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Article

Exploratory Study of the Neurophysiological Monitoring of the Efficacy of Transcranial Alternating Current Stimulation as a Treatment for Alzheimer's Disease

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ABSTRACT

Neurophysiological changes due to either real or sham transcranial alternating current stimulation (tACS) when paired with cognitive exercises were assessed in 35 patients with Alzheimer's disease (AD) or AD mixed with cerebrovascular disease utilizing Electrovestibulography (EVestG) in comparison with ADAS-Cog, as the primary outcome measure of cognitive function. Both measures were made at baseline (Week 0, W0), post (W5) and follow-up (W12). For EVestG a comparative analysis of the interval histogram (IH33) of the neuronal firing pattern was made. The results were further analysed based on the patients' modified Hachinski Ischaemic Score (HIS) to determine the impact of cerebrovascular disease (cvd) on EVestG responses. Important findings include: (i) For real tACS stimulation the differences observed between right and left side responses were primarily a consequence of the tACS electrodes' positioning. (ii) Based on EVestG responses, those with HIS ≥ 2 benefit more than those with HIS < 2 from real tACS stimulation by W12 ($p = 0.014$). (iii) The EVestG-detected frequency shifts in neural activity for real tACS show significant differences for subgroups HIS < 2 and HIS ≥ 2 ($p = 0.012$, W5), supporting a different time course and possible mechanisms. (iv) For the real tACS stimulation an improved cognitive score generally manifested at W12 as an increase in firing rate. (v) Cognitive exercises alone (sham tACS) appear to slow or prevent further overall decline. We conclude cognitive exercises plus real tACS appears to be effective but depending on cvd levels have different time constants and perhaps different overall modes of action. Further, the IH33 measure is shown to be effective at monitoring the effect of cognitive exercises alone (sham tACS) or with real tACS.

KEYWORDS: EVestG; Alzheimer's; tACS; cognitive exercises; double-blind clinical trial

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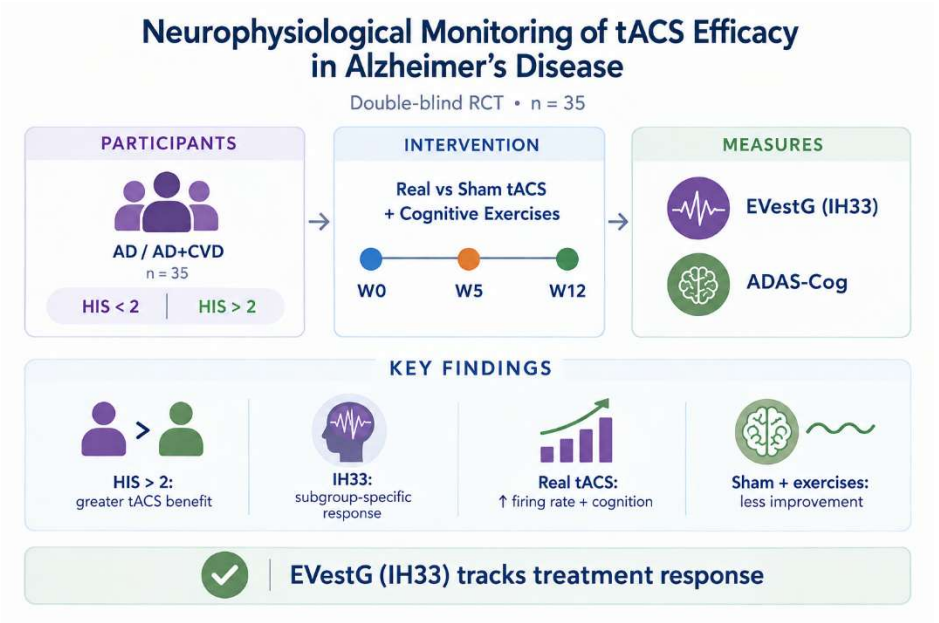


Graphical Abstract

INTRODUCTION

Dementia poses a significant public health challenge; it is currently affecting over 733,000 Canadians, and this number will continue to rise with our aging population. Non-pharmaceutical treatments such as transcranial alternating current stimulation (tACS) at gamma band (40 Hz) have recently been investigated by many groups as a treatment for dementia, in particular, Alzheimer's disease (AD) with some encouraging although not-consistent results [1–3].

One important factor to note when it comes to interpreting the treatment outcomes is that the majority of older adults with dementia (up to 84%) also suffer from cerebrovascular disease (cvd) [4,5]; herein called ADcvd. Interestingly, the way blood flow changes during AD follows a specific pattern, starting in areas like the precuneus and cingulate gyrus and later spreading to other regions of the brain [6]. This pattern suggests a major component of the problem is not only the altered metabolic demand but also there is a problem with blood supply even at early stages of the disease [6].

The standard primary outcome measures for efficacy of AD treatments are questionnaires, such as Alzheimer Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) scores [7]. Neurophysiological changes have been attempted to be measured by several different means such as EEG [8–10], fNIRS [11,12] and Electrovestibulography (EVestG) [13–15], out of which EVestG had an accuracy of ~89% for separating patients with AD or ADcvd [16]

EVestG is a non-invasive recording made from the vestibulo-acoustic system in both background (no motion) and in response to a passive whole-body tilt [16,17]. EVestG has demonstrated the ability to distinguish between AD and ADcvd [14,17], which is critical for understanding the

nuances of patient response to treatment. EVestG measures are hypothesized to reflect, in part, channelopathies and alterations in descending input to the vestibular periphery. We further hypothesize that vascular dysfunction disrupts signal transmission within the vestibular–locus coeruleus–limbic network, resulting in characteristic EVestG signatures that reflect the underlying pathophysiological changes. It has been observed that individuals with coexisting vascular issues may react differently to neuromodulatory interventions such as magnetic or electrical stimulation [14,17].

In this study, we recruited patients with AD and ADcvd who underwent a double-blind clinical trial of real/sham tACS, both paired simultaneously with cognitive exercises, and recorded EVestG at baseline (Week 0, W0), immediately post-treatment (W5) and at approximately 2 months-follow-up (W12). We analysed the responses of patients in either real and sham tACS groups, while subgrouping patients using their modified Hachinski Ischaemic Score (HIS) score to investigate the differences in the response of AD and ADcvd groups to each treatment. To the best of our knowledge, this is the first study that investigates the plausible neurophysiological changes due to tACS in an AD population while teasing out the cvd comorbidity.

METHODS

Thirty-five patients with AD or ADcvd were recruited as a sub study from the participants of a double-blind, placebo-controlled cross-over clinical trial investigating the effect of real/sham tACS paired with cognitive exercises [18]. Summary patient demographics are shown in Table 1 and more fully in the Table S1. The treatment was either real or sham tACS, paired with cognitive exercises simultaneously in two 30-min sessions with 30-min break in between, daily (5 days/week) for 4 weeks. That study was a cross-over design (two blocks of 4-week treatment with either real or sham tACS and cognitive exercises) with 4 assessments at: baseline (Week 0), post-intervention of block 1 treatment (Week 5), follow-up and baseline of the second block (Week 12) and post-intervention of block 2 of treatment (Week 17).

It should be noted that the EVestG experiments were a sub study of the above clinical trial. The number of participants in this sub study is only 35, while the main clinical trial concluded with 42 participants. Further, the main clinical trial was designed as a cross-over design study with 4 assessments. However, we missed EVestG recording of many of the 35 participants due to excessive ear wax or patient “wear” attrition over time within the allotted assessment weeks. This led to sample sizes < 5 in HIS subgroups at Week 17. Thus, in this paper, we present the results of EVestG analysis of three assessments: baseline at Week 0, immediate post-intervention at Week 5, and 2-month follow-up at approximately Week 12.

Table 1. Demographics (REAL-GP1 = real tACS (n = 18), SHAM-GP2 = sham tACS (n = 17)).

		Age	Gender	MOCA	MADRS	NPIQ (W0, 5, 12)	Modified HIS	REAL-GP1: HIS < 2, HIS ≥ 2
average	REAL-GP1	71.5	9F, 9M	15.8	3.3	5.8, 2.9, 4.8	1.3	N = (12, 6)
	SHAM-GP2	75.7	5F, 12M	15.6	4.9	5.9, 3.3, 5.3	1.9	Average: (0.67, 2.67)
stdev	REAL-GP1	8.2	-	5.9	3.4	4.8, 3.4, 4.9	1.2	**SHAM-GP2: HIS < 2, HIS ≥ 2**
	SHAM-GP2	10.2	-	5.1	5.8	4.8, 3.4, 4.1	2.1	N = (10, 7)
p		0.094	0.458	0.448	0.164	0.488	0.156	Average: (0.50, 4.00)

Real-GP1 = group 1-real stimulation. Sham-GP2 = group 2-sham stimulation. Note: The p-values correspond to appropriate e.g., two sample t-test to compare REAL-GP1/SHAM-GP2 baseline characteristics. There were no significant differences between groups in terms of age, MOCA, MADRS, HIS, NPIQ or gender.

Treatment Details

Sinusoidal tACS at 40 Hz, with 1.5 mA amplitude (peak-to-peak) was delivered using the Soterix Medication tACS Stimulator (Model: 2001). The active and reference electrode were placed over the left dorsolateral prefrontal cortex (DLPFC) (F3 on the 10–20 electroencephalogram systems) and on the contralateral supraorbital area, respectively. Sham tACS using the Soterix device administers an initial increasing ramp up of current intensity for 30 s and ramp down to 0 mA for another 30 s and remains at 0 mA until the last minute of stimulation where the current again ramps up and ramps down within 1 min. The cognitive exercises were administrated with the trained treatment administrator using MindTriggers app, while the participants received either real or sham tACS [2].

Assessments

The primary outcome measure was change in ADAS-Cog from baseline to immediate post-treatment (W0–W5). ADAS-Cog ranges from 0 to 70, with lower scores indicating better cognitive performance and higher scores reflecting greater cognitive impairment. An ADAScog score improvement between 1 and 2 is considered mild, 2 and 3 moderate and > 3 significant for measuring treatment efficacy. The secondary outcome measures were the changes in Neuropsychiatric Inventory Questionnaire (NPI-Q) [19] and the Montgomery–Åsberg Depression Rating Scale (MADRS) [20]. The NPI-Q assesses the severity of neuropsychiatric symptoms over the past month using 12 questions. Symptom severity is rated on a scale from 1 (mild) to 3 (severe), with a total severity score ranging from 0 to 36. The version used in this study does not include caregiver burden. MADRS assesses depression severity across 10 items and the total score ranges from 0 (no depression) to 60 (severe depression).

In addition to the above, EVestG was recorded from 35 participants as mentioned above and was investigated as a neurophysiological measure of the treatment efficacy. Ten healthy controls with matching recording electrode type and age > 65 years were included and analysed for comparison.

Modified HIS score

Some vascular symptomology (e.g., some of hypertension, cardiovascular disease, diabetes, or a history of stroke) is represented in a Hachinski Ischemic Score (HIS) > 4 [21]. Representative of ADcvd or MxD (mixed AD/vascular dementia) is a HIS score > 4 and < 7 [22]. A score greater than 7 is considered vascular dementia. Alternative scales to diagnose vascular and "AD with cerebrovascular disease (cvd)" include the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) scale [23] that has the advantage of including imaging data in their scoring, a limitation of the HIS. However, NINDS-AIREN lacks sensitivity as a neuropathological study demonstrated a sensitivity/specificity for possible vascular classification using the NINDS-AIREN scale of 55/84% [23]. On the other hand, using a HIS threshold of 4 without imaging data 73.3% are correctly determined as AD and AD with vascular symptomatologies (ADcvd), and if an HIS threshold of 3 is used the accuracy increases to 77.8% [24].

"The HIS, while lacking neuroimaging criteria, may be more suitable for identifying the majority of dementia patients with vascular dementia (symptomatology), that is, those with at least some cerebrovascular pathology, because of the low sensitivity of the NINDS-AIREN and California criteria [25]." The presence and extent of white matter hyperintensities (WMH), is often a radiographic marker of small cerebral vessel disease and an important predictor of the life-long risk of stroke, cognitive impairment [26,27], and functional disability [28]. Thus, we made a modified HIS to be a 14-point scale by adding white matter hyperintensities (WMH) as an extra 1 point to the original 13 points, similar to our previous studies [14,29]. The WMH herein was identified from the brain's MRI diagnostic report of each participant.

Further by using a threshold HIS of 2 rather than 3 or 4 improved efficacy detection was achieved for AD versus ADcvd patient rTMS treatment [17]. Herein we investigate the responses of the patients with cvd based on their modified HIS when a threshold of 2 is a measure of its impact on cognitive changes post-treatment.

EVESTG RECORDING

The detailed methodology for EVestG recordings is given in [17]. Briefly, EVestG recordings are made inside an electromagnetically shielded and sound attenuated (>30 dB) chamber. As the EVestG signal is buried in noise, shielding is necessary to minimize electromagnetic interference including powerline artefacts. The recordings are vestibuloacoustic so minimization of the acoustic component with a sound attenuated chamber is necessary. To minimize movement (muscle) artefacts subjects are positioned either in a supine or sitting position on a hydraulic table/chair. The recordings were bandpass filtered from 300 to 4500 Hz to minimize muscle artefact and limit high frequency noise. During EVestG recordings, participants

have their eyes closed and are in a relaxed state with their neck supported. Bilaterally, a gelled wick electrode was visually positioned close to the tympanic membrane (Figure 1A). Bilateral reference and single common lead(s) were placed on the outer ear canal and forehead, respectively. The subject remained passive with closed eyes and is not required to interact cognitively during the measurement. Whilst the chair was stationary (static) responses were recorded. A background recording 1.5 s immediately prior to chair's movement is considered as the static phase response. Static recordings were made in the sitting position.

Each subject's BGi (stationary) recording was the average of 5 recordings. A software program called the Neural Event Extraction Routine (NEER V5.1) [16] was used to find then average the detected spontaneous and driven field potentials (FPs) from the EVestG recording to produce an average FP plot and generate a firing pattern interval histogram (IH). The NEER algorithm [16] extracts the average FP and IH curves from each EVestG recorded signal using a complex Morlet wavelet analysis of phase. The IH timings were then converted to frequencies (f = 1/time) and plotted based on the gap between every 33 firings (e.g., Figure 1B) to focus proximal to 9Hz, which corresponds to the low end of the vestibular efferent spontaneous activity and is within the alpha and hippocampal theta bands.

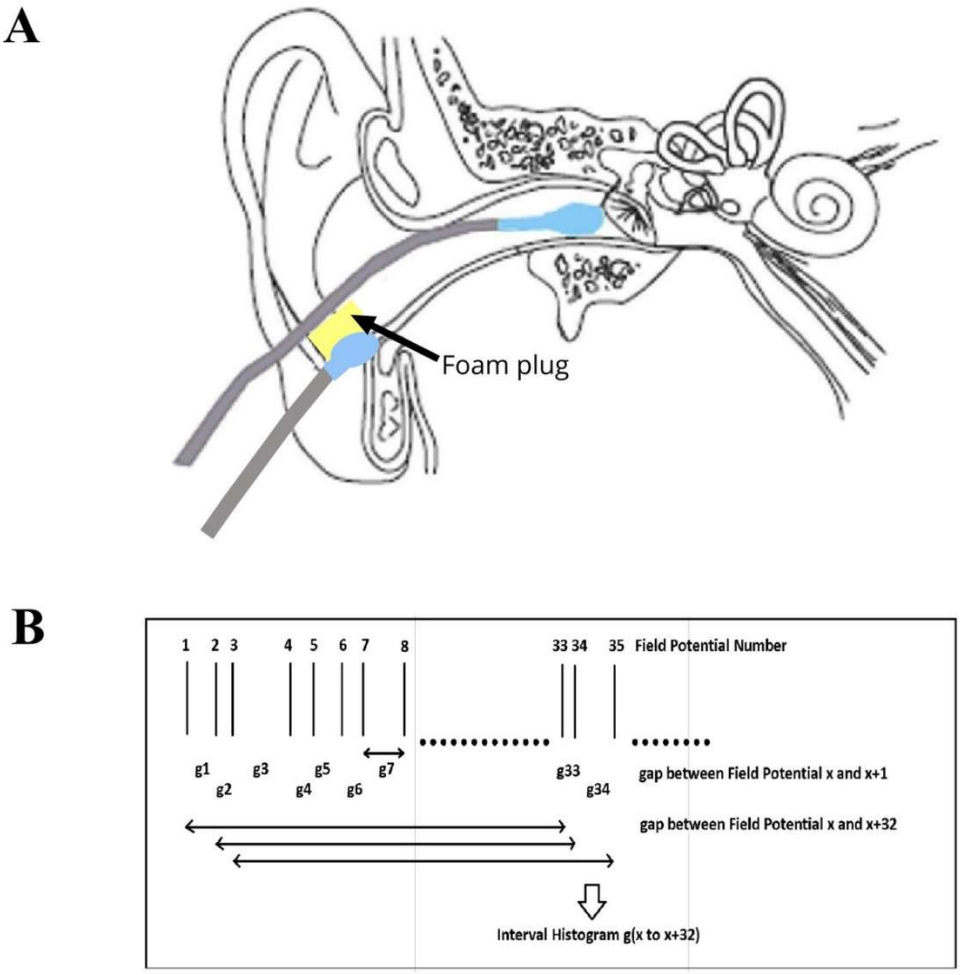


Figure 1. EVestG methodology: (**A**) Active electrode placement. (**B**) IH33 derivation.

STATISTICS

The EVestG measures of tACS treatment study had 3 assessment times: baseline (Week 0, immediate post-treatment at Week 5 and then at Week 12 2-month follow-up). The averaged changes of ADAS-Cog score at immediate post-treatment (W5) and 2-month follow-up (W12) with respect to baseline for each group were calculated from data in Supplemental Table 1.

A repeated measures analysis of variance (ANOVA) was conducted between the real (REAL-GP1) and sham (SHAM-GP2) (All HIS, HIS < 2 and HIS ≥ 2) groups. Post-hoc analysis, simple model analysis including estimated marginal models and t-tests are presented as appropriate. We mainly investigated the following hypotheses:

1. Active and sham tACS paired with cognitive exercises for HIS All, HIS ≥ 2 and HIS < 2 have significantly different ADAScog change and EVestG frequency shift feature results across time.
2. HIS ≥ 2 and HIS < 2 participants have significantly different ADAScog change and EVestG frequency shift feature results for REAL-GP1 (tACS&CE) and SHAM-GP2 (sham tACS&CE).

RESULTS

Each ear's EVestG signals were analysed separately given the tACS electrodes LHS orientation and compared between the two (REAL-GP1 and SHAM-GP2) stimulus groups over the three assessment sessions. Their results are presented separately below.

LEFT EAR SIGNALS

Figure 2A shows the left ear's IH33 plot results (with Standard Error (SE) bars) for Group 1 (REAL-GP1: stimulus sequence; baseline (W0), immediate post-treatment (W5) tACS plus cognitive exercises (CE), 2-month follow-up (W12)). Figure 2B shows the left ear's IH33 plot results for Group 2 (SHAM-GP2: stimulus sequence; baseline (W0), immediate post-treatment (W5) of sham plus CE, 2-month follow-up (W12)). Figure 2A, B are IH33 plots for all participants regardless of their HIS level measured at baseline (W0), immediate post-treatment (W5) and 2-month follow-up (W12) with healthy controls overlayed (REAL-GP1: N = 17 at W0, 18 at W5, 16 at W12 plus 10 controls and SHAM-GP2: N = 16, 15, 14, 10 respectively). Twenty-eight had all 3 (W0, W5, W12) recordings, 4 missed W12, 1 missed W5, 1 missed W0 and 1 missed W0&W5. Overlayed within a text box on the plots are each time plots correlation with the control curve and the average ADAS-Cog score change at each time point measured from baseline. A shift towards higher frequencies of the curve corresponds to an increase in neural activity (firing rate).

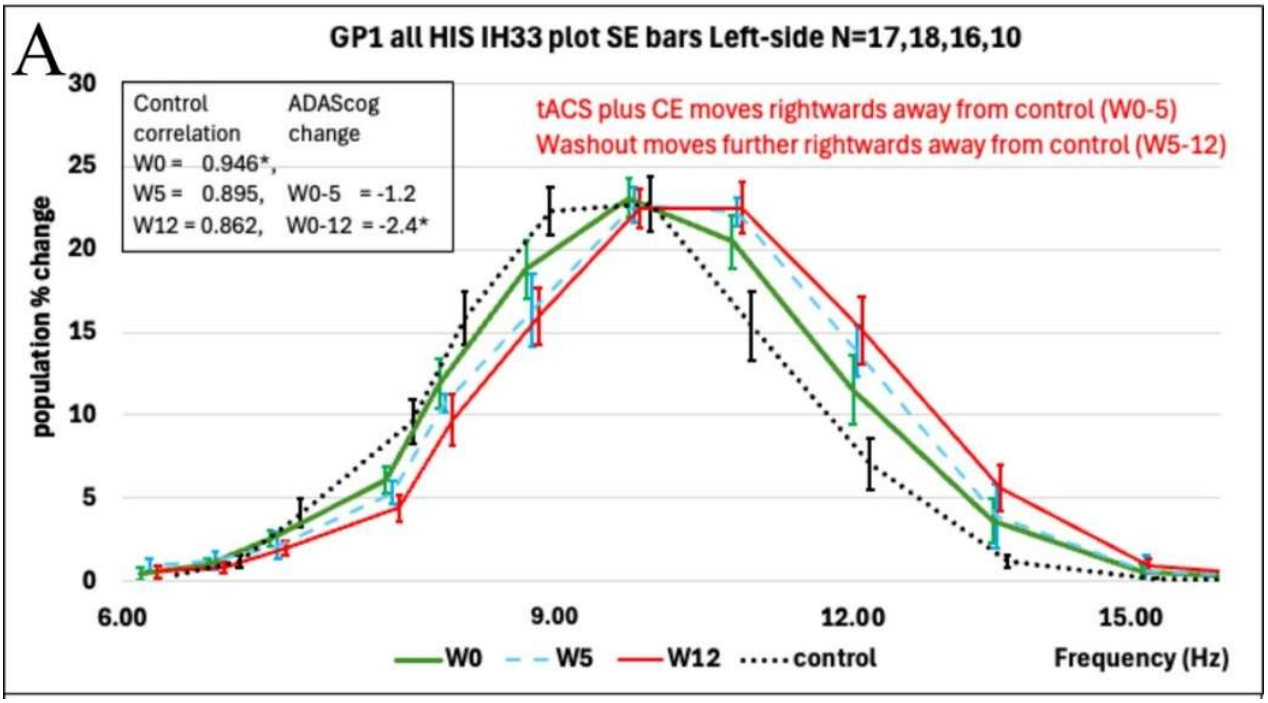
From Figure 2A,B we can observe: (i) For baseline (W0) to immediate post-treatment (W5), for REAL-GP1 (real tACS & Cognitive Exercises (CE)) the plot moves towards higher frequencies (shorter time intervals) away

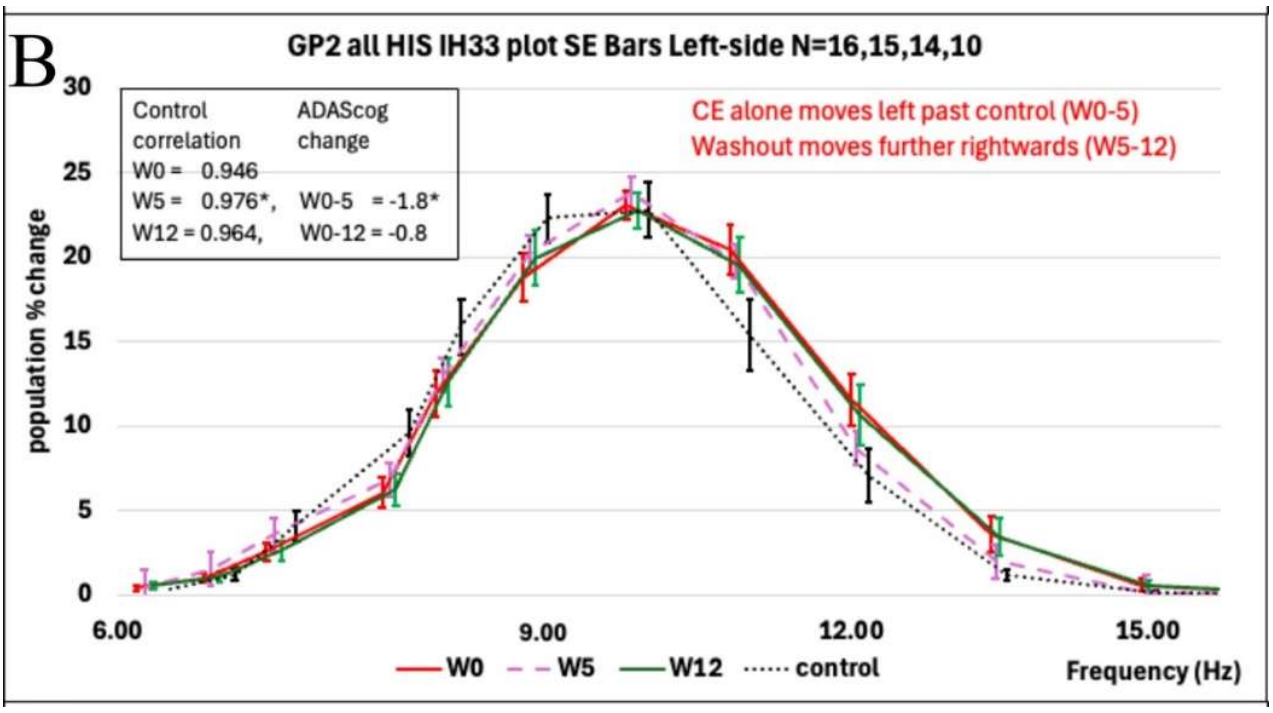
from control, whereas for SHAM immediate post-treatment (W5) to 2-month follow-up (W12) (washout period) for REAL-GP1 there is a further movement towards higher frequencies and away from control (note: the 2-month follow-up (W12) curve is significantly different to baseline) whereas for SHAM-GP2 there is a small movement towards higher frequencies and away from controls. (ii) When each time plot is correlated with control and then used as a potential metric for improvement in cognition the REAL-GP1 results are contrary as correlation decreased as ADAS-Cog score improved (decreased) from baseline (W0) through 2-month follow-up (W12). For SHAM-GP2 ADAS-Cog improvement was seen for W0 through 12 and correlation was marginally increased at all time points. Figure 2C compares the active/sham baselines for REAL-GP1 and SHAM-GP2 at baseline (W0) and 2-month follow-up (W12).

Based on the Figure 2C significantly different bins a feature (F1) was defined as the bin value at the 8.9 Hz bin minus that of the 12.1 Hz bin. This was used on each of the IH33 plots as a measure of frequency shift. Note: The Square root of F1 (sqrtF1) was used as this transformation improved normality. Using sqrtF1 the two groups of real and sham tACS with CE were found to be significantly different at 2-month follow-up (W12) by applying a repeated measures ANOVA (time*GP, $F(2, 42) = 4.324$, $p = 0.02$, $\eta^2 = 0.325$, power = 0.733, Table 2C). Also interesting, using feature sqrtF1 the two groups of real and sham tACS with CE were found to be significantly different at W5 (independent samples t-test, $p = 0.007$, 1-sided, Hedges (unequal variances) point estimate effect size = −0.849, Table 2B). For baseline (W0) to 2-month follow-up (W12) and Real (REAL-GP1) stimulation a multivariate signficant interaction was observed between time and REAL-GP1 (wilkes-l, $F(2, 20) = 6.381$ $p = 0.007$, $\eta^2 = 0.314$, power = 0.850 bonferroni correction; pairwise baseline (W0) to 2-month follow-up (W12), $p = 0.017$; pairwise immediate post-treatment (W5) to 2-month follow-up (W12), $p = 0.009$). Sham (SHAM-GP2) was not significant ($p = 0.496$). For this ANOVA covariates were Age and MADRS, Fixed factors were Group (and HIS group). These data are supportive of real and sham stimuli evoking significantly different responses by 2-month follow-up (W12). We see a marked increase in neural activity (shift to the right toward higher frequencies) in REAL-GP1 relative to SHAM-GP2. There are obvious but not necessarily significant visual differences between Figure 2A,B. There may be more than one physiological impact for each stimulation type, e.g., a vascular and a neural impact which have different time courses and perhaps even opposite impacts on the IH33 plots. A sub analysis based HIS score may clarify these findings.

In Figure 3A–F the left side data are broken into those with HIS scores < 2 and ≥2, i.e., those mostly without and those with some cerebrovascular symptomology respectively. For the justification for the HIS < 2 level selection see [17] and methods. For all following repeated measures ANOVA analysis at baseline (W0), immediate post-treatment (W5) and 2-month follow-up (W12): (i) the covariates are age and MADRS; (ii) the fixed

factors are HIS group (HIS < 2, HIS ≥ 2) and Stimulation Group (REAL-GP1/REAL-GP1). Sex was removed as a factor as group size would become too small—this is recognised as a limitation. A one-sided p value was used as we predicted an increase in frequency (neural activity) or ADAScog decrease with treatment (doubling it gives the 2-sided p value).





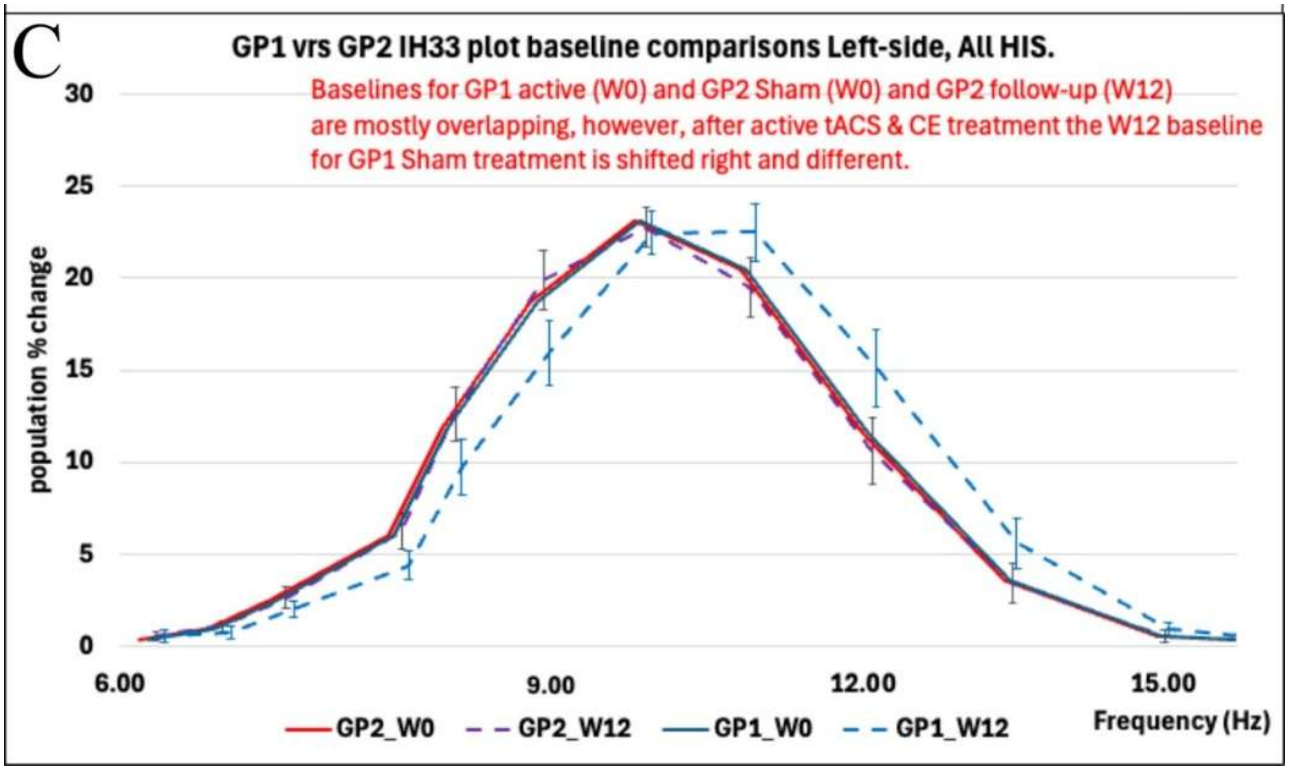
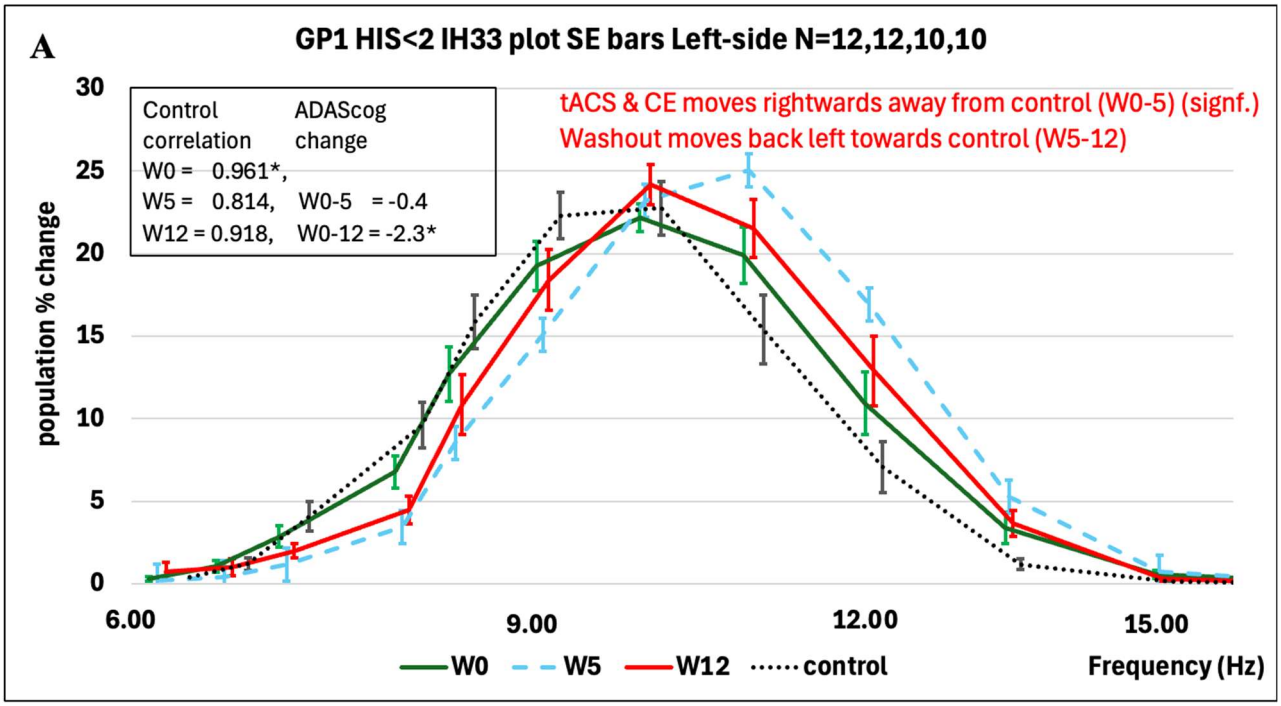
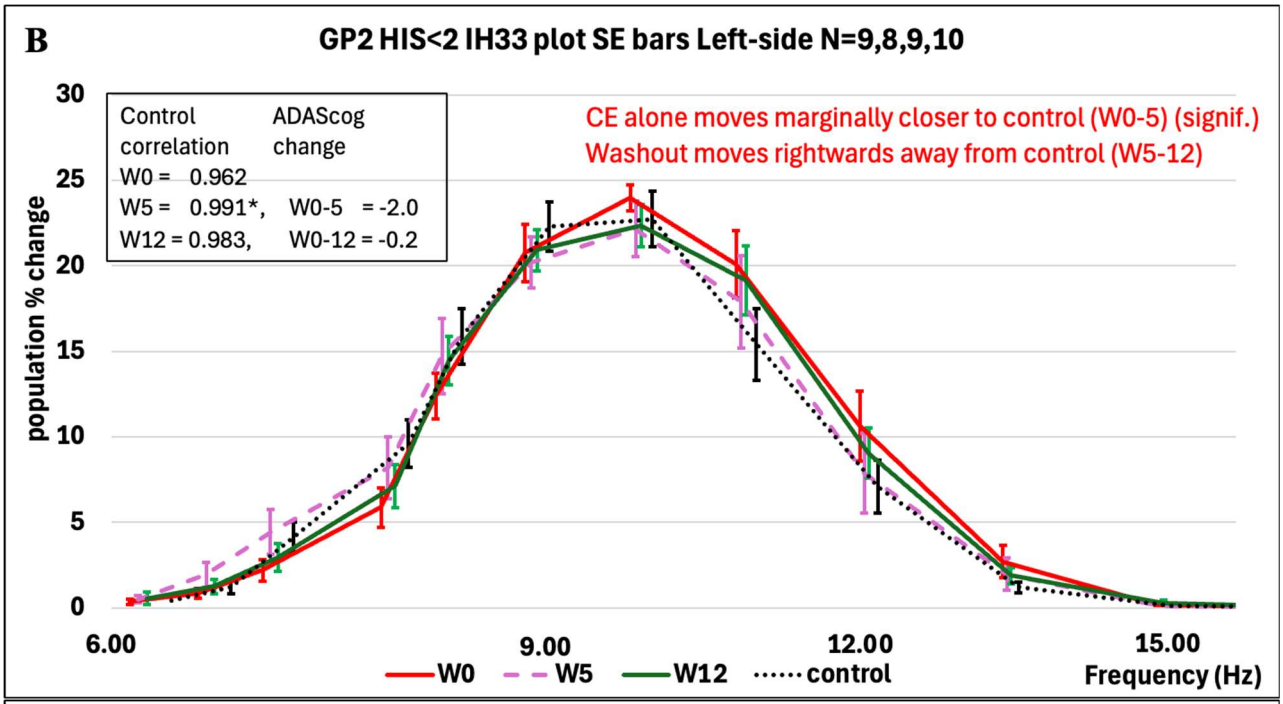
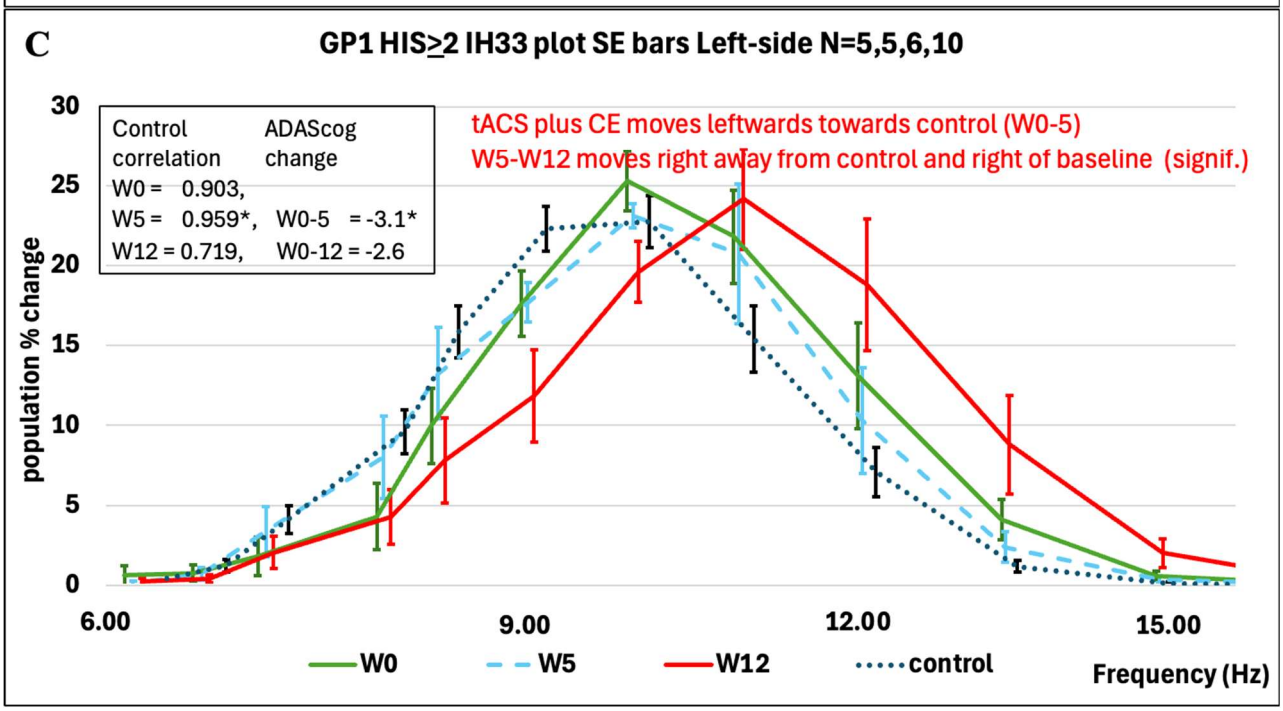
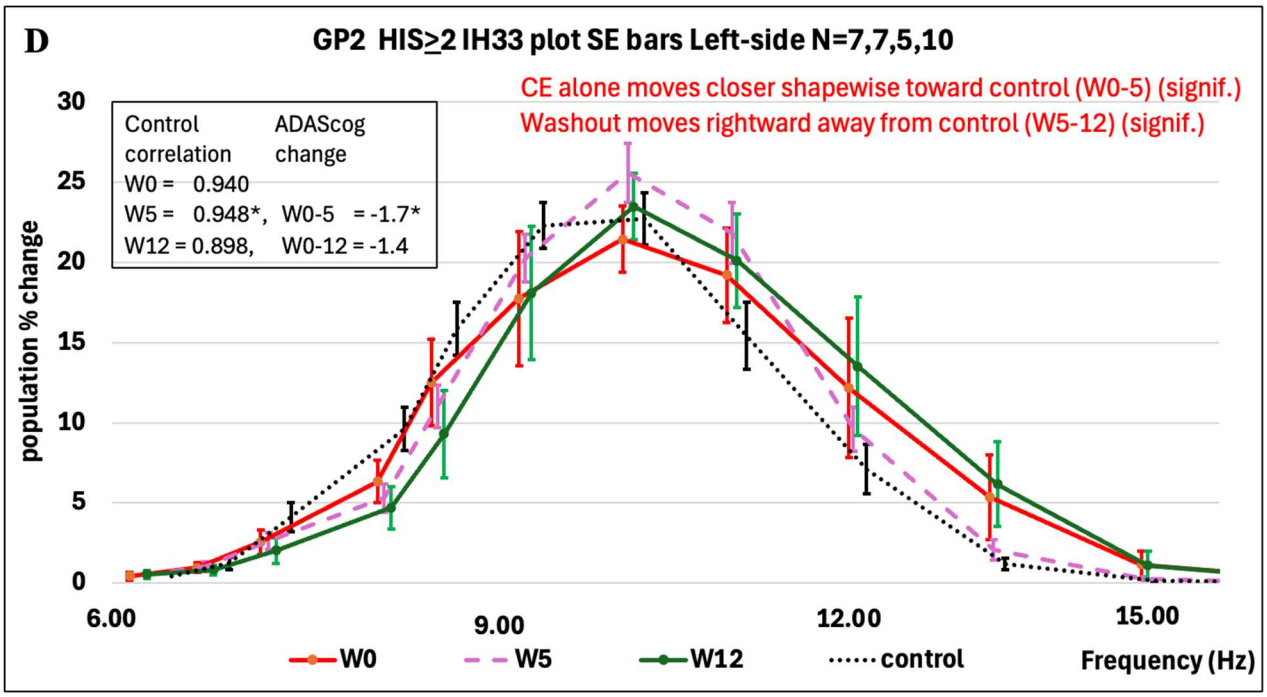


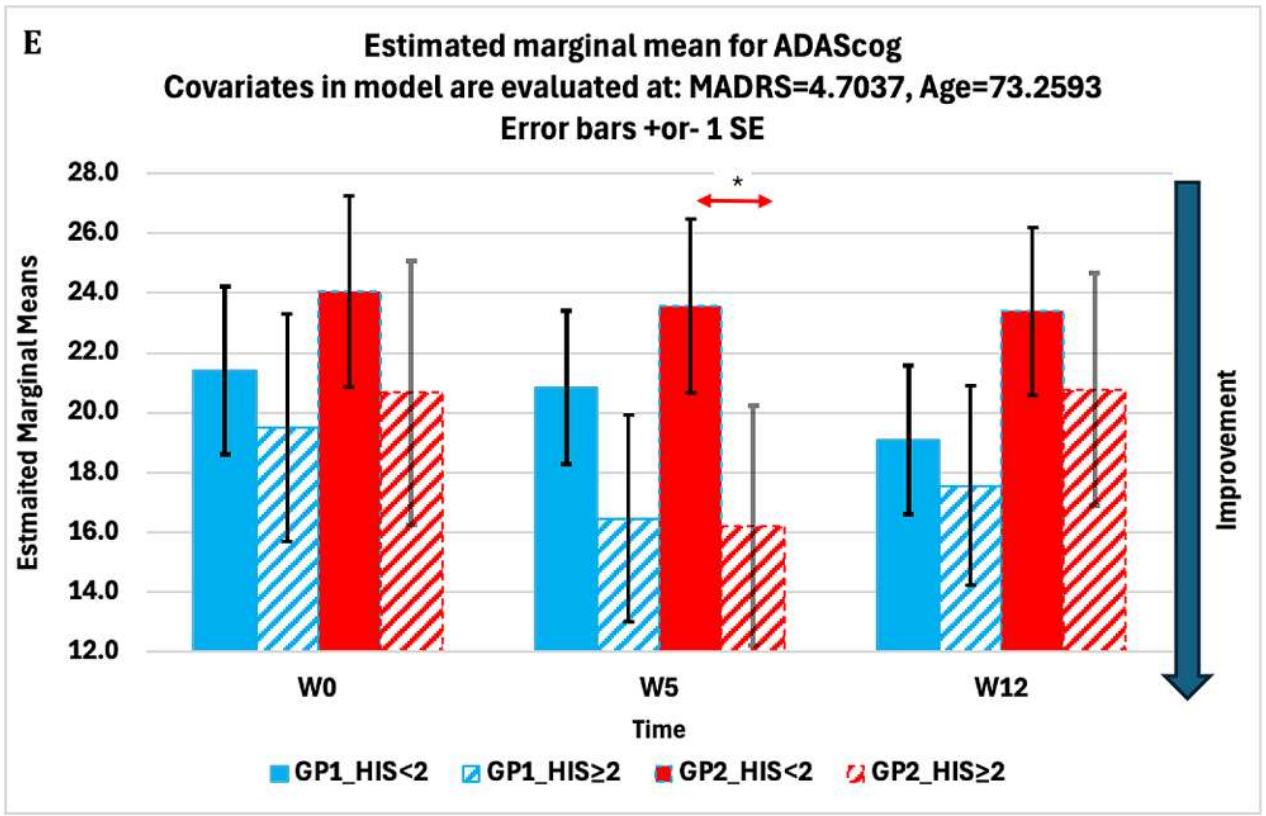
Figure 2. (**A**,**B**) are IH33 plots for all modified Hachinski Ischemic Score (HIS) values combined and measured at baseline (W0), immediate post-treatment (W5), 2-month follow-up (W12) with healthy controls overlaid (REAL-GP1: N = 17 at W0, 18 at W5, 16 at W12 and 10 for control; SHAM-GP2: N = 16, 15, 14, 10 respectively). **(C)** clearly shows REAL-GP1 and SHAM-GP2 baselines (W0) overlapping but at 2-month follow-up (W12) the REAL-GP1 and Sham-GP2 responses are different—i.e., tACS&CE produces a different response to CE alone. * Asterisks indicate largest correlation with control or change in ADAScog change.




B
GP2 HIS<2 IH33 plot SE bars Left-side N=9,8,9,10
Control correlation
W0 = 0.962
W5 = 0.991*,
W12 = 0.983,
ADAScog change
W0-5 = -2.0
W0-12 = -0.2
CE alone moves marginally closer to control (W0-5) (signif.)
Washout moves rightwards away from control (W5-12)
population % change
30
25
20
15
10
5
0
6.00
9.00
12.00
15.00
Frequency (Hz)
W0
W5
W12
control


C
GP1 HIS≥2 IH33 plot SE bars Left-side N=5,5,6,10
Control correlation
W0 = 0.903,
W5 = 0.959*,
W12 = 0.719,
ADAScog change
W0-5 = -3.1*
W0-12 = -2.6
tACS plus CE moves leftwards towards control (W0-5)
W5-W12 moves right away from control and right of baseline (signif.)
population % change
30
25
20
15
10
5
0
6.00
9.00
12.00
15.00
Frequency (Hz)
W0
W5
W12
control


D
GP2 HIS≥2 IH33 plot SE bars Left-side N=7,7,5,10
CE alone moves closer shapewise toward control (W0-5) (signif.)
Washout moves rightward away from control (W5-12) (signif.)
Control correlation
ADAScog change
W0 = 0.940
W5 = 0.948*, W0-5 = -1.7*
W12 = 0.898, W0-12 = -1.4
population % change
30
25
20
15
10
5
0
6.00
9.00
12.00
15.00
W0
W5
W12
control
Frequency (Hz)


E
Estimated marginal mean for ADAScog
Covariates in model are evaluated at: MADRS=4.7037, Age=73.2593
Error bars +or- 1 SE
Estmaited Marginal Means
28.0
26.0
24.0
22.0
20.0
18.0
16.0
14.0
12.0
*
W0
W5
W12
Time
Improvement
GP1_HIS<2
GP1_HIS≥2
GP2_HIS<2
GP2_HIS≥2

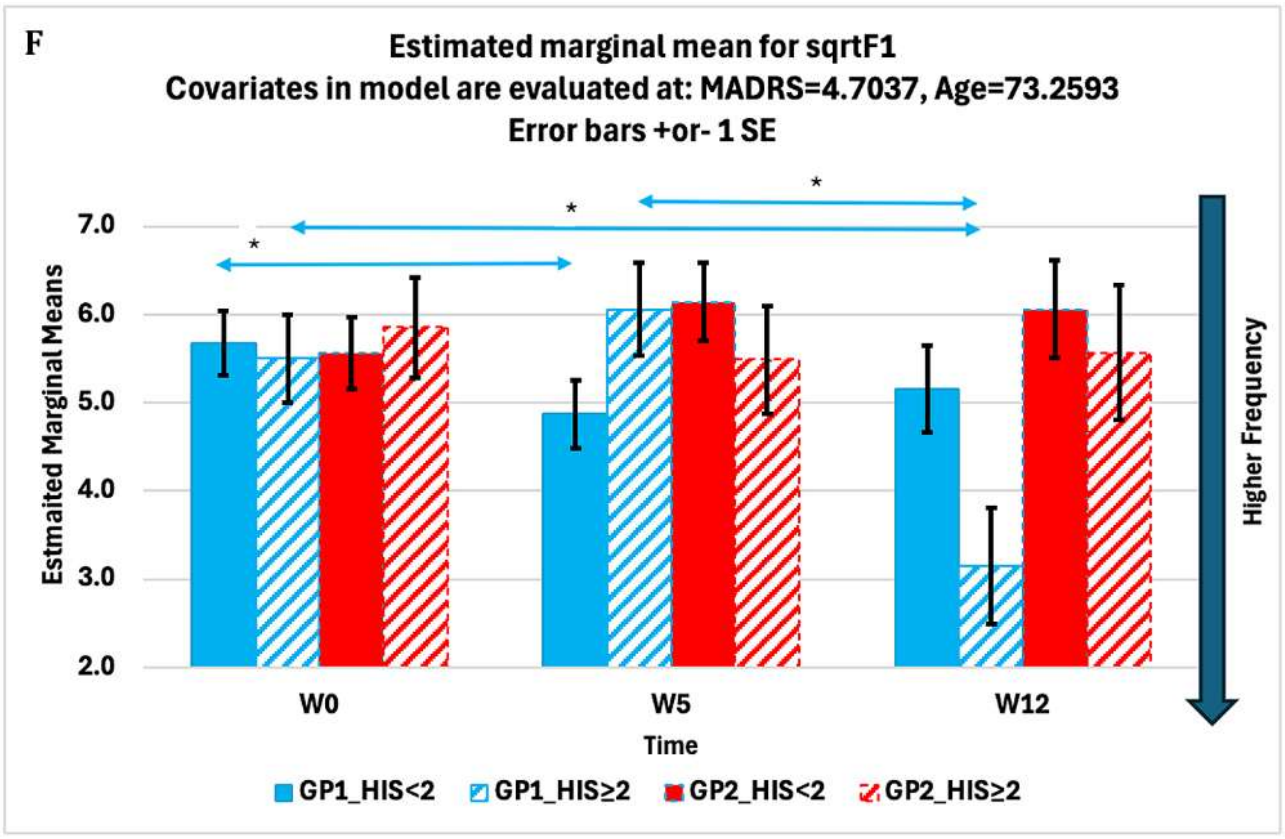


Figure 3. (**A**) The left side (GP1) data of Figure 2A only for those with HIS scores < 2. (**B**) The left (GP2) side data for Figure 2B for those with HIS < 2. Standard Error bars (SE) are overlaid. (**C**) The left side (GP1) data of Figure 2A only for those with HIS scores ≥ 2. (**D**) The left (GP2) side data for Figure 2B for those with HIS ≥ 2. Standard Error bars (SE) are overlaid. * Asterisks indicate the largest correlation with the control or the largest ADAScog change in Figure 3A–D. (**E**) shows the Estimated Marginal Means (SPSS-V32) for ADAS-Cog score across baseline (W0)-immediate post-treatment (W5)-2-month follow-up (W12) for the HIS < 2 and HIS ≥ 2 subgroups with Real (REAL-GP1) and Sham (Sham-GP2) stimulations. Both REAL-GP1 and SHAM-GP2 show ADAS-Cog improvement. (**F**) shows the Estimated Marginal Means (SPSS) for sqrtF1 plot for times baseline (W0)-immediate post-treatment (W5)-2-month follow-up (W12) for REAL-GP1 and SHAM-GP2 using feature sqrtF1. Covariates Age and MADRS, fixed factors Stimulation group and HIS group. * Asterisks indicate a significant difference (p = 0.05) in Figure 3E and 3F.

For HIS < 2 Figure 3A,B show: (i) For baseline (W0) to immediate post-treatment (W5), for REAL-GP1 the IH33 curve significantly moves towards higher frequencies (i.e., increase in neural activity) away from controls, whilst, for SHAM-GP2 there is a small shift towards controls. For HIS < 2, real and sham were found to have significantly different baseline (W0) to immediate post-treatment (W5) and immediate post-treatment (W5) to 2-month follow-up (W12), IH33 frequency shifts (paired t-test, p = 0.008/0.018, 1-sided, Hedges (unequal variances) point estimate effect size = 0.771/−0.709 respectively Table 2A). Additionally, at immediate post-treatment (W5) was a significant difference between real and sham (p = 0.012, point estimate effect size = −1.136, Table 2B) and; (ii) When correlation of each time point curve with control is used as a metric for improvement in cognition the decreasing correlation results are contrary to the observed ADAS-Cog score improvement from baseline (W0) to 2-

month follow-up (W12) for REAL-GP1. For SHAM-GP2 the correlation marginally improved with the ADAS-Cog improvements. These results are not too dissimilar to those for the "All" HIS group. The correlations of the IH33 curve across time for REAL-GP1 with that of the Control group were poor.

The results for the HIS ≥ 2 data appear quite different (Figure 3C,D). What was seen is: (i) For baseline (W0) to immediate post-treatment (W5) for REAL-GP1 and SHAM-GP2 the plots move non-significantly toward lower frequencies and control. (ii) During the immediate post-treatment (W5) to 2-month follow-up (W12) for REAL-GP1 ($p = 0.062$, Table 2A) and SHAM-GP2 ($p = 0.220$) there was a large and small respectively movement toward higher frequencies and away from controls.

For HIS ≥ 2 the interval baseline (W0) to 2-month follow-up (W12) for REAL-GP1 (real) but not SHAM-GP2 (sham, $p = 0.296$) the movement toward higher frequencies was significant (paired t test, $p = 0.05$, effect size = 0.758, Table 2A). The separation of real and sham response at 2-month follow-up (W12) for HIS ≥ 2 was significant (GP*HIS ≥ 2*W12, $F(1, 21) = 5.625$, $p = 0.027$, $\eta^2 = 0.211$, power = 0.619, Table 2C). When correlation with control is used as a metric for improvement in cognition the REAL-GP1 and SHAM-GP2 highest correlation occurred at immediate post-treatment (W5).

Table 2C data indicate a significant HIS*time interaction: (i) for immediate post-treatment (W5) and 2-month follow-up (W12) real stimulation there are significant differences across HIS groups (HIS*time, $F(2, 20) = 4.573$, $p = 0.023$, $\eta^2 = 0.314$, power = 0.709, pairwise $p = 0.02$ for HIS*(W5–W12), Table 2C) and (ii) For HIS ≥ 2 and real stimulation there are significant changes across time periods baseline (W0) to 2-month follow-up (W12) and immediate post-treatment (W5) to 2-month follow-up (W12) (GP*HIS ≥ 2, $F(2, 20) = 10.604$, $p < 0.001$, $\eta^2 = 0.515$, power = 0.975; pairwise, W0–W12, 0.014; pairwise, W5–W12, $p < 0.001$, Table 2C). In Figure 3E,F is can be seen that the EVestG detected frequency shifts toward higher frequencies (increase in neural activity) detected in the interval histograms occur at immediate post-treatment (W5) for HIS < 2 ($p = 0.008$) these decreasing by 2-month follow-up (W12) ($p = 0.018$). For HIS ≥ 2 (Figure 3F and Table 2C) most frequency increase occurs by 2-month follow-up (W12) for supportive of a different time course and possible mechanism(s) for HIS ≥ 2 compared to HIS < 2 (Figure 3A).

It is also demonstrated in Table 2 where the increase in neural activity (shift toward higher frequencies) is increased for baseline (W0) to immediate post-treatment (W5) and decreased for immediate post-treatment (W5) to 2-month follow-up (W12) for HIS < 2 but shows a delayed increase from immediate post-treatment (W5) to 2-month follow-up (W12) for HIS ≥ 2 (note the opposite trend for baseline (W0) to immediate post-treatment (W5) for HIS ≥ 2). By 2-month follow-up (W12) all left side tACS impacts (Figure 2 and 3) were seen as a shift toward higher frequencies (increase in neural activity) of the IH33 curve generally away from the control curve. Sham stimulation evokes a much smaller response changes by 2-month follow-up (W12) ($p = 0.019$ and Figure 3F).

Table 2. Statistical Analysis of significant and relevant data.

A. Change in feature F1 over time and as a function of Group (REAL-GP1, SHAM-GP2) and HIS (All, <2, ≥2). * Indicated significant result (p < 0.05)										
F1 feature		**REAL-GP1&2**	**Hedges'**		**REAL-GP1**	**Hedges'**		**SHAM-GP2**	**Hedges'**	
	period	**paired t-test**	**unequal var**		**paired t-test**	**unequal var**		**paired t-test**	**unequal var**	
		p (1-sided)	**effect size**	**N**	**p (1-sided)**	**effect size**	**N**	**p (1-sided)**	**effect size**	**N**
All HIS	W0–W5	0.351	0.067	32, 32	0.088	0.327	17, 17	0.187	−0.225	12, 12
	W5–W12	0.147	0.196	28, 28	0.239	0.173	16, 16	0.197	0.238	11, 11
	W0–W12	0.068	0.282	28, 28	0.022*	0.54	15, 15	0.422	−0.052	10, 10
HIS < 2	W0–W5	0.066	0.338	20, 20	0.008*	0.771	12, 12	0.35	−0.126	8, 8
	W5–W12	0.058	−0.385	17, 17	0.018*	−0.709	10, 10	0.418	0.071	7, 7
	W0–W12	0.432	0.044*	18, 18	0.144	−0.268	10, 10	0.211	−0.89	8, 8
HIS ≥ 2	W0–W5	0.105	−0.357	12, 12	0.204	−0.33	5, 5	0.207	−0.288	7, 7
	W5–W12	0.035*	0.562	11, 11	0.062	0.632	6, 6	0.22	0.305	5, 5
	W0–W12	0.041*	0.564	10, 10	0.050*	0.758	5, 5	0.296	0.207	5, 5

B. Group (REAL-GP1, SHAM-GP2) comparisons at W0, W5, W12 in feature F1 and as a function of HIS (All, <2, ≥2),									
	All HIS	**Hedges'**		**HIS < 2**	**Hedges'**		**HIS ≥ 2**	**Hedges'**	
period	**t-test**	**unequal var**		**t-test**	**unequal var**		**t-test**	**unequal var**	
	p (1-sided)	**effect size**	**N**	**p (1-sided)**	**effect size**	**N**	**p (1-sided)**	**effect size**	**N**
W0	0.423	−0.067	17, 16	0.741	−0.142	12, 9	0.461	−0.054	5, 7
W5	0.007*	−0.849	18, 15	0.012*	−1.136	12, 8	0.402	−0.137	6, 7
W12	0.045*	−0.615	16, 14	0.105	−0.738	10, 9	0.15	−0.601	6, 5

C. Significant and relevant Repeated Measures ANOVA at W0, W5, W12 results. (Bonferroni corrected). * Interaction of time with GP.					
Covariates: age, MOCA. Fixed Factors: Group (Real/Sham, 15/12), HIS Group (<2, ≥2, 17/10).					
sqrtF1-dependant variable		**Box's Test p = 0.037** **(Given group sizes are similar use Pillai's trace)**			**Mauchley's Test p = 0.821** **(Main within subjects test)**
					Lavene's W12 p = 0.028 **(Given group sizes are similar this is not serious)**
		Pillai's Trace	**p**	**η^2**	**power**
Multivariate	time*HIS	F (2, 20) = 6.013	0.009	0.376	0.828
Within subjects	time*HIS	F (2, 42) = 6.119	0.005	0.226	0.865

EMM's	time*GP	F (1, 21) = 4.878	0.038	0.189	0.559	GP*W12
	time*GP	F (2, 20) = 5.550	0.012	0.357	0.795	
		pairwise	0.015			Real*(W0–W12)
		pairwise	0.026			Real*(W5–W12)
	time*HIS	F (1, 21) = 6.765	0.017	0.244	0.699	W12*HIS
	time*HIS	F (2,20) = 7.172	0.004	0.418	0.891	
		pairwise	0.003			HIS2*(W5–W12)
	GP*HIS*time	F (1, 21) = 4.881	0.038	0.189	0.559	GP*HIS ≥ 2*W12
	GP*HIS*time	F (1, 21) = 4.671	0.042	0.182	0.541	Real*HIS*W5
	GP*HIS*time	F (1, 21) = 7.973	0.01	0.275	0.768	Real*HIS*W12
	GP*HIS*time	F (2, 20) = 9.577	0.001	0.489	0.961	Real*HIS ≥ 2
		pairwise	0.012			Real*HIS ≥ 2*(W0–W12)
		pairwise	<0.001			Real*HIS ≥ 2*(W5–W12)

Prior to conducting the repeated measures ANOVA, preliminary assumption testing was performed. Mauchly's test of sphericity indicated that the assumption of sphericity was met, (η^2 = 1.071, p = 0.821). However, Levene's test (p = 0.028) and Box's M test (p = 0.037) both reached statistical significance, indicating a violation of the assumption of homogeneity of variance and covariance matrices. Because group sizes were approximately equal, the repeated measures ANOVA was deemed sufficiently robust to proceed without further data transformation.

ADAS-Cog

Figure 3E shows the ADAS-Cog score change across time for the real (REAL-GP1) and sham (SHAM-GP2) participants and their HIS level subgroup participants. The full details of the ADAS-Cog analysis can be obtained in Uehara, 2025 [2]. In that parent study we found a significant difference before and after tACS for real (p = 0.019) stimulation. Second, during the washout period there was a significant difference between the measured ADAS-Cog change supporting difference between real versus sham stimulation (p = 0.048). Comparatively, herein the 'All' HIS data (Table 2) herein also supports those ADAS-Cog findings ((i) Pairwise t test W0–W5, p = 0.043, Hedges effect size = 0.305 and; (ii) t-test using ADAS-Cog change (not raw score) across times W5–W12, p = 0.049, Hedges effect size = 0.635).

Comparisons of Figure 3E,F indicate for ADAScog cognitive compared to measured sqrtF1 physiological changes: (i) For the Real&HIS < 2 group for ADAS-Cog the improvement continued almost linearly till 2-month follow-up (W12) whilst for the sqrtF1 feature improvement to W5 was similar but then showed a smaller decline from immediate post-treatment (W5) to 2-month follow-up (W12); (ii) For the Real&HIS ≥ 2 group for ADAS-Cog the improvements continue to immediate post-treatment (W5) then there is a smaller decline during washout whilst for the sqrtF1 feature there was a smaller decline to immediate post-treatment (W5) followed by a much larger and significant improvement from immediate post-treatment (W5) to 2-month follow-up (W12); (iii) For the Sham&HIS < 2 group for ADAS-Cog there was a very small improvement from baseline (W0) to immediate post-treatment (W5) to 2-month follow-up (W12) whilst for the sqrtF1 feature there was a decline to immediate post-treatment (W5) which remained plateaued to 2-month follow-up (W12) and; (iv) For the Sham&HIS < 2 group for ADAScog there was improvement to immediate post-treatment (W5) which rebounded back to baseline by 2-month follow-up (W12) whilst for the sqrtF1 an improvement was seen to W5 which plateaued through to 2-month follow-up (W12). Both measures support Real compared to Sham stimulation though CE alone may have some efficacy (non-decline). Both measures (and more particularly sqrtF1) provide potential support for HIS ≥ 2 and HIS < 2 patients having different time courses of response. It appears the ADAS-Cog and sqrtF1 features are not directly comparable from a physiological and cognitive point of view

(Figure 3E,F). However, (i) both ADAS-Cog and sqrtF1 measures agree that there is a significant baseline (W0) to 2-month follow-up (W12) response change for real stimulation (REAL-GP1, p = 0.029 c.f., p = 0.022, respectively, Table 2) and; (ii) both ADAS-Cog and sqrtF1 measures agree that there is a significant baseline (W0) to 2-month follow-up (W12) or immediate post-treatment (W5) to 2-month follow-up (W12) response change for real stimulation of HIS < 2 subjects (REAL-GP1, p = 0.016 c.f., p = 0.018, Table 2).

Sham stimulation produced no significant changes across time (Table 2A). However, encouragingly, there were small non-significant improvements (and importantly no decline) in SHAM-GP2 for HIS < 2 levels for ADAScog and HIS ≥ 2 for sqrtF1 measures which appear to persist at least up to W12. Less encouraging was a small decline in the SHAM-GP2 sqrtF1 measures for HIS < 2. When averaged across both HIS groups it appears there was either a marginal improvement or little to no decline when using CE only. According to sqrtF1data but not ADAScog data REAL-GP1 patients with HIS < 2, more so than HIS ≥ 2, benefit more from tACS at immediate post-treatment (W5) (p = 0.012, 1 sided).

On the left hand side (LHS) for REAL-GP1 tACS&CE stimulation an improved (p = 0.029 'All' HIS, p = 0.016 HIS < 2, SE level HIS ≥ 2) ADAS-Cog score generally manifested by W12 as an increased firing rate or a shift toward higher frequencies of the IH33 response curve (p = 0.022 'All' HIS and p = 0.05 HIS ≥ 2, see Table 2A, Figure 3A,C). Comparatively, for LHS CE alone (SHAM-GP2) changes were non-significant (Table 2A). The effect of any positive improvements for CE alone appears to either dissipate during washout or plateaux. Comparatively, tACS&CE stimulation mostly produces a shift toward higher frequencies (increase in neural activity) by 2-month follow-up (W12) for all HIS groups which can be distal from controls.

The right and left ears' data were not the same; that supports a left/right asymmetry and/or different left/right stimulation strengths (electrodes were F3 and right supraorbital supporting a stronger left side tACS stimulation). Below the right ear's results are summarized similar to left ear's signals.

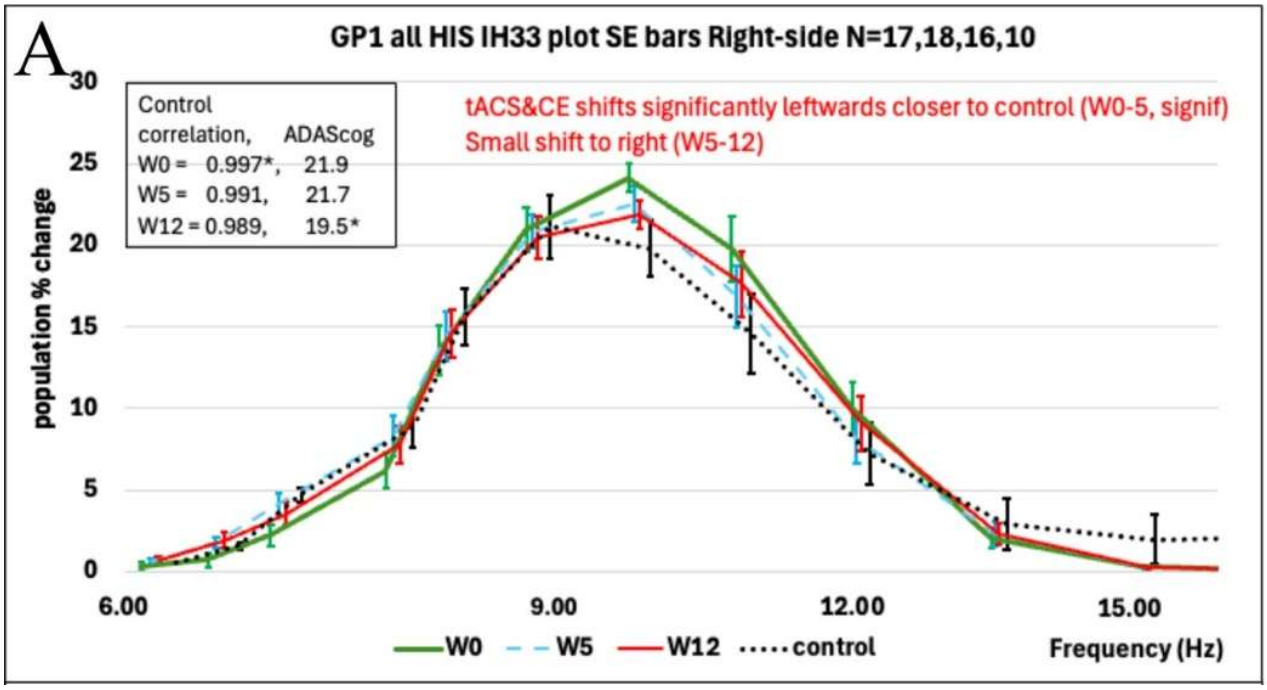
RIGHT EAR SIGNALS

Figure 4A,B shows the right side IH33 plot results for REAL-GP1 (tACS&CE) and SHAM-GP2 (CE only) respectively. What can be seen in Figure 4A,B is: (i) During W0-5 significantly for REAL-GP1 and SHAM-GP2 the plot moves toward lower frequencies and control—(for REAL-GP1 the tACS appears to have little impact compared to that observed on the LHS likely related to F3-right supraorbital electrode positioning) and; (ii) During immediate post-treatment (W5) to 2-month follow-up (W12) for REAL-GP1 and SHAM-GP2 there is a smaller and larger (significant) respectively, movement toward higher frequencies and away from control. Figure 4C compares the real/sham responses at baseline (W0) and 2-month follow-up (W12). At 2-month follow-up (W12) the baseline for REAL-GP1

and SHAM-GP2 stimulation are both marginally shifted toward higher frequencies and/or plot kurtosis is reduced. A comparison of Figure 2C and 4C show on the right-hand side (RHS) but not LHS the 2-month follow-up (W12) plots are similar. The impact of tACS on the RHS compared to LHS is markedly reduced, i.e., on the RHS tACS&CE compared to CE alone appear to have similar impacts. For completeness a statistical sub analysis based HIS score was also made on the RHS.

Figure 5 is the RHS equivalent of Figure 3F. Both show the estimated marginal means for a repeated measures ANOVA with covariates MADRS and age, fixed factors stimulus group and HIS group. Clearly apparent on the RHS is the differences between sham and real stimulation responses are smaller. This is in contrast to the LHS where for real stimulation (blue and blue hash) there are much larger changes across time especially for HIS ≥ 2 (blue hash). This is not to say there were no changes: (i) For GP*time interaction ($F(2, 20) = 3.870$, $p = 0.047$, $\eta^2 = 0.263$, power = 0.593; pairwise, W5–W12*real $p = 0.044$). and; (ii) A marginally significant GP*HIS*time interaction ($F(2, 20) = 3.284$, $p = 0.058$, $\eta^2 = 0.247$, power = 0.556; pairwise, HIS ≥ 2*W5–W12*real $p = 0.052$).

The RHS results are not the same as on the LHS. The tACS electrodes were positioned over F3 (left side) and contralateral supraorbital area (above right eye), i.e., closer to the left ear supporting a causal stimulus strength difference on RHS and LHS.



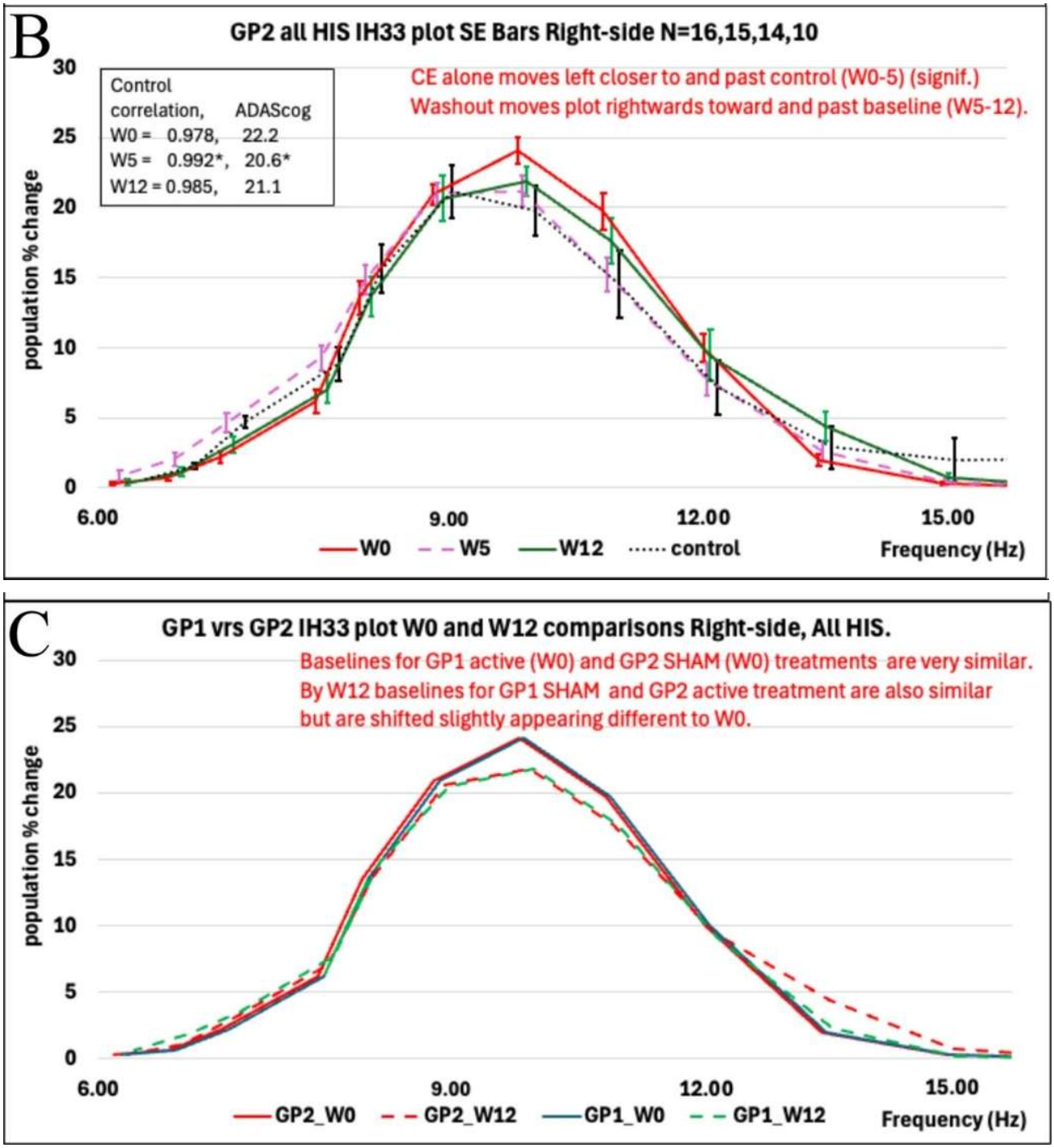


Figure 4. (**A**,**B**) The RHS IH33 plots (SE error bars) for Real-GP1 and Sham-GP2 stimulation. tACS was applied to the LHS. **(C)** Comparison of baseline W0) and 2-month follow-up (W12) response. Note: the dissimilarity between 2-month follow-up (W12) responses on RHS and LHS (Figure 2C). The RHS response is barely changed. * Asterisks indicate the largest correlation with control or change in ADAScog change.

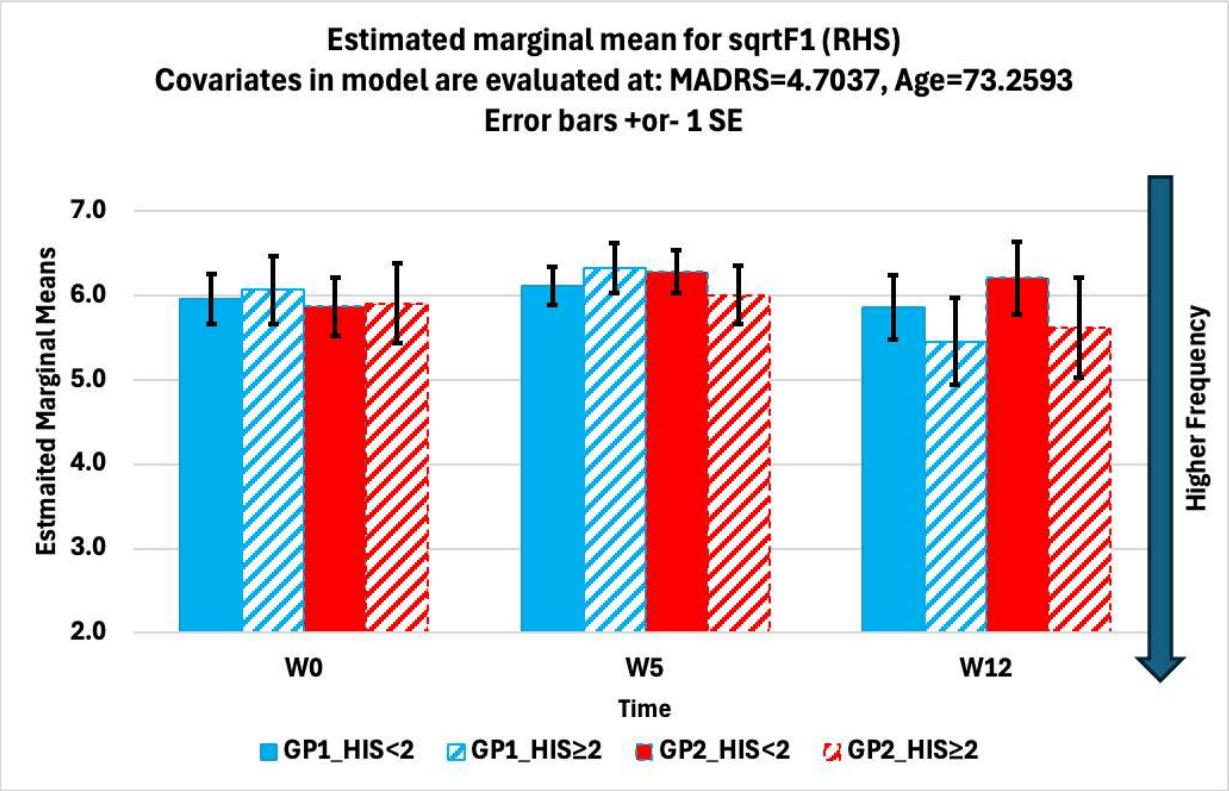


Figure 5. It shows the Estimated marginal means plot (SPSS V31) for the variable sqrtF1 plotted for times baseline (W0), immediate post-treatment (W5) and 2-month follow-up (W12) for REAL-GP1 and SHAM-GP2.

DISCUSSION

This study provides several insights into the interaction between transcranial alternating current stimulation (tACS), cognitive exercises (CE), and cerebrovascular burden in individuals with Alzheimer's disease (AD). Overall, the findings suggest that stimulation effects depend strongly on electrode configuration [30], vascular pathology [31], and the temporal dynamics of neural responses measured using EVestG.

First, electrode positioning appears to play a critical role in determining the lateralized effects of tACS. The configuration used in this study (right supraorbital–F3) preferentially modulated neural activity on the left side, while the right side showed weaker responses. This asymmetry indicates that the observed differences between left- and right-sided responses are largely attributable to current distribution rather than intrinsic hemispheric differences. Alternative electrode placements (e.g., F5–left supraorbital) may therefore produce stronger modulation of right-sided responses. Future work should explore whether combining complementary electrode configurations could provide more balanced bilateral stimulation and potentially enhance therapeutic outcomes.

Second, cerebrovascular burden, as reflected by the modified Hachinski Ischemic Score (HIS), appears to influence the response to stimulation. Participants with higher vascular involvement (HIS ≥ 2) showed greater improvement in ADAS-Cog scores at W5 following

combined tACS and cognitive exercises (Figure 3E). This trend for participants with higher vascular involvement (HIS ≥ 2) also showed a greater improvement in EVestG feature sqrtF1 at W12 following combined tACS and cognitive exercises (Figure 3F). This observation suggests that vascular pathology may modulate treatment responsiveness, possibly through altered neurovascular coupling or compensatory neural mechanisms.

Third, the temporal dynamics of neural activity differed substantially between groups. Participants with lower vascular burden (HIS < 2) showed earlier changes in neural activity, with EVestG frequency shifts (Figure 3F) occurring primarily by week 5 and diminishing thereafter. In contrast, participants with higher vascular burden (HIS ≥ 2) demonstrated delayed responses that became more improved by week 12. These findings must be interpreted cautiously as the ADAS-Cog changes across time (Figure 3E) were almost opposite. These observations however suggest that the mechanisms underlying treatment response may differ between subgroups, potentially reflecting differences in neurovascular regulation, neural plasticity, or compensatory processes associated with mixed AD pathology.

Fourth, from Figure 3E,F cognitive exercises alone were associated with some measurable improvements in ADAS-Cog and EVestG scores for HIS ≥ 2 at W5. For HIS < 2 for EVestG measures there was an initial shift toward lower firing frequencies suggests decreased resting neural activity. One possible explanation is that cognitive exercises increase regional cerebral blood flow, which may influence ion channel regulation in vestibular hair cells and downstream neural firing patterns. During the washout period (W5–W12) for ADAScog and EVestG a rebound decrease or plateau in neural activity was observed, possibly reflecting homeostatic regulatory processes. These findings highlight the dynamic interplay between vascular and neural mechanisms during cognitive training.

Fifth, combined tACS and cognitive exercises produced sustained improvements in cognitive performance that were generally associated with increased neural firing rates (reflected by shifts toward higher frequencies in the IH33 curve). This effect was most apparent on the left side, consistent with the electrode configuration used. Because tACS was not administered alone in this study, its isolated contribution cannot be directly quantified; however, comparisons between left- and right-sided responses suggest that tACS provided an additional modulatory effect beyond cognitive exercises alone.

Taken together, the results suggest that tACS and cognitive exercises may influence neural activity through partially opposing mechanisms with different temporal dynamics. Cognitive exercises may initially reduce resting neural activity (as seen in Figure 2B and 3B), possibly through vascular-mediated processes, whereas tACS appears to increase resting neural excitability. The net outcome likely reflects the interaction between these mechanisms, along with the underlying progression of AD pathology.

An interesting observation is that cognitive improvements associated with tACS were accompanied by EVestG shifts away from the control curve, indicating increased neural activity. This may represent a compensatory neural response to neurodegenerative decline. In contrast, the reductions in neural activity observed with cognitive exercises alone in some subgroups may reflect decreased compensatory activation due to improved efficiency of neural processing, although this hypothesis requires further investigation.

The IH33 frequency shift appears to be a sensitive measure of neural response to either tACS and/or cognitive exercises; however, its interpretation is influenced by cerebrovascular burden. For this reason, IH33 alone may not be sufficient as a biomarker of stimulation efficacy. Additional EVestG-derived measures, such as the average field potential, may provide complementary information. Previous EVestG studies [14] have shown that AD patients exhibit narrower average field potentials, whereas mixed AD with cerebrovascular disease is associated with broader field potentials. Combining these measures may therefore provide a more robust biomarker framework for evaluating stimulation effects.

Future studies should investigate the combined use of IH33 and field potential features to better characterize neural responses to tACS and cognitive interventions. In addition, exploring alternative electrode configurations and bilateral stimulation strategies may further clarify the role of stimulation geometry in modulating neural activity.

The main limitation of this study is the relatively small sample size, particularly in subgroup analyses based on HIS score. This limitation reduces statistical power and warrants cautious interpretation of subgroup differences. Additionally, the study design did not include a right-sided tACS condition, which would have provided a more direct comparison of stimulation effects across hemispheres.

ETHICAL STATEMENT

Ethics Approval

The study was approved by the Institutional Ethics Committee of University of Manitoba (protocol code HS25171(B2021:089) and 8 oct 2021). for studies involving humans. Also, HS13541(B2010:050) Amendment for EVestG was approved on Jan. 10, 2022. Informed consent was obtained for this study from all patients or carers. Clinical trial Registry: NCT05203523 for the main study.

Declaration of Helsinki STROBE Reporting Guideline

This study adhered to the Helsinki Declaration. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guideline was followed.

SUPPLEMENTARY MATERIALS

The following supplementary materials are available online, Table S1: Demographics.

DATA AVAILABILITY

The dataset of the study is available from the authors upon reasonable request.

AUTHOR CONTRIBUTIONS

BL wrote the initial version of the paper. ZM and BL were responsible for Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing—Review & Editing, Visualization, Proof reading. ZM was responsible for Funding Acquisition.

CONFLICTS OF INTEREST

BL has <1% shares in NeuralDX and has acted as a consultant for them. There are no other conflicts of interest.

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