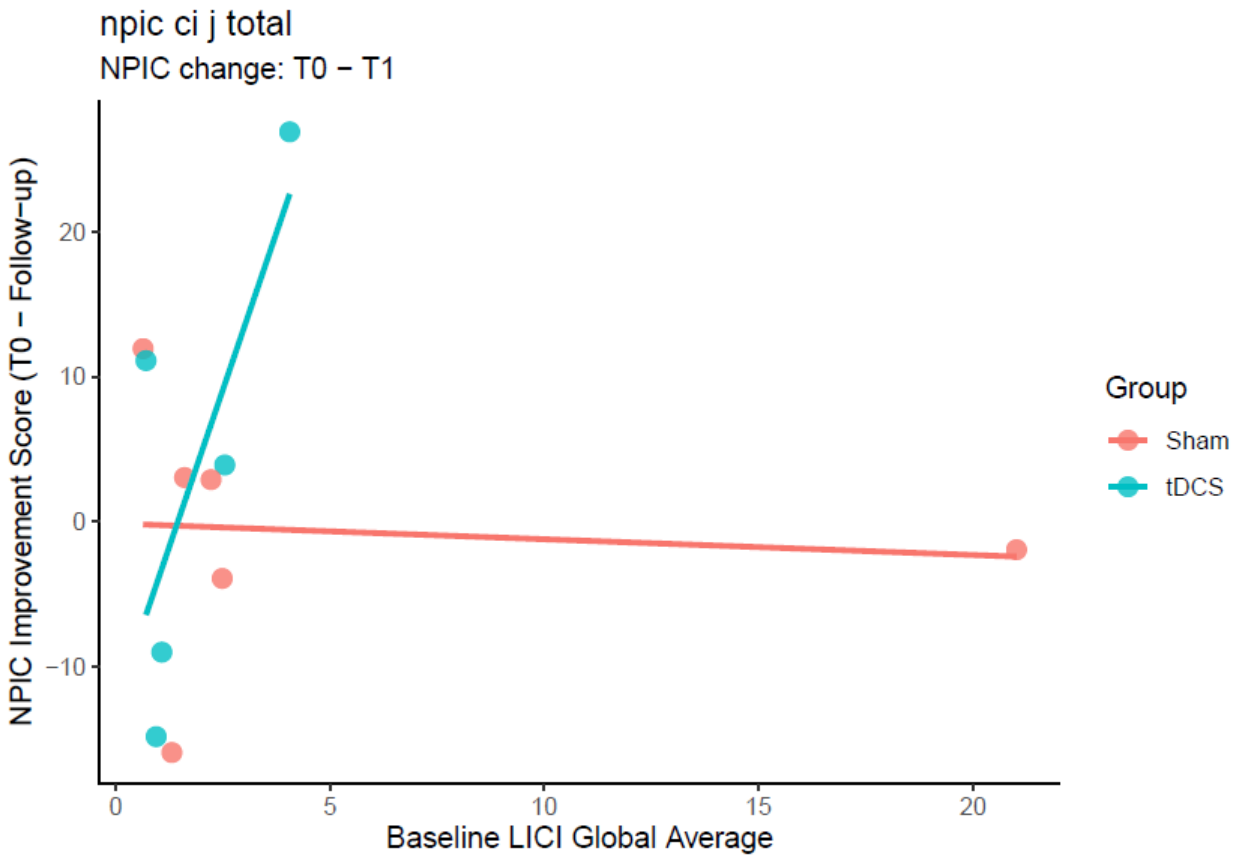

Figure XVI: NPI-C irritability change from follow-up vs baseline LICI global averages for sham and tDCS treatment groups