

Suboptimal engagement of high-level cortical regions predicts random noise-related gains in sustained attention

Running title: tRNS and inter-individual variability

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ABSTRACT

Inter-individual variability in outcomes across individuals poses great challenges for the application of non-invasive brain stimulation in psychological research. Here, we examine how the effects of high-frequency transcranial random noise stimulation (tRNS) on sustained attention vary as a function of a well-studied electrocortical marker, spontaneous theta/beta ratio. Seventy-two subjects were administered sham, 1mA, and 2mA tRNS in a double-blind, cross-over manner, while performing a sustained attention task. 1mA was associated with improved sustained attention, whereas the effect of 2mA was similar to sham. Furthermore, individuals' baseline theta/beta ratio moderated the effects of 1mA tRNS, and provided explanatory power over and beyond baseline behavioural performance. The tRNS-related effects on sustained attention were also accompanied by reductions in theta/beta ratio. These findings impart novel insights into mechanisms underlying tRNS effects, and emphasize how designing studies that link variability in cognitive outcomes to variability in baseline neurophysiology can improve inferential power in neurocognitive research.

KEYWORDS

Inter-individual variability, Non-invasive brain stimulation, Electrophysiology, Theta/beta ratio

Non-invasive brain stimulation (NIBS) is a valuable tool for assessing how experimentally induced changes in neural processes affect behaviour. But, there have been

increasing concerns about reported variability in response patterns across individuals. While there is abundant evidence of physiological factors influencing inter-individual variability (Harty, Sella, & Cohen Kadosh, 2017; Li, Uehara, & Hanakawa, 2015), remarkably little work has been explicitly directed at identifying baseline markers that could identify individuals who are more likely to be sensitive to NIBS. Recent investigations have highlighted how offline electroencephalography (EEG) recordings acquired prior to NIBS interventions could be particularly viable in this regard (see Thut et al., 2017). The present study had the dual aims of examining the impact of a relatively novel NIBS technique known as high-frequency transcranial random noise stimulation (tRNS) on sustained attention and evaluating the potential for baseline levels of an EEG marker, spontaneous theta/beta ratio (TBR), to inform variability in response patterns across individuals.

TBR is one of the most studied physiological markers in relation to *normal* variation in cognitive functioning. And, particularly consistent associations have been documented between TBR and performance on tasks that demand top-down attention (Angelidis et al. 2016; O'Connell et al. 2007; Putman et al. 2010). A prevailing interpretation of these findings is that greater theta relative to beta power reflects poorer top-down cortical regulation of subcortical processes (e.g. Angelidis et al. 2016). TBR has also repeatedly been found to be higher in clinical groups with sustained attention deficits (Arns et al. 2013), albeit developmental changes in EEG power may undermine its reliability and predictive value in pediatric groups (e.g. Saad et al., 2015). Elevated baseline TBR has furthermore been associated with a favorable response to stimulant medications and neurofeedback protocols tailored to improve top-down regulation of attention (Arns, et al., 2013). Together, these findings highlight the potential for TBR to be informative with regard to differences in the ability to regulate top-down attention and the extent to which individuals are likely to benefit from interventions that target the associated neural systems.

tRNS delivers alternating current at frequencies and intensities that vary in a randomized manner within specified ranges. The effect of tRNS, at least when applied within the .75-2 mA range, is believed to be excitatory due to the fast-oscillating electrical fields

putatively depolarizing neurons irrespective of the current polarity (Fertonani, Pirulli, and Miniussi 2011; Terney et al. 2008; but see Parkin et al., in press). Studies have demonstrated the potential for tRNS to modulate a range of capacities from motor (Terney et al., 2008) and sensory (Van der Groen & Wenderoth, 2016), to cognitive abilities such as arithmetic learning (Snowball et al., 2013), selective attention (Shalev et al., 2018), adaptive reasoning (Brem et al., 2018) and procedural learning (Frank et al., in press).

Here, we examined the impact of sham, 1mA, and 2mA tRNS applied over key nodes of the sustained attention system, right dorsolateral prefrontal cortex and right inferior parietal lobule (Langner & Eickhoff, 2013; Posner & Petersen, 1990; Singh-Curry & Husain, 2009), using a double-blind, within-subjects, randomized design. As previous research with both tRNS (van der Groen & Wenderoth, 2016) and other NIBS approaches (e.g. Benwell et al., 2015) have suggested greater stimulation intensity does not necessarily produce greater benefits, we anticipated that the overall relationship between tRNS-induced gains and tRNS intensity would not necessarily be linear. We additionally examined the potential for TBR to predict objective sustained attention performance, subjective appraisal of attentiveness in everyday life, and, of foremost interest, the extent to which individuals would gain from tRNS. We predicted that individuals with relatively high, compared to individuals with relatively low, baseline TBR would be more likely to benefit from tRNS.

METHODS AND MATERIALS

Sample size calculation and Participants

Given that this is the first study to employ a within-subjects design to examine the effects of tRNS on high-level cognition, it was not possible to do a precise *a priori* sample size calculation. However, previous research involving the application of tRNS to frontal and

parietal regions (Cappelletti et al., 2013; Snowball et al., 2013), using between-group designs, has revealed large effect sizes (Cohen's $d > 1$). Based on the assumption that these effect sizes could be inflated (Button et al., 2013), we used G*Power (Faul, Erdfelder, Lang, & Buchner, 2009) to determine what sample size we would need to have 80% power to detect a small effect (Cohen's $d = 0.2$), for an alpha level of 0.05. This calculation suggested that a sample of 42 would be sufficient to detect even a small effect of tRNS on performance. But, given that we were additionally interested in examining individual differences in tRNS-effects based on variability in TBR, we elected to collect data on a larger sample of 72 subjects.

These 72 subjects included 33 females and 39 males, aged between 19 and 35 years (M: 25.1; 95% CI: 24–26.1). Exclusion criteria for participation included left-handedness, visual impairment, history of fainting, history of neurological or psychiatric illness, neurological insult, drug or alcohol abuse, and/or reporting current use of anti-psychotic or anti-depressant medications. All participants were asked to refrain from consuming more than 1 unit of alcohol in the 24 hours preceding each testing session. All participants provided written consent and all aspects of the study were approved by the University of Oxford Medical Sciences Interdivisional Research Ethics Committee.

Procedure Overview

An overview of the study procedure is schematically depicted in Figure 1. Participants were required to attend three testing sessions on three consecutive days. On each day participants underwent the same experimental procedure aside from the three following deviations: 1) At the beginning of their first session they completed a self-report measure of attentiveness in daily life, the cognitive failures questionnaire (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982; described in supplemental information). This was only administered once as it measures trait-like characteristics that are relatively stable over time (Bridger, Johnsen, & Brasher, 2013); 2) During the first session participants were also introduced to the continuous monitoring task (described below) and completed a practice block (consisting of 14 targets) while the experimenter observed their performance and

provided verbal feedback. For the subsequent two sessions they were offered the opportunity to complete the practice block again, but the vast majority declined; and 3) To compare the relative impact of sham, 1mA, and 2mA tRNS, each participant received a different stimulation condition at each session. The order in which they received each stimulation condition across the three sessions was assigned in a double-blind and fully randomized manner. In an effort to control for the known influence of circadian rhythms on cortical excitability, the testing sessions for each participant were scheduled at the same time each day.

Before, during, and after the delivery of tRNS on each day, subjects performed a continuous monitoring task devised by O'Connell, Kelly and Dockree (O'connell, Dockree, & Kelly, 2012). In an effort to guard against the possibility that the monotony of the experimental procedure would affect participants' motivation to perform their best on each block of the task, on each day of testing, participants were informed that they had the opportunity to win an extra £25 based on their performance. Specifically, they were informed that one of their 36 task blocks from across the three sessions would be randomly selected and compared to 9 (72/8) other participants that participated directly before/after them. The participant whose block was found to have the fastest RTs and highest accuracy would be awarded £25. The experimenter highlighted to participants that randomly selecting a block in this manner meant that they should not be discouraged about their potential to win if they felt they performed short of their best on any individual block.

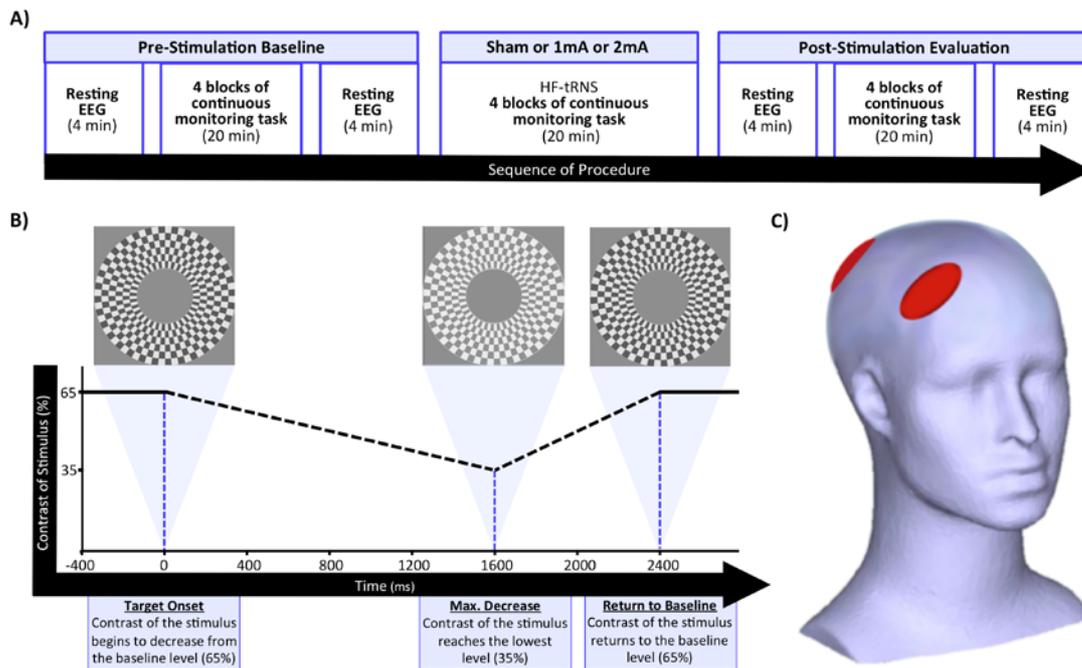


Figure 1. Schematic of experimental procedure. A) The sequence of the experimental procedure; B) The Continuous Monitoring Task. Participants were instructed to make a speeded button press as soon as they were certain that the contrast of the annulus was fading; C) Illustration of the transcranial random noise stimulation electrode montage. The electrodes were placed over right DLPFC (F4) and right IPL (P4) according to the 10–20 international EEG system.

Questionnaire measures

All participants completed questionnaires to assess attentiveness in daily life, subjective fatigue, and perceived sensations. Details about these questionnaire measures can be found in the *Supplementary Materials*.

Continuous monitoring task

The continuous monitoring task (O’Connell et al., 2012) we employed is tailored to evaluate what is widely considered the defining property of sustained attention: the ability to reliably detect rarely and unpredictably occurring signals over prolonged periods of time (Dockree et al., 2017; Sarter, Givens, & Bruno, 2001). Subjects are instructed to continuously monitor a flickering (21.25Hz) annular pattern stimulus for intermittent targets, which are defined by linear contrast changes from 65% to 35% over 1.6s (see Figure 1B). Please see the *Supplementary Materials* for further details about the stimuli used in this task.

As outlined in Figure 1, participants performed 12 blocks of this task on each day of testing. Each block comprised of 25 targets and lasted approximately 4 min. The inter-target interval was randomly 4, 7.2 or 10.4s. Participants were instructed to avoid guessing and make a right index finger mouse button press *as soon as* they were certain that the annular pattern was fading.

If participants' attention is tightly focused on the task goal, response times (RT) should be consistently both fast and accurate. However, if attention is not tightly focused on the task goal, lapses of attention can occur. In this context, lapses in attention will likely result in either prepotent responses guiding behavior and hence the occurrence of fast reflexive RT (Unsworth, Schrock, & Engle, 2004) or much slower than normal RT (Unsworth, Redick, Lakey, & Young, 2010). Sustained attention proficiency can accordingly be captured by measuring intra-individual variation in RT (O'Connell et al., 2008). Since there is typically a strong relationship between standard deviation (SD) of RT and overall mean RT (Bellgrove, Hester, & Garavan, 2004), we used individuals' coefficient of variation (CoV; $SD_{RT}/mean_{RT}$; thus controlling for differences in mean RT) as our primary metric of interest on this task.

Transcranial Random Noise Stimulation

The tRNS was delivered through circular electrodes using a StarStim device (Neuroelectronics®, Barcelona, Spain). The electrodes were encased in a pair of saline-soaked sponges (25 cm²), and were secured within a Neuroelectronics EEG cap over right DLPFC (F4) and right IPL (P4; see Figure 1C), according to the 10–20 international EEG system. Before commencing the stimulation, the impedance levels of the tRNS electrodes were measured, and if they exceeded 5 kΩ, additional saline solution was injected onto the surface of the sponges. The 1mA tRNS condition consisted of 1 mA peak-to-peak (-.5 mA to .5 mA) high frequency noise (100-500 Hz (the maximum frequency supported by the StarStim device)), with amplitude values that were normally distributed and had a mean of zero. The only factor that varied for the 2mA tRNS condition was that the high frequency noise had a peak-to-peak

of -1 mA to 1mA as opposed to -.5 mA to .5 mA. For both of these conditions the stimulation was delivered for 20 minutes, with a ramping period of 30 seconds at the onset and offset. The sham tRNS condition involved 30 seconds of 1.5 mA tRNS, with a ramping period of 30 seconds at the onset and offset. This procedure ensured that, in both the Active and Sham conditions, participants experienced the sensations associated with the onset of transcranial electrical stimulation (e.g., tingling sensation; (Gandiga, Hummel, & Cohen, 2006)).

Some readers may wonder why we chose 1.5mA as the sham condition. This decision was motivated by some pilot testing which suggested that a sham condition that mounted transiently to 1mA would be less optimal than a sham condition that mounted transiently to 2mA for producing the level of sensation akin to the 2mA condition, and vice versa. We accordingly reasoned that there would be less of a discrepancy in the sensations produced during a sham condition that mounted to 1.5mA and the sensations produced during each of the active conditions.

Electroencephalography Acquisition and Analysis

Continuous EEG data were acquired using the Enobio 20 (Neuroelectronics®). The 20 EEG channels were secured to Ag/AgCl coated electrodes (1cm²) and were positioned in accordance with the 10-20 International EEG system at the following locations: Fp1, Fpz, Fp2, F3, Fz, Fc1, Fc2, C3, Cz, C4, Cpz, Pz, P3, PO3, PO4, PO7, O1, Oz, O2, and the reference electrodes (CMS; DRL) were adhered over the right mastoid via stickrodes (*Covidien*, H124SG). The EEG data were sampled at a rate of 500 Hz with 24-bit resolution and transmitted via Bluetooth to NIC software (Neuroelectronics®) on a standard Windows 7 desktop computer. For the resting-state EEG recordings participants were requested to stare at a fixation-cross presented centrally on a uniform black background and endeavour to avoid mental activities as well as eye movements or muscular contractions for the duration of each 4-minute recording.

The EEG data were processed in MATLAB (Mathworks, Natick, MA, USA) using a

combination of custom scripts and EEGLAB routines (Delorme & Makeig, 2004). During some EEG recordings there was transient ‘packet loss’ whereby samples failed to record due to miscellaneous sources of interference. For these samples, the NIC software, by default, repeats the amplitude values for the preceding successful sample, and assigns a marker code ‘255’ to the trigger column for these imputed samples so that they can be easily identified. All EEG data files for each participant were screened for packet loss in excess of 10%. Nine files were found to have packet loss exceeding this criterion. Given that five and four of these files were from just two participants, respectively, all EEG data from these two participants were excluded from the EEG analyses. Packet loss for all other files was low (0-6%). A 40 Hz low-pass filter was then applied to all remaining participants’ files using a fourth-order Butterworth filter. Noisy channels were identified by visual inspection of signal variance and were interpolated using spherical spline interpolation. The EEG data were then re-referenced to an average reference that excluded electrodes that did not have an electrode in the homologous location on the right hemisphere of the scalp due to the placement of the tRNS electrodes (i.e. F3 and P3).

The resting-state EEG data were segmented into two-second epochs. Epochs wherein any channel exceeded $\pm 100 \mu\text{V}$ at any time during the epoch were rejected in order to exclude excessive electromyogram, electro-oculogram and other noise transients. One further participant was excluded at this stage due to excessive artifacts (>50% epoch loss). The clean epochs of the remaining 69 participants were then transformed into the frequency domain via Fast Fourier Transform (FFT). The number of EEG epochs used for each FFT ranged from 151 to 208 (M: 176.2; 95% CI: 173.9-178.8). Frequency data <1.5 Hz were excluded from further analysis to circumvent the inclusion of slow lateral eye movements.

Relative power (μV^2) for the Theta (4–7.5 Hz) and Beta (14–30 Hz) bands was calculated by dividing the absolute power within each frequency band by the absolute power within the 1.5-30 Hz range, and resulting values were natural log transformed to normalise the data. Each power estimate was derived separately for frontal (Fz) central (Cz) parietal

(Pz) and occipital (Oz) regions. The TBR over each of these regions were subsequently calculated.

In line with the majority of studies that have examined the relationship between TBR and executive functions (see Arns et al. 2011), the analyses reported below are based on TBR measured over the central electrode sites. However, we found that a similar pattern of results was also evident for TBR measured over frontal sites, but not parietal or occipital sites.

Statistical Analysis

We used the Friedman test to compare levels of subjective fatigue at the baseline period of each testing session. Friedman tests, along with follow-up Wilcoxon signed rank tests, were also used to compare the perceived sensations reported by participants at the end of each testing session.

Our behavioural analyses were centred on our main index of sustained attention proficiency, CoV on the continuous monitoring task. For information about analyses and results relating to the other performance metrics of the task, please refer to the *Supplementary Materials*. We used a one-way repeated measures ANOVA to assess the extent to which CoV on the continuous monitoring task was matched at the baseline period for each testing session. To evaluate the impact of tRNS on CoV we used a repeated-measures ANOVA, with Time (Pre-, During, Post-) and tRNS condition (sham, 1mA, 2mA) as within-subjects factors. The significant interaction was followed up with planned one-way ANOVA and paired sample t-tests. All results are accompanied by effect sizes in the form of partial eta-squared (η^2_p), and the error bars on plotted data points represent within-subject 95% confidence intervals.

‘Online’ and ‘Offline’ effects, which refer to the effects during and after tRNS, respectively, were calculated by subtracting CoV measured during-tRNS from CoV measured pre-tRNS (Online effect), and CoV measured post-tRNS from CoV measured pre-tRNS (Offline effect). We verified that there was a correspondence between the observed online and offline changes with a partial correlation between CoV during-tRNS and CoV post-tRNS,

while controlling for CoV pre-tRNS. We used Pearson's r correlations to test the respective relationships between baseline TBR, baseline CoV and attentiveness in daily life; to test our hypothesis that the effect of tRNS on the Online and Offline changes would depend on individuals' baseline levels of TBR; and consistent with previous work (Angelidis, van der Does, Schakel, & Putman, 2016) to examine the retest reliability of baseline TBR. We used Spearman's correlations for instances where the data were not normally distributed, such as to examine the correspondence between and tRNS-related changes in performance and perceived sensations (which were measured on a Likert-type scale).

We used principle components analysis (PCA) to derive a single component of baseline TBR with the view to capturing the maximum systematic variance and minimizing the measurement error associated with a single measure of TBR. To compare the relative strengths of the correlations between tRNS effects and this PCA component versus the single baseline measures of TBR, we employed Lee and Preacher's approach for comparing correlation strengths between dependent correlations (Lee & Preacher, 2013). This approach entails converting the correlation coefficients into z -scores and then computing the asymptotic covariance of the estimates (Steiger, 1980) for use in an asymptotic z -test to account for the samples being dependent rather than independent.

Finally, we fit linear mixed models using the `lme` function from the `nlme` package in *R* to compare and quantify the goodness of fit of models with, and without, baseline TBR included an independent predictor, using a likelihood-ratio test. In each of these models subject was included as a random intercept.

RESULTS

Pre-tRNS baseline measures of behaviour and neurophysiology

Subjects exhibited similar levels of CoV at each baseline testing phase ($F(2,142) =$

.027, $p = .974$, $\eta^2 < .01$). There were also no differences in self-reported levels of fatigue at each baseline testing phase ($X^2(2) = 1.15$, $p = .563$, Kendall's $W < .01$). These observations provided confidence that tRNS-related effects were being compared to a common baseline for each tRNS condition, and accordingly allowed us to exclude the possibility that there were significant carry-over effects with respect to either tRNS or practice on the task. Further, individuals who reported more frequent attentional failures in everyday life also exhibited greater CoV at each 'Pre-' tRNS testing phase (Pre-Sham $r(72) = .299$, $p = .011$; Pre-1mA $r(72) = .351$, $p = .002$; Pre-2mA $r(72) = .235$, $p < .047$), supporting the assumption that CoV on this continuous monitoring task provides a valid index of attentional lapses.

In line with the well-documented association between high TBR and poorer executive functioning, we observed a positive correspondence between baseline TBR and attentiveness in daily life scores (all $r(69) > .297$; all $p < .05$;) and between baseline TBR and CoV at each 'Pre-' tRNS testing phase (all $r(69) > .324$; all $p < .01$), irrespective of the day that each was measured. We examine this latter association further in the linear mixed effect model below.

There was also a strong correspondence between the measures of resting TBR at each 'Pre-' tRNS testing phase (Pre-Sham and Pre-1mA: $r(69) = .885$, $p < .001$; Pre-Sham and Pre-2mA: $r(69) = .896$, $p < .001$; Pre-1mA and Pre-2mA: $r(69) = .893$, $p < .001$; see Figure S1). Thus, consistent with previous research there was good retest reliability for resting TBR (Angelidis et al., 2016).

tRNS-related effects on CoV

We found effects of Time ($F(2,142) = 4.76$, $p = .010$, $\eta^2 = .06$), tRNS ($F(2,142) = 3.06$, $p = .050$, $\eta^2 = .07$), and a Time X tRNS interaction ($F(4,284) = 3.08$, $p = .017$, $\eta^2_p = .04$) for CoV (see Figure 2). Planned follow-up tests indicated that the effect of Time was evident for the 1mA tRNS condition ($F(2,142) = 11.06$, $p < .001$, $\eta^2 = .14$), but was not present for either the Sham tRNS or the 2mA tRNS condition (all $p > .4$, $\eta^2 < .02$). For the 1mA condition, the effect of Time was driven by a Pre-1mA to During-1mA reduction in

CoV (Online effect: $t(71)= 4.17, p < .001, \eta^2 = .19$) and a Pre-1mA to Post-1mA reduction in CoV (Offline effect: $t(71)= 3.20, p = .002, \eta^2 = .13$). A highly similar pattern of effects was observed for SD_{RT} (see *Supplementary Materials*).

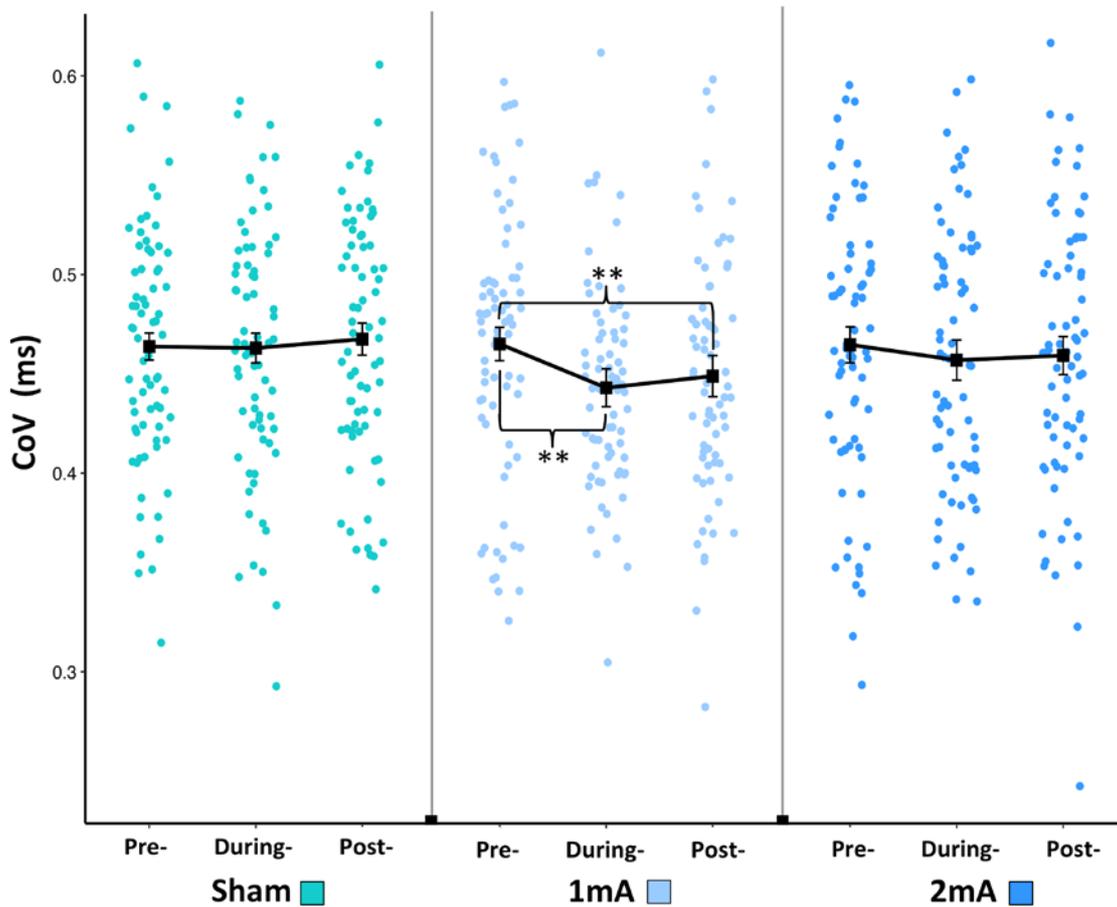


Figure 2. The effects of transcranial random noise stimulation (tRNS) on coefficient of variation (CoV). Significant Time X tRNS condition interaction for CoV, indicating that online (‘during-’ and offline (‘post-’) reductions in CoV were solely evident for the 1mA tRNS condition. Each data point corresponds to each individual’s CoV at each specified time point. Error bars represent within-subject 95% confidence intervals.

There was no difference between CoV measured During-1mA and Post-1mA ($t(71)= -1.43, p = .158, \eta^2 < .03$), and there was a close correspondence between the tRNS-related changes observed at these two time points ($r_p = .558, p < .001$, controlling for CoV measured Pre-tRNS)

When we examined the impact of 1mA tRNS on CoV with greater temporal resolution, we found that CoV was significantly lower for all blocks at both the ‘During-’ and

‘Post-’ phase relative to each of the blocks at the ‘Pre-’ phase (all $p < .05$, $\eta^2 > .05$). Further, there was no difference between any of the blocks at the ‘During-’ and ‘Post-’ phase (all $p > .36$, $\eta^2 < .02$), suggesting that the tRNS-related effects endured in a stable manner. Thus, 20 minutes of 1mA tRNS was associated with an improvement in sustained attention, and this was still evident for at least ~24 min after the tRNS had terminated. However, the observation that participants were matched on all performance indices at each baseline period of each testing session provides us with basis for inferring that effects from the tRNS had dissipated within 24 hours, which is not surprising given the relatively brief stimulation period. Please see the *Supplementary Materials* for an additional analysis to appraise the longevity of the effect.

TBR as a predictor of tRNS-related effects

Of primary relevance, we found that baseline TBR was a significant predictor of the changes in sustained attention for the 1mA tRNS condition. Again, this association was evident irrespective of the day that TBR was measured, for both the Online (all $r(69) > .422$; all $p < .001$; see Figure 3) and Offline (all $r(69) > .469$; all $p < .001$; see Figure 4) effects, supporting its viability as a marker for predicting responsiveness to tRNS.

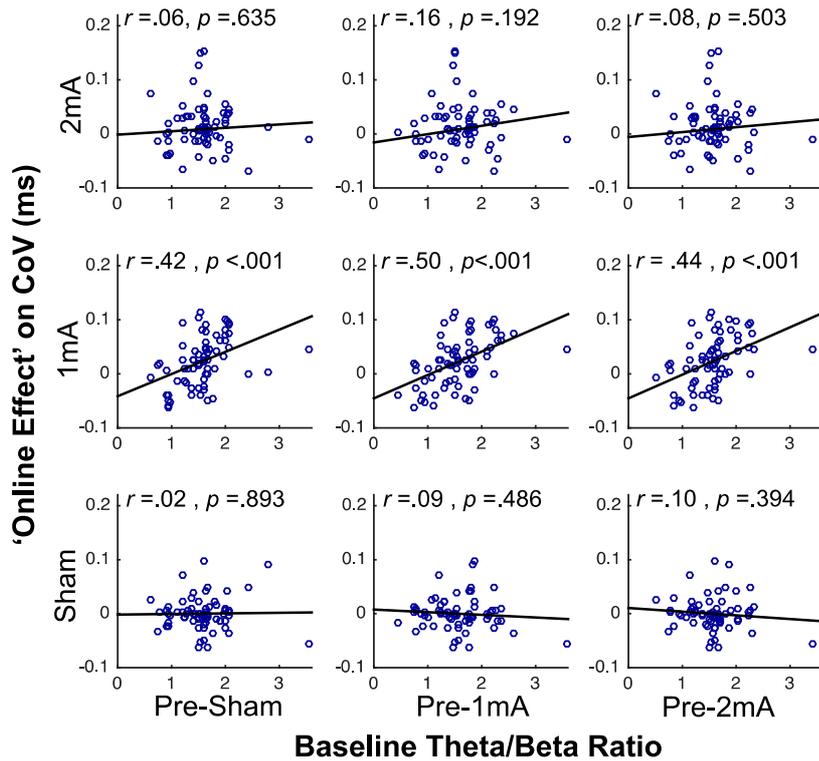


Figure 3. Relationship between baseline theta/beta ratio and 'online effects' on coefficient of variation (CoV). There was a correspondence between resting theta/beta ratio at each 'Pre-' tRNS testing phase and the observed online effect on CoV for the 1mA condition. Online effect is defined as CoV measured during-tRNS subtracted from CoV measured pre-tRNS; positive CoV values thus reflect a reduction in response time variability.

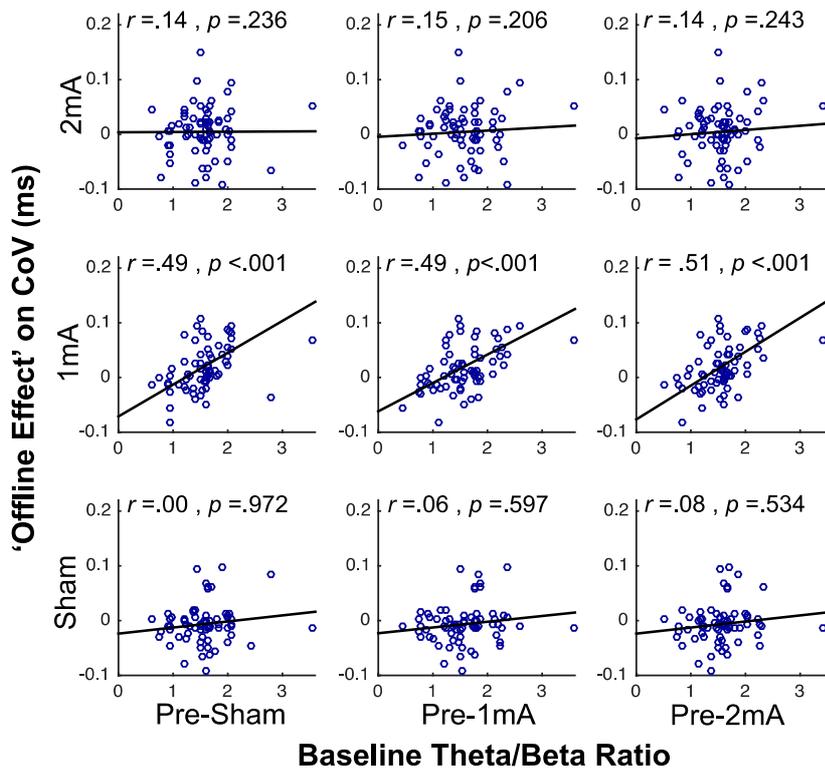


Figure 4. Relationship between baseline theta/beta ratio and ‘offline effects’ on coefficient of variation (CoV). There was a correspondence between resting theta/beta ratio at each ‘Pre-’ tRNS testing phase and the observed offline effect on CoV for the 1mA condition. Offline effect is defined as CoV measured post-tRNS subtracted from CoV measured pre-tRNS; positive CoV values thus reflect a reduction in response time variability.

A PCA component of TBR, derived from the three measures of resting TBR at each ‘Pre-’ tRNS testing phase, also predicted the observed Online ($r(69) = .480; p < .001$) and Offline effects ($r(69) = .484; p < .001$). But, asymptotic z-tests indicated that the predictive power of this PCA component was not greater than any of the single measures of TBR for predicting either Online (all $p > .6$) or Offline (all $p > .6$) effects. This observation further substantiates the potential utility and feasibility of acquiring a single measure of TBR to predict tRNS-related gains.

These results were recapitulated when we fit the linear mixed effect model. Of primary relevance for the present study, we observed three-way interactions between tRNS condition, TBR, and Time. These interactions were driven by TBR influencing how individuals responded to the 1mA tRNS condition at both the ‘During-’ and ‘Post-’ stimulation time periods, relative to the ‘Pre-’ stimulation time period, and relative to the sham tRNS and 2mA tRNS conditions (see Table 1, *Supplementary Materials*). Figure 3 illustrates the CoV values predicted by this model at relative high, mean, and relative low levels of TBR, at each time point, within each stimulation condition. The observation that baseline TBR and baseline CoV were reliably correlated on each day of testing (all $r(69) > .324$; all $p < .01$), calls to question whether the observed variability in tRNS-related effects on sustained attention could be attributable to there simply being more ‘room-to-improve’ in individuals with poorer baseline performance. However, we confirmed that the goodness of fit of the model which included baseline CoV was poorer at explaining the data than the model that included both baseline CoV and baseline TBR ($\chi^2 = 34.22, p < .001$; see Table 1, *Supplementary Materials*). Thus, the electrocortical marker, TBR, provides significant explanatory power over and beyond baseline behavioural performance.

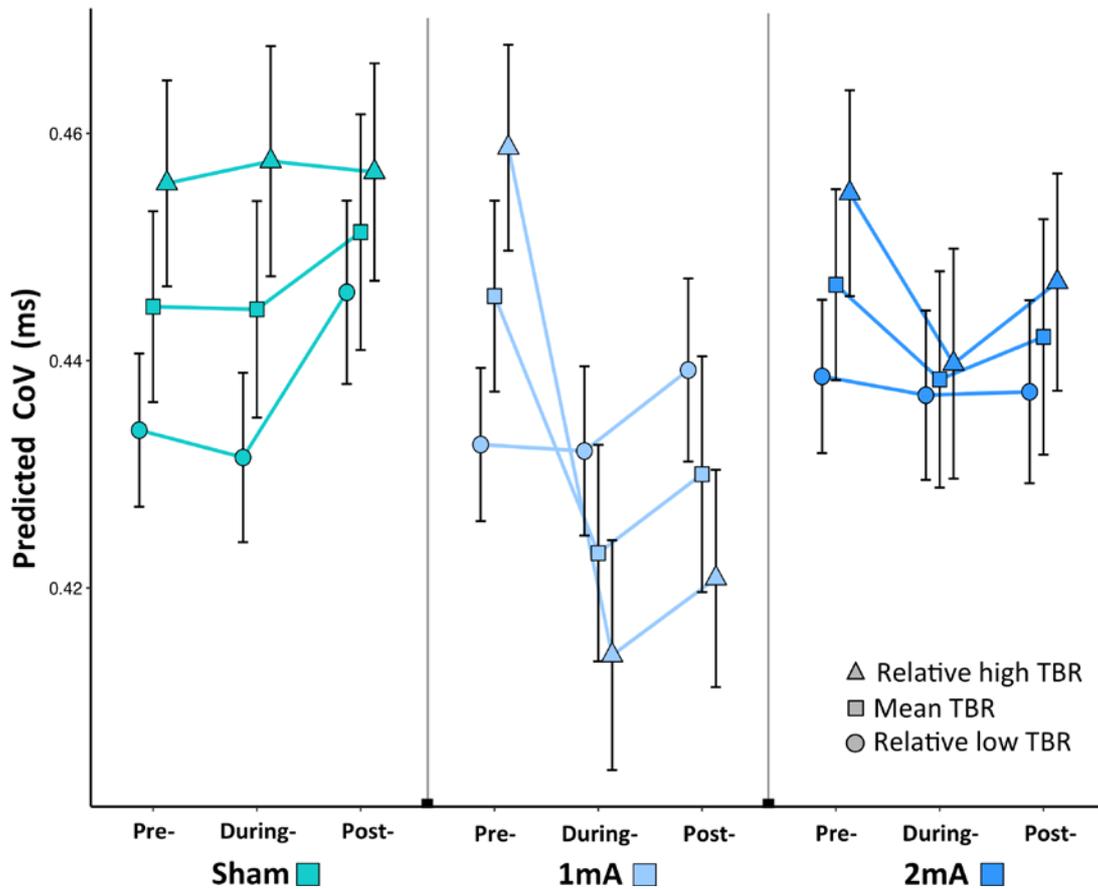


Figure 5. Predicted values for coefficient of variation (CoV) from the linear mixed effects model. CoV varies as a function of tRNS condition, time, and relative baseline TBR values. Following Aiken and West (Aiken, West, & Reno, 1991) suggestion for plotting three-way interactions that involve continuous variables, we plotted regression lines for one SD above the mean (mean + 1 SD; ‘Relative High TBR’), the mean (‘Mean TBR’), and one SD below the mean (mean – 1 SD; ‘Relative Low TBR’) of baseline TBR. Error bars correspond to 95% prediction intervals.

We additionally verified whether other individual difference factors such as age and gender which have been linked to tES outcomes in previous research (e.g. Fertoni & Miniussi, 2017) provided any explanatory power over and beyond baseline performance. Neither gender ($\chi^2 = 5.46, p = .793$; see Table 2 in the *Supplementary Materials*). or age ($\chi^2 = 5.46, p = .793$; see Table 2 in the *Supplementary Materials*) improved the fit of the model.

tRNS-related effects on theta/beta ratio

Next, we examined whether the tRNS-related gains in sustained attention were reflected at the electrophysiological level, as indexed by a reduction in TBR. We observed a Time X tRNS interaction for TBR ($F(2,136) = 5.93, p = .003, \eta^2_p = .08$). Similar to the

behavioral results, this interaction reflected a Pre- to Post- reduction in TBR that was specific to the 1mA tRNS condition ($t(69) = 2.14, p = .036, \eta^2 = .07$; see Figure 4). Greater tRNS-induced reductions in TBR were, in turn, associated with greater reductions in CoV (Online: $r(69) = .460, p < .001$; Offline: $r(69) = .422, p < .001$) for the 1mA tRNS condition, providing further support for the intimate relationship between this index of sustained attention and TBR.

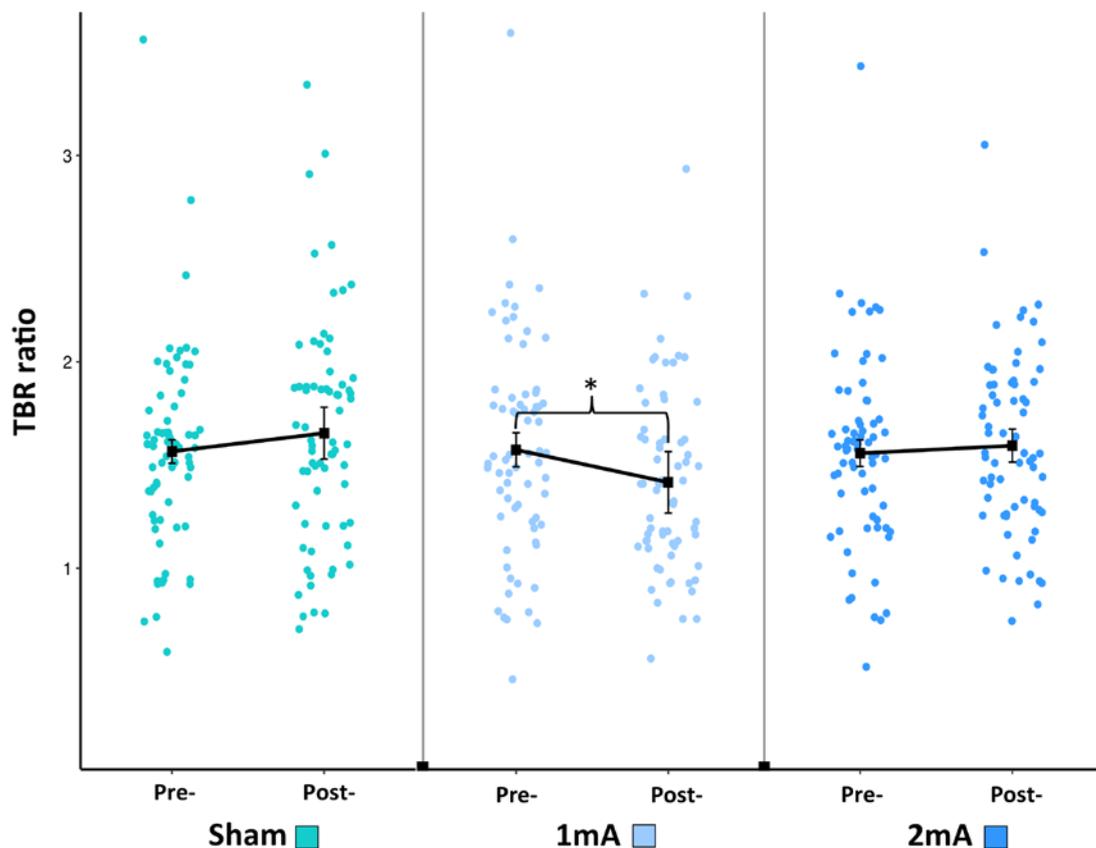


Figure 6. The effects of transcranial random noise stimulation (tRNS) on Theta/Beta Ratio (TBR). A) Significant Time X tRNS condition interaction for TBR, indicating that pre-to post- reductions in TBR were solely evident for the 1mA tRNS condition. Each data point corresponds to each individual's TBR at each specified time point. Error bars represent within-subject 95% confidence intervals.

Perceived Sensations

The results of the perceived sensations questionnaire indicated that the perceived sensations differed across the three tRNS conditions ($\chi^2(2) = 44.56, p < .001$, Kendall's $W =$

.309). Follow-up analyses indicated that participants reported significantly more sensations for the 2mA tRNS condition compared to both the 1mA tRNS condition (mean rank = 14.43 vs. 24.03, respectively, $Z = -4.69$, $p < .001$) and the sham tRNS condition (mean rank = 14.42 vs. 24.86, respectively, $Z = -5.04$, $p < .001$). There was no difference between the 1mA tRNS condition and the sham condition (mean rank = 17.78 vs. 23.73, respectively, $Z = -1.64$, $p = .102$). More importantly, however, there was no difference across conditions for the question ‘How much did these sensations affect your performance?’ ($X^2(2) = .86$, $p < .651$, Kendall’s $W = .006$). There was also no correspondence between the reported sensations and the tRNS-related changes in CoV for each of the conditions (Sham: $r_s = .207$, $p = .081$; 1mA: $r_s = .035$, $p = .773$; 2mA: $r_s = .004$, $p = .972$). Thus, although the 2mA tRNS condition was associated with greater perceived sensations, we can infer that it is unlikely that these sensations had a significant impact on the observed tRNS-related effects.

DISCUSSION

We had two primary aims in the present study. The first aim was to examine the differential impact of sham, 1mA, and 2mA tRNS on sustained attention. The second aim was to appraise the potential for a well-studied electrocortical marker, spontaneous TBR, to provide an index of the extent to which individuals are likely to exhibit gains in sustained attention. Our main findings were threefold. First, 1mA tRNS was associated with improvements in sustained attention, as indexed by reductions in response time variability on a continuous monitoring paradigm and pre- to post- reductions in TBR. Second, our results substantiate existing evidence that resting TBR constitutes a functionally relevant electrocortical marker of top-down attention. Third, the effects of 1mA, but not 2mA or sham, tRNS were moderated by individuals’ baseline TBR.

Previous findings from both clinical and healthy populations have suggested that TBR can predict scores on various measures of high-level cognitive functioning (e.g. O’Connell et al., 2007; Putman et al., 2010). Here, we corroborate this research by showing

correspondence between high TBR and poorer sustained attention, as indexed by higher response time variability on the continuous monitoring paradigm, as well as greater self-reported propensity for attentional failures in everyday life. These relationships were reliably evident across the measures of baseline TBR acquired on three different days. These findings, in turn, support the assumption that relatively high TBR reflects relatively weak top-down cortical regulation processes that are required during tasks that demand top-down attention.

The observation that TBR explained a significant proportion of variability in the tRNS-related gains in sustained attention is also consistent with previous research demonstrating the potential for resting TBR to predict gains from pharmacological and neurofeedback interventions tailored to modulate top-down attentional capacities (Arns et al., 2013). Cumulatively, these findings indicate that resting TBR may be capable of distinguishing subsets of individuals who are not engaging the cortical network required for sustained attention in an optimal manner.

NIBS research has previously highlighted neural, anatomical, and genetic markers that distinguish responders from non-responders (Krause & Cohen Kadosh, 2014; Li et al., 2015). But, acquiring these physiological assays is often prohibitively expensive. A few studies have also identified behavioral markers that have potential predictive power (e.g. London & Slagter, 2015). However, in order to derive meaningful metrics from behavioral performance it is typically necessary to administer tasks for prolonged durations. In contrast, the predictive value of TBR can be readily derived from four-minute recordings of resting EEG activity acquired from just one central or frontal electrode. Moreover, TBR demonstrated predictive power over and beyond that observed for the baseline behavioral measure. Our data additionally substantiate previous research that has highlighted its excellent intra-individual retest reliability (Angelidis et al., 2016).

The observed sensitivity of individuals with high TBR to 1mA, but not 2mA, of tRNS supports models that emphasise the state-dependency of NIBS (e.g. Miniussi et al., 2013), and is consistent with a number of other NIBS studies that have reported non-linear relationships between stimulation intensity and behavioural performance (e.g. Benwell et al., 2015). One

possible non-linear mechanism that has been invoked to explain such effects is stochastic resonance. Stochastic resonance, or more aptly termed stochastic facilitation (SF; McDonnell & Ward 2011), describes the phenomenon whereby adding an *appropriate* level of noise can enhance the output of subthreshold signals in non-linear systems. An inherent tenet of this perspective is that the signal enhancing potential of NIBS will depend on both the task-induced state of the targeted region and the level of noise introduced (Fertonani & Miniussi, 2017; Miniussi et al., 2013). Accordingly, individuals with high TBR may have had task-relevant neurons that were not reaching thresholds for signal transmission and could accordingly be potentiated through SF from the random noise introduced for the 1mA condition. On the other hand, for individuals with lower TBR, the 1mA of tRNS conceivably amounted to quantities of noise that interfered with information processing which was already quite optimal.

Following this line of reasoning, the null effect for the 2mA condition is plausibly attributable to this level of tRNS, on average, giving rise to excessive and maladaptive levels of noise, irrespective of whether task-relevant neurons were subthreshold or suprathreshold, and is consistent with the suggestion that the neuronal response begins to *saturate* as the *dose* increases beyond the optimal point (Miniussi et al. 2013). However, it should be acknowledged that other possible phenomena could underlie the non-linear effects. For instance, increases in the intensity of the injected current could change the spatial specificity of the current for the 2mA condition (Batsikadze et al., 2013). It is conceivable how this could lead to the enervation of brain regions that may not be optimal for task performance. While this experiment serves primarily as a proof-of-concept, our approach could have important implications for both basic and translational research. From a basic research perspective, these findings emphasize the importance of being mindful of how the data we acquire and analyze as psychologists are from diverse, multifaceted and dynamic entities that will exhibit both intra- and inter-individual differences in response to experimental manipulations. Designing experiments in a manner that can identify *for whom*,

experimental manipulations are effective could greatly improve the inferential power and transparency of research.

From a translational perspective, these findings align with the premise of the precision medicine initiative, namely, that individual variability in physiology leads to inevitable heterogeneity in treatment response. This initiative has gained widespread traction due to awareness about the massive resource and ethical challenges that accompany response heterogeneity. Our data indicate that acquiring theoretically relevant electrophysiological markers as part of screening protocols may be a feasible means for determining a priori whether individuals are likely to benefit from interventions. In the present experiment, we only examined the extent to which TBR was informative with regard to tRNS-related gains in sustained attention. However, given that elevated TBR putatively reflects suboptimal engagement of cortical regions required for top-down attention, and has been linked to poor performance on several other high-level cognitive functions, there is basis for exploring whether TBR could be informative for predicting tRNS-related gains for other cognitive functions. Furthermore, prior research examining the relationship between TBR and responsiveness to neurofeedback protocols and stimulant medications (Arns et al., 2013) suggests that the predictive value of TBR may extend to a range of different interventions that are tailored to increase functioning in high-level cortical regions.

In the present study we observed that the tRNS-related gains in sustained attention for the 1mA condition were maintained for up to 24 minutes beyond the termination of the stimulation. But, these gains had dissipated within 24 hours. The transience of the effects is not surprising based on previous research suggesting that prolonged gains from NIBS likely necessitates multiple sessions concurrent to challenging and adaptive cognitive training (Cappelletti et al., 2013; Elmasry et al., 2015). Future work in this area will also need to appraise the real-world feasibility of prolonged or repeated sessions of tRNS, with appropriate consideration of potential habituation or tolerance effects. In this context, the random nature of the input with tRNS could hold an alluring advantage over pharmacological

agents (e.g. Dockree et al. 2017) or even alternative NIBS interventions that rely on direct current.

Finally, our findings corroborate an already large body of evidence and theory emphasizing the importance of right frontal and parietal regions for sustained attention. But, it should be acknowledged that sustained attention deficits are frequently accompanied by changes in neural functioning across a wide range of other brain areas (see Fortenbaugh et al., 2017). While the focus of the present investigation was to assess the effect of right fronto-parietal tRNS as a function of dose and individual differences in TBR, it will be of value for future work to determine the regional specificity of the current flow with the present electrode montage, and establish whether similar improvements are also observed when the tRNS electrodes are placed over other cortical regions that are commonly implicated in sustained attention. Examining the extent to which these findings generalize to the heterogeneous clinical populations that are known to exhibit sustained attention deficits should also be a priority for future investigations.

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