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Cortical excitability affects mood state in patients with idiopathic generalized epilepsies (IGEs)

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ABSTRACT

Previously, we demonstrated an association between cortical hyperexcitability and mood disturbance in healthy adults. Studies have documented hyperexcitability in patients with idiopathic generalized epilepsies (IGEs; long-interval intracortical inhibition [LICI]) and high prevalence of mood comorbidities. This study aimed to investigate the influences of cortical excitability and seizure control on mood state in patients with IGEs. Single and paired-pulse transcranial magnetic stimulation (TMS) was applied to 30 patients with IGEs (16 controlled IGEs [cIGEs], 14 with treatment-resistant IGEs [trIGEs]), and 22 healthy controls (HCs) to assess cortical excitability with LICI. The Profile of Mood Sates (POMS) questionnaire was used to assess total mood disturbance (TMD), as well as, six mood domains: Depression, Confusion, Anger, Anxiety, Fatigue, and Vigor. To assess the effects of seizure control (HC vs. cIGEs vs. trIGEs) and LICI response (inhibitory vs. excitatory) on TMD, a two-way multivariate analysis of variance (MANOVA) was performed. Analyses revealed a significant main effect of long-interval intracortical inhibition (LICI) response on TMD ($F(1, 46) = 4.69$, $p = 0.04$), but not seizure control ($F(2, 46) = 0.288$, $p = 0.75$). Excitatory responders endorsed significantly higher TMD scores, indicating greater mood disturbance, than inhibitory responders ($MD = -2.12$; $T(50) = -2.47$, $p = 0.04$). Also, excitatory responders endorsed more items than inhibitory responders on the Depression ($MD = -2.12$; $T(50) = -2.47$, $p = 0.04$) and Fatigue ($MD = -3.42$; $T(50) = -2.96$, $p = 0.03$) subscales of the POMS. These findings provide further evidence of a relationship between hyperexcitability and mood disturbance, and indicate that cortical excitability may have greater influence on mood state than seizure control in patients with IGEs. Results also support theories for the underlying role of gamma-aminobutyric acid (GABA) network dysfunction in the etiology of depression. To better understand the clinical relevance and causal nature of these relationships, further investigation is warranted.

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1. Introduction

We previously conducted an explorative study in a sample of healthy individuals to assess the relationship between cortical excitability and mood utilizing single and paired-pulse TMS [1]. Long-interval intracortical inhibition (LICI) served as the main outcome measure of cortical excitability, with excitatory responses on this paradigm indicating hyperexcitability, and likely gamma-aminobutyric acid (GABA) network dysfunction [2–4]. The individuals who exhibited excitatory responses on LICI endorsed significantly greater mood disturbance than participants with inhibitory responses ($p = 0.029$) [1]. In the healthy subject study, the LICI recovery curve with excitatory responses closely resembled the LICI recovery curves of patients with idiopathic generalized epilepsies (IGEs) published in other studies [5–7].

In general, patients with epilepsy frequently suffer from psychiatric comorbidities with mood disorders being the most common [8]. Among patients with IGEs specifically, 20–30% have psychiatric comorbidities [8]. However, as a result of lifelong seizures, patients with treatment-resistant IGEs (trIGEs) are especially likely to demonstrate emotional and mood problems [9]. Patients with trIGEs are significantly more likely to exhibit psychiatric comorbidities than those who have controlled IGEs (cIGEs) [10]. A premorbid history of mood disorders in patients with epilepsy was shown to be predictive of future antiseizure drug (ASD)-resistance [11,12]. This suggests a bidirectional relationship between mood and ASD-response, which "may be explained by the existence of common pathogenic mechanisms" [12]. Based on our previous study, we hypothesized that cortical excitability would have a significant effect on mood state in patients with both cIGEs and trIGEs, with increased cortical excitability being associated with greater mood

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disturbance. This hypothesis is supported further by the presence of increased mood problems in other clinical populations that exhibit hyperexcitability — attention-deficit hyperactivity disorder (ADHD) and Tourette's syndrome [13–16]. Based on the literature, we also hypothesized an effect of seizure control on mood state, with patients with trIGE endorsing greater mood disturbance than patients with cIGE, and both groups with IGE endorsing greater mood disturbance than HCs.

2. Methods

2.1. Participants

Participant details are described in the companion paper [17]. Briefly, 30 participants with IGEs were recruited and classified as cIGE (N = 16) or trIGE (N = 14) based on the Alabama State Law driving restriction of 6-month seizure freedom. Participants were recruited after review of available records and consulting with the managing epilepsy specialist. The 24 healthy adults from our previous study were included in these analyses to serve as a healthy control (HC) comparison group [1]. However, two healthy controls were excluded from this study because of incomplete mood assessment data. Thus, all mood analyses were conducted with 22 HCs. Participants, including HCs, ranged from 18 to 53 years of age ($M = 28$); 80.8% were Caucasian; 38.5% were male, and the mean years of education was 15 ($SD = 2.89$). This study was approved by the UAB Institutional Review Board and followed the Declaration of Helsinki ethical protocols. All participants provided written informed consent.

2.2. Procedure

The study protocol is outlined in Fig. 1. In addition to demographic forms, participants also completed the Edinburgh Handedness Inventory (EHI) [18]. In accordance with safety guidelines, women of childbearing age were required to complete a pregnancy test prior to TMS [19]. All TMS procedures were applied over the right primary motor cortex, determined using the standard 10–20 system. Mood assessment was administered as part of a larger neuropsychological assessment battery (approximately 45 min) in which a simultaneous electroencephalogram (EEG) was also conducted. Following all study procedures, a neurological exam was performed to ensure subject readiness and safety to leave the visit.

2.3. Transcranial magnetic stimulation

As in our previous studies and the companion study, a Magstim 200® stimulator connected through a Bistim® module to a 70-mm figure-8 coil (Magstim Co., Wales, UK) was used to conduct all TMS protocols [1,20]. A detailed description of the TMS protocol used in this study is described in our previous manuscript [1]. Briefly, stimulations were applied using a figure-of-eight coil held in a tangential position over the right motor cortex. To ensure accuracy and consistency of stimulations, a frameless stereotaxic system (Brainsight, Rogue Inc., Montreal, Canada) was used to provide online feedback throughout the TMS session. Swim caps were used to measure and identify vertex and individual "hotspot" locations [21]. Single-pulse TMS was conducted to determine resting motor threshold (RMT), or the minimum stimulus intensity required to produce a motor-evoked potential (MEP) between 50 and 100 μV in at least 5 out of 10 consecutive stimulations when the first dorsal interosseous muscle was at rest [22].

Paired-pulse TMS was used to assess LICI at interstimulus intervals (ISIs) of 50, 80, 110, 140, 170, and 200 [2–4]. To determine LICI, pairs of stimuli were administered randomly across ISIs at 120% RMT, with a minimum interval of 15 s between trials, until a total of 10 trials at each ISI were obtained. Fig. 2 uses raw data from two participants in this study to demonstrate an inhibitory vs. excitatory response to a single stimuli pair on LICI. The LICI recovery curves were constructed by determining the ratio of the mean peak-to-peak amplitude of the second, or test response (TR) to the mean peak-to-peak amplitude of the first, or conditioned response (CR) at each ISI. These ratios were then expressed as a percentage (TR/CR%), with percentages less than 100% indicating inhibition and percentages greater than 100% indicating facilitation [23]. As another measure of LICI, the total area under the curve (AUC) across all ISIs was calculated with respect to the 100% baseline for each participant. As a continuous variable, a larger total AUC indicates more facilitation, (i.e., excitation) on an LICI recovery curve, whereas a smaller total AUC indicates more inhibition. However, given that LICI is expected to produce inhibitory responses, and excitatory responses are generally considered indicative of hyperexcitability and GABA dysfunction, it may also be appropriate to conceptualize total AUC as a categorical variable as we did in our previous study [1]. Individual electromyography (EMG) responses characterized by noise or artifacts were excluded (<1%), and stimulations were readministered if noticeably affected by participant movement (<1%).

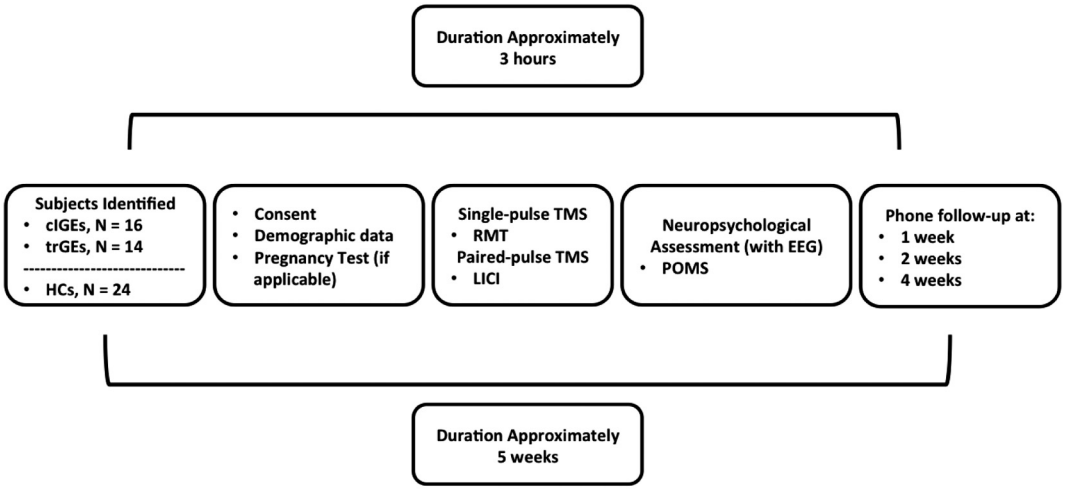

Fig. 1. Flow diagram outlining the study protocol for all participants. cIGEs = controlled idiopathic generalized epilepsies, trIGE = treatment-resistant idiopathic generalized epilepsies, and HCs = healthy controls. TMS = transcranial magnetic stimulation; RMT = resting motor threshold; LICI = long-interval intracortical inhibition; EEG = electroencephalogram; POMS = Profile of Mood States.

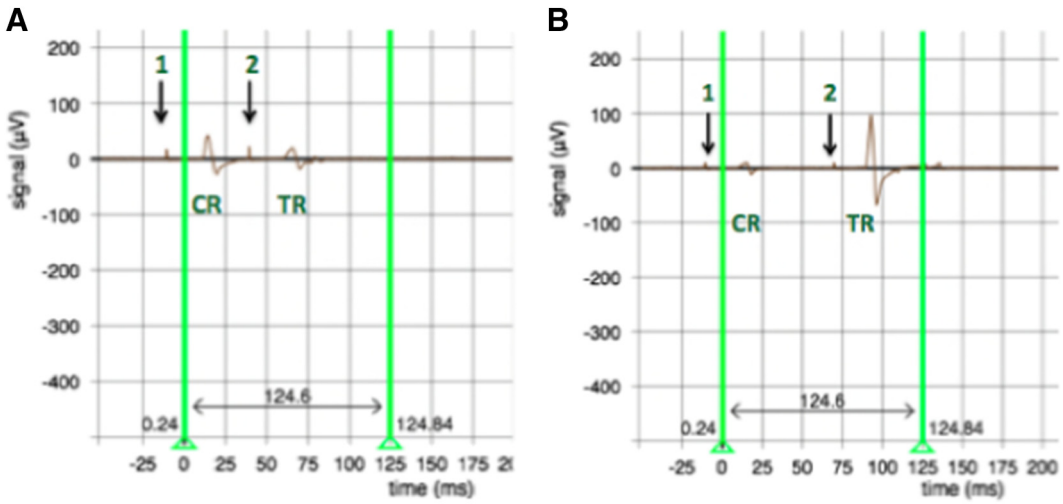

Fig. 2. Motor-evoked potential (MEP) responses to paired-pulse stimulation in long-interval intracortical inhibition (LICI). (A) The second, or test response (TR) is smaller than the first, or conditioned response (CR) indicating inhibition. (B) The TR is larger than the CR indicating facilitation, or an excitatory response.

2.4. Electroencephalogram

Following completion of TMS procedures, an EEG, using a research EEG system (Compumedics NeuroScan Inc.), was obtained using a standard 10–20 electrode positioning system. A board-certified epilepsy specialist reviewed all EEGs qualitatively and quantitatively for any abnormalities. Since the EEG duration varied based on the completion of neuropsychological testing, the ratio of generalized spike and wave discharge (GSWD) duration to total EEG time was calculated for each participant. Of note, the epilepsy specialist was blinded to group assignment of patients with IGE (i.e., cIGE vs. trIGE).

2.5. Mood assessment

The Profile of Mood States (POMS) was administered to assess affective mood state [24]. It is a self-report measure that asked participants to rate how closely 65 different adjectives described their current mood on a five-point scale ranging from "not at all" to "extremely." These adjectives provided scores for 6 different mood state subscales: Anger, Confusion, Depression, Fatigue, Anxiety/Tension, and Vigor. In addition, a Total Mood Disturbance (TMD) score was calculated by subtracting the Vigor score from the sum of all the other mood scale scores to measure overall mood state. The score for TMD ranges from −32 to 200, with lower scores indicating less mood disturbance; TMD is considered a highly reliable and clinically relevant measure of overall mood and mood problems [24]. Significant correlation between POMS and Beck Depression Inventory (BDI) has been reported [25].

2.6. Statistical analyses

All participants were first categorized as either "excitatory" (N = 26) or "inhibitory" (N = 26) responders according to their total AUC response on LICI [1]. We then examined the effects of LICI response type and seizure control on POMS TMD using a two-way analysis of variance (ANOVA) with between-subject factors of seizure control (3 levels: HC vs. cIGE vs. trIGE) and LICI response type (2 levels: inhibitory vs. excitatory). Follow-up independent sample *t*-tests were conducted on all POMS scales to further examine the ANOVA findings. The Benjamini–Hochberg method was used to control the false discovery rate [26]. We then conducted bivariate Pearson correlations to characterize the relationships between the continuous total AUC cortical excitability measure and the POMS scales. A bivariate correlation was also conducted to examine the relationship between POMS TMD score and GSWD duration among patients with IGEs that exhibited GSWDs on EEG. All statistical tests were two-tailed; SPSS 25.0 software was used to perform all statistical analyses.

3. Results

3.1. Data analyses

Group demographics are presented in Table 1 of the companion paper, and are only briefly described here [17]. The tests comparing demographic measures between seizure control groups and LICI response type groups did not reveal any significant differences (all p's > 0.05). Analyses regarding group differences in cortical excitability outcome measures (i.e., RMT, LICI) demonstrated no significant differences in RMT between HCs ($M = 34.52$, $SD = 5.14$), cIGEs ($M = 33.75$, $SD = 6.47$), and trIGEs ($M = 33.93$, $SD = 6.75$) [$F(2, 50) = 0.089$, $p = 0.92$] [17]. Excitatory responders exhibited lower RMTs ($M = 32.68$, $SD = 4.67$) than inhibitory responders ($M = 35.76$, $SD = 6.75$), indicating higher cortical excitability, but the difference was not significant at the 0.05 level [$F(1, 51) = 3.80$, $p = 0.057$]. As expected, participants with cIGEs ($M = 1.44$, $SD = 0.63$) reported taking fewer ASDs than participants with trIGEs ($M = 2.21$, $SD = 0.80$; $T(28) = -2.97$, $p = 0.006$). Additional information regarding individual ASDs is provided in Table 1. Given the small sample size and variability in ASD usage among our participants, no further analyses were conducted utilizing ASD data. The LICI recovery curves for all groups are provided in Fig. 1 of the companion paper. Responses for HCs, group with cIGE, and group with trIGE

Table 1
Differences in the number of different antiseizure drugs (ASDs) taken by participants with controlled idiopathic generalized epilepsies (cIGEs) and treatment-resistant idiopathic generalized epilepsies (trIGEs). *Note*: ASD dosage data were not collected.

ASD	cIGEs	trIGEs	Total
Levetiracetam	7	5	14
Lamotrigine	2	12	12
Lacosamide	2	1	3
Phenytoin	1	0	1
Valproic Acid/Valproate	3	1	4
Zonisamide	3	6	9
Brivaracetam	0	1	1
Clobazam	0	1	1
Ethosuximide	0	2	2
Methsuximide	0	1	1
Carbamazepine extended release	0	1	1
Total	**18**	**31**	**49**

did not significantly differ across any LICI ISIs (all p values > 0.05). However, excitatory responders exhibited significantly higher responses than inhibitory responders across all ISIs, except ISI 200 ms (p's < 0.05; $p = 0.47$ for ISI 200 ms).

3.1.1. Mood

Prior to performing the main analyses, we performed diagnostic procedures to identify potential violations of the assumptions for ANOVA tests. No significant outliers in TMD score were detected, as evidenced by standardized scores >3.29. Variances did not significantly differ among groups (Levene's test: $p = 0.28$). The TMD was normally distributed for all groups, although a significant deviation from normality was identified for the inhibitory HC group (Shapiro–Wilks $p = 0.048$). However, because ANOVA is generally robust to small violations of normality, no transformations were conducted prior to analyses [27]. The two-way ANOVA on POMS TMD scores did not reveal a significant interaction between seizure control and LICI responder type on TMD score [$F(2, 46) = 0.377$, $p = 0.69$] or an effect of seizure control [$F(2, 46) = 0.288$, $p = 0.75$]. However, it did reveal a significant main effect of LICI responder type ([$F(1, 46) = 4.69$, $p = 0.04$, partial $\eta 2 = 0.093$]) (Fig. 3).

To further explore mood state differences between excitatory and inhibitory responders, independent-sample t-tests were conducted on POMS TMD and each of the POMS subscales. Analyses showed that excitatory responders ($M = 12.43$, $SD = 3.44$) exhibited significantly higher TMD scores than inhibitory responders ($M = 1.83$, $SD = 3.48$; $T(50) = -2.44$, $p = 0.04$). Excitatory responders also demonstrated significantly higher scores than inhibitory responders on the Depression ($MD = -2.12$; $T(50) = -2.47$, $p = 0.04$) and Fatigue ($MD = -3.42$; $T(50) = -2.96$, $p = 0.03$) subscales (Fig. 4). No significant differences in Anxiety, Anger, Vigor, or Confusion scores were found between excitatory and inhibitory responders. Correlational analyses did not reveal a significant linear relationship between total AUC and any of the POMS scales, all p's > 0.05. Finally, the TMD score was not correlated with duration of GSWDs in patients with IGE that demonstrated GSWDs (r = −0.022, $p = 0.96$). Of note, only 8 patients with IGE exhibited GSWDs, 7 trIGEs and 1 cIGE.

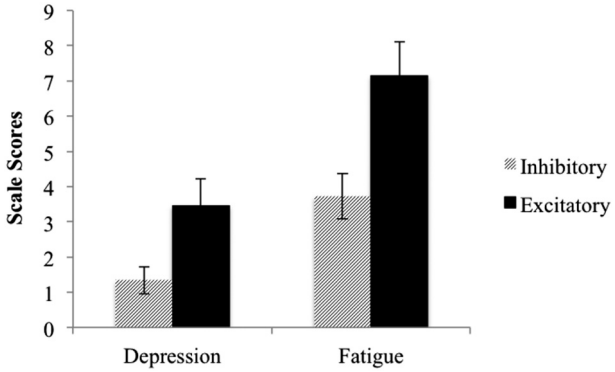

Fig. 4. POMS Depression and Fatigue subscale scores in participants who were primarily inhibitory vs. excitatory responders on the LICI paradigm. Higher scores indicate greater symptom endorsement.

4. Discussion

4.1. Cortical excitability and mood

To build on our previous findings [1], this study aimed to assess the influence of cortical excitability and seizure control on mood state in patients with IGEs. Across all groups (HCs, cIGEs, and trIGEs), participants with primarily excitatory responses on LICI, indicating higher cortical excitability, endorsed significantly greater mood disturbance than participants with primarily inhibitory responses. In fact, LICI response had an even greater effect on self-reported mood state than seizure diagnosis, as no differences in TMD score were found between HCs, patients with cIGEs, and patients with trIGEs. These results demonstrate that cortical excitability influences mood state in patients with IGEs, providing new insight into the underlying pathophysiology of mood problems in patients with IGEs.

Upon further examination, it was revealed that inhibitory and excitatory responders differed most significantly on the Depression subscale of the POMS, with excitatory responders endorsing significantly more depressive symptoms compared with inhibitory responders. Previous studies have found the POMS Depression subscale to be moderately to strongly correlated with the Beck Depression Inventory — II (BDI-II) in both the general population (r = 0.61), and in patients with treatment-resistant epilepsies (r = 0.75) [24,25]. The BDI-II was developed to correspond with the criteria for diagnosing major depression set forth by the Diagnostic and Statistical Manual — Fourth Edition (DSM-IV) and is one of the most widely used instruments for detecting depression [28]. It is important to note that the average Depression subscale scores among inhibitory as well as excitatory responders were still well below the clinically significant range [25]. As such, the clinical relevance regarding the relationship between cortical excitability and

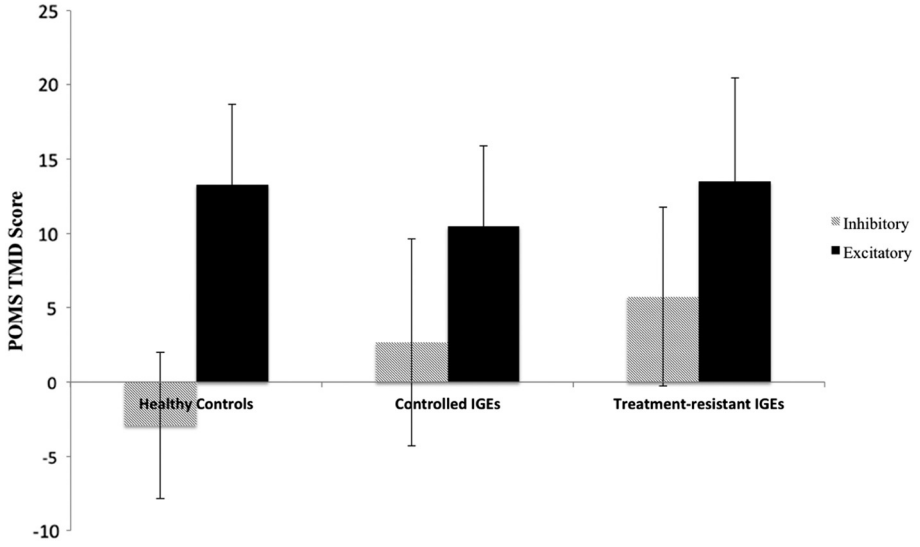

Fig. 3. Differences in total mood disturbance (TMD) score between inhibitory and excitatory responders within each group (e.g., HCs, patients with cIGEs, and patients with trIGEs). Higher scores indicate greater mood disturbance. Error bars represent the standard error of the mean (SEM). POMS = Profile of Mood States.

depressive symptomatology remains unclear. While healthy participants and participants with IGE with past or current mood diagnoses were not excluded from this study, we only included participants with symptoms that were reportedly well-controlled at the time of participation. This may have not only affected the range of depression scores in our sample of patients with IGEs, but it also may have contributed to our lack of significant findings in mood disturbance between patients with cIGE and trIGE. Future studies should consider recruiting patients with IGE with active mood symptoms to better understand the relationship between cortical excitability and depression.

Dysfunction of the GABAergic network has long been implicated in the pathophysiology of psychiatric disorders, such as major depression and anxiety, with GABA specifically being hypothesized in the etiology of depression [29]. In addition, abnormalities in GABA receptor expression have been found in patients with temporal lobe epilepsy with comorbid mood disorders in postmortem analyses [30]. Our results provide additional evidence of a relationship between depressive symptoms and GABA network dysfunction, and may offer a novel approach for assessing this relationship through the LICI paradigm. Additional investigation regarding the causal nature of this relationship would be useful in developing new treatments for depression, particularly in clinical populations like IGE that exhibit decreased LICI.

Excitatory responders also endorsed significantly more symptoms than inhibitory responders on the POMS Fatigue subscale. In patients with epilepsy, fatigue has been significantly correlated with depression as well as sleep quality [31]. However, we did not collect data on sleep-related factors in this study, introducing a potential confound to these results. Cortical excitability is also affected by sleep, with sleep deprivation shown to increase cortical excitability in patients with epilepsy, including IGEs [32,33]. We recommend that future researchers obtain thorough sleep data, particularly on patients with IGEs, when further investigating the possible relationship between cortical excitability and fatigue.

Although differences in LICI response were associated with affective mood scores, correlational analyses between continuous total AUC and mood scores were not significant. While this may seem contradictory, we argue that these findings support our conceptualization that excitatory responses to LICI represent a dysfunctional response compared with the "normal" or "healthy" inhibitory response that is generally expected. Rather than analyzing AUC as a continuous variable, it may make more sense to examine AUC responses dichotomously (i.e., excitatory vs. inhibitory) when relating LICI to behavioral constructs. In this study, we obtained LICI data from ISIs 50 to 200 ms to construct AUCs, and it is unclear whether excitatory response to one or more of these ISIs in particular is more related to behavioral factors than others. As such, future studies utilizing larger sample sizes are encouraged to investigate the relationships between individual LICI ISIs and various behavioral factors to further explore this possibility. Furthermore, previous studies have shown differences between healthy controls and patients with IGEs on ISIs 250 and 300 [6,23]. Examining mood differences in excitatory and inhibitory responders at these ISIs may improve our understanding of the relationship between cortical excitability and mood disturbance, especially in patients with IGEs. It may be useful to examine interindividual differences in these relationships as well. Lastly, duration of GSWDs was not correlated with POMS TMD scale, contradictory to our hypothesis. Given that TMD score did not differ between cIGEs and trIGEs, however, these results are not too surprising. Furthermore, the likelihood of detecting a significant relationship between these variables was reduced given that only 8 participants with IGE even exhibited GSWDs.

4.2. Limitations

Limitations of this study include a relatively small sample size; however, the current sample is an extension of our previous study on healthy adults and produced results similar to those findings [1]. Participant inclusion criteria used for this study allowed for the recruitment of participants with well-managed mood disorders in both the healthy control and groups with IGE. While we recognize that this decision may have introduced a potential confound to our data, we argue that this inclusion criteria improves the generalizability of our findings, particularly given the high comorbidity of mood disorders in patients with IGEs. As mentioned above, we did not collect data regarding participants' sleep behavior the night(s) prior to testing, which may be a potential confound to this study. Because of our small sample size and the variability in ASDs, we were also not able to assess or control for the effects of specific ASDs on our analyses. Future studies are strongly encouraged to investigate the potential role of ASDs and ASD combinations on these findings, particularly given the known impact of ASDs on cortical excitability. Despite these limitations, we believe our findings provide novel insight into the underlying relationship between cortical excitability and mood. We recommend that future studies utilize larger samples sizes and exercise greater control over potential confounds to further investigate this relationship in both healthy and clinical populations.

4.3. Conclusions

Findings indicate that cortical excitability influences mood state more than seizure control in patients with IGEs. Specifically, results demonstrated that increased cortical excitability is associated with greater mood disturbance in healthy controls and patients with IGEs. The data also indicate a relationship between GABA network dysfunction and depressive symptomatology, which is supported by the literature. To explore the treatment implications of these findings, further investigation is warranted.

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Disclosures of Interest

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