Explaining and Predicting the Effects of Neurostimulation via Neuronal Excitation/Inhibition

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Abstract

Previous research has highlighted the role of the excitation/inhibition ratio (E/I) for typical and atypical development, mental health, cognition, and learning. Parallel research has highlighted the benefits of high-frequency random noise stimulation (tRNS)—an excitatory form of neurostimulation—on learning. We examined the E/I as a potential mechanism and whether tRNS effect on learning depends on E/I as measured by the aperiodic exponent. In addition to manipulating E/I using tRNS, we also manipulated the level of learning (learning/overlearning) that has been shown to influence E/I. One hundred and two participants received either sham stimulation or 20 min DLPFC tRNS during a mathematical learning task. We showed a lower aperiodic exponent, which reflects higher E/I, after tRNS, and that higher baseline aperiodic exponent, which reflects lower E/I, predicted greater benefit from tRNS specifically for the learning task. In contrast to previous MRS-based E/I studies, we found no effect of the learning manipulation on E/I. Our results highlight the role of E/I as a marker for neurostimulation efficacy and learning. This mechanistic understanding could provide stronger potential to augment learning. At the same time, we offer new insights on the quantification of E/I using EEG vs MRS to foster better theoretical understanding and its utilisation in future research.

Keywords: mathematics; skill acquisition, learning; overlearning; aperiodic activity; brain stimulation

Introduction

Previous human and animal studies have indicated the importance of levels of excitation and inhibition (E/I) for learning, i.e., skill acquisition (Dorrn et al., 2010; Nishiyama et al., 2010; Shibata et al., 2017). Previous magnetic resonance spectroscopy (MRS) studies highlighted the neurotransmitters glutamate and gamma-aminobutyric acid (GABA) as the underlying building blocks of E/I, and suggested their role in memory and learning, including predicting educational levels later in life (Barron et al., 2016; Shibata et al., 2017; Wijtenburg et al., 2017; Zacharopoulos et al., 2021a; Zacharopoulos et al., 2021b).

Recent findings show that an excitatory form of noninvasive neurostimulation—high-frequency transcranial random noise stimulation (tRNS, Terney et al., 2008)—influences E/I in mice by reducing GABAergic activity (Sanchez-Leon et al., 2020). During tRNS, a small current with randomized frequency and current intensity is applied over targeted brain areas. It is assumed that tRNS amplifies subthreshold neuronal activity that does not reach the necessary threshold to yield an action potential (i.e., stochastic resonance; Fertonani & Miniussi, 2017). Thus, this amplification of the signal has been linked to increases in signal-to-noise ratio, which is assumed to relate to successful enhancements in learning, perception, and cognitive performance (Antal & Herrmann, 2016; Cappelletti et al., 2013; Fertonani et al., 2011; Herpich et al., 2019; Snowball et al., 2013; Van der Groen & Wenderoth, 2016). Despite the growing interest in applying tRNS in cognitive studies, there is little understanding of the neurophysiological changes induced (Potok et al., 2022). Mostly, tRNS studies that use an electroencephalogram (EEG) focus on periodic brain activity, such as theta/beta ratio, for the predicted efficacy of electrical stimulation on skill acquisition (Harty & Cohen Kadosh, 2019; Rufener et al., 2017). Considerable research has been done to investigate oscillatory rhythms as potential electrophysiological predictors for cognitive or behavioral processing in healthy and clinical populations (Harty & Cohen Kadosh, 2019,

Uhlhaas & Singer, 2010; Voytek & Knight, 2015). However, explaining tRNS, as well as other neurostimulation, efficacy by investigating the E/I has been overlooked, despite the emerging theoretical motivation (Krause et al., 2013).

Recently, the interest in electrophysiology has been expanded from this oscillatory (i.e., periodic or spectral power) perspective to include an aperiodic perspective, e.g., aperiodic activity (Donoghue et al., 2020). Aperiodic activity is shown in the EEG spectrum as a 1/*f*-like structure and is dominant in the spectrum even when there is no periodic or oscillatory activity. The power of aperiodic activity decreases exponentially with increasing frequency (see **Figure 1A**), and relates to the negative slope in log-log space (see **Figure 1B**). In contrast to the previous assumption that aperiodic activity reflects a background noise in the EEG spectrum, accumulating evidence shows the importance of aperiodic activity in understanding brain functions and behavior. Also, periodic activity has been shown to be confounded due to misestimating spectral power since participants vary in center frequencies if a predefined spectral range is applied (Lansbergen et al., 2011). Therefore, Donoghue et al. (2020) recommend to parameterize neural power spectra by also analyzing the aperiodic activity in the spectrum. Aperiodic activity consists of an aperiodic exponent that can be defined as x in a $1/f^x$ function, which reflects the previously mentioned negative slope in log-log space and, thus, the pattern of power across frequencies. The exponent of aperiodic activity is thought to underlie the integration of underlying synaptic currents (Buzsáki et al., 2013), and a likely mechanism of changes in the aperiodic exponent has been linked to the E/I of field potentials shown by EEG recordings (Gao et al., 2017). A higher E/I relates to a lower aperiodic exponent and vice versa. The power of inhibitory GABA currents leads to a rapid decay in the power spectrum at higher frequencies, and, thus a steeper (negatively sloped) exponent (see **Figure 1C)**. The opposite happens for excitatory currents, where power is stable for lower frequencies and declines more slowly for higher frequencies, which is shown

in a flatter (closer to zero) exponent (see **Figure 1C**). Shortly, the higher the E/I, the lower the exponent value (see **Figure 1D**).

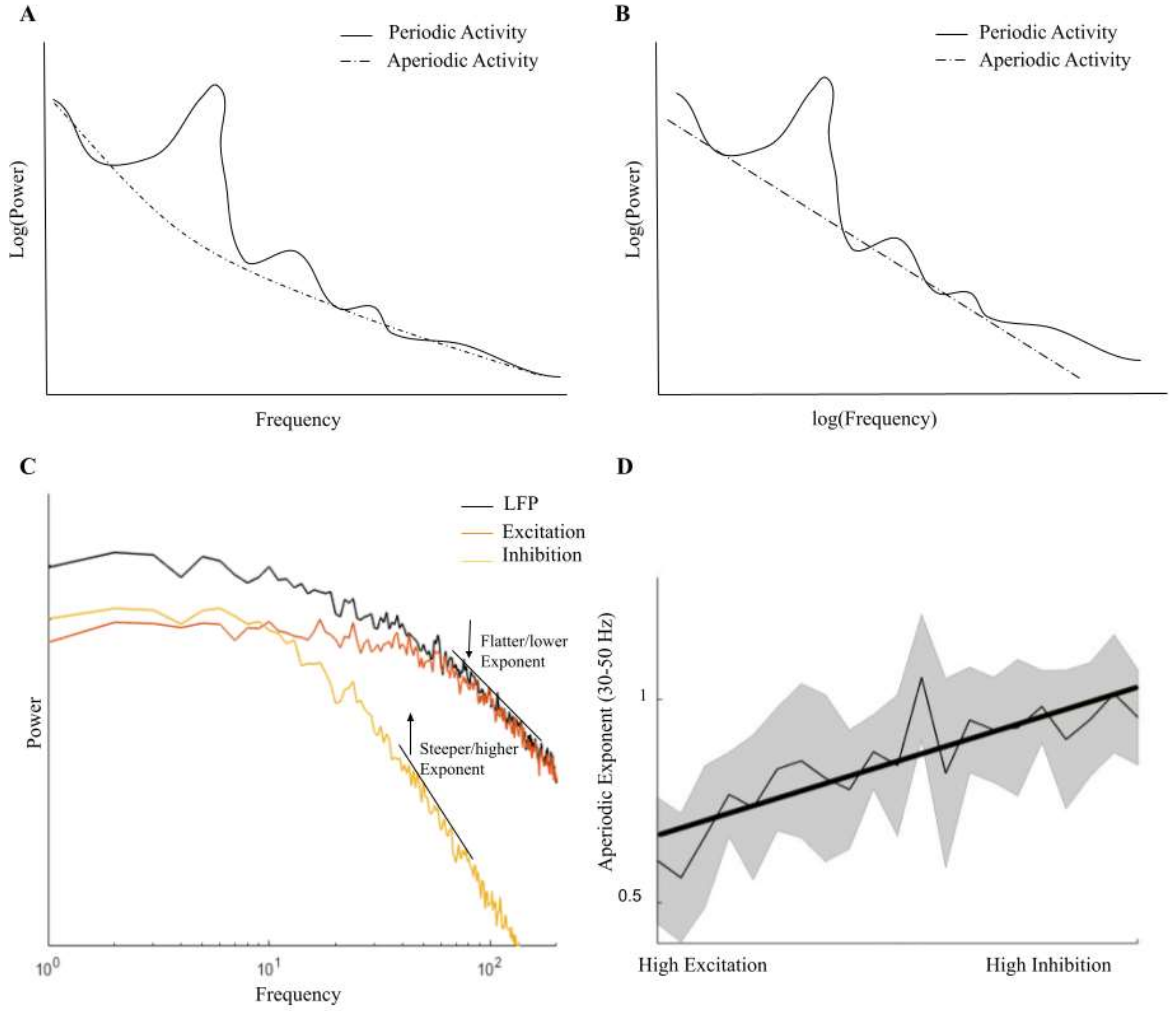

Figure 1| E/I and the aperiodic exponent. A) A simplistic overview of the difference between periodic and aperiodic activity in the EEG power-frequency spectrum. **B)** The aperiodic exponent in log-log space as shown in the EEG spectrum. **C)** and **D)** are adapted with permission from Gao et al. (2017) which show that high E/I is related to a flatter (closer to zero) aperiodic exponent and low E/I (i.e., high inhibition) to a negatively steep exponent, compared to the local field potential (LFP) (license number: 5293660690695).

Donoghue and colleagues (2020) showed that decreased aperiodic activity (i.e., lower exponent) in the EEG spectrum relates to flattening the power spectrum as seen in ageing, and has also been related to behavioral performance. Other developmental and clinical studies also

indicated the importance of inter-individual differences in aperiodic activity in health and disease (He et al., 2019; Molina et al., 2020; Robertson et al., 2019; Voytek et al., 2015).

Recent MRS findings have linked better mathematical skills to higher E/I in young adults and the reverse in younger participants (Zacharopoulos et al., 2021b). Moreover, MRS-based E/I can predict future mathematical reasoning (Zacharopoulos et al., 2021c). Since previous studies report a link between E/I and mathematical achievement, we applied tRNS while participants solved arithmetic multiplications during a mathematical learning paradigm. Furthermore, we manipulated the degree of skill acquisition to induce learning or overlearning. Based on previous studies, we defined learning as practising a skill during performance improvement (i.e., before learning plateaus) and overlearning as the point after performance improvement when a plateau has been reached (Shibata et al., 2017). Learning and overlearning have been linked to an increase and a decrease in E/I, respectively, in an MRS study (Shibata et al., 2017).

We aimed to impact E/I directly using tRNS, as well as indirectly by manipulating the level of skill acquisition (learning/overlearning) to examine whether: 1) tRNS will increase E/I as measured by aperiodic exponent; 2) The direction of change in aperiodic exponent between pre- and posttest depends on the learning condition: it decreases in the learning condition and increases in the overlearning condition; 3) tRNS efficacy on a learning/overlearning task depends on the individual baseline aperiodic exponent. That is, the tRNS-induced reduction of the aperiodic exponent differs across participants, depending on their baseline aperiodic exponent (i.e., E/I levels) (Krause et al., 2013).

Results

Phase of Skill Acquisition Efficacy

Both groups were matched in baseline performance and aperiodic exponent (see Methods 'Baseline Matching'). To determine the efficacy of our learning and overlearning task manipulation, the average learning slope (based on response times (RTs); Newell & Rosenbloom, 1981) was computed for all participants separately in the learning and overlearning mathematical task who received sham stimulation (see **Figure 2** and **Figure S1** for individual data). This allowed us to prevent confounding the effect of learning/overlearning with the effect of active tRNS. For participants in the learning task, the slope showed a negative linear gradient, whereas participants in the overlearning task showed a clear plateau of performance improvement due to the repetition of presented stimuli. This indicated the efficacy of our task design in manipulating learning and overlearning.

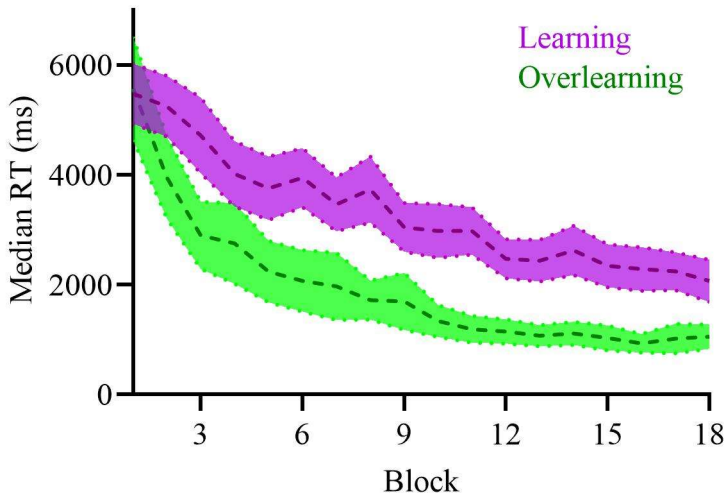

Figure 2| Averaged learning curves of the median RTs of the learning or overlearning task of the sham stimulation. The mean learning curve of the participants (n=22) during learning shows a linear gradient as shown in purple. The mean learning curve of the participants (n=21) during overlearning (in green) shows a clear plateau of performance improvement after approximately block 10, and faster RTs overall. Shading indicates 95% confidence intervals.

The Impact of tRNS and Learning on the Aperiodic Exponent

First, we investigated the effects of tRNS and type of mathematical task (learning/overlearning) on the aperiodic exponent (i.e., E/I). The aperiodic exponent change was calculated by subtracting the pre from the post aperiodic exponent, with positive values that indicate an increase in the exponent from pre to post learning/overlearning. We ran an ANCOVA with the factors task (learning/overlearning) and stimulation (tRNS/sham), while controlling for the individual plateau (as it may impact E/I; Shibata et al., 2017). The main effect of stimulation was significant ($F(1,67)=6.63$, $p=.012$, $MSE=1.20$, $\eta^2_{partial}=.09$). No significant main effects were found for task ($F(1,67)=0.25$, $p=.611$, $MSE=0.04$, $\eta^2_{partial}=.005$), individual plateau ($F(1,67)=0.37$, $p=.540$, $MSE=0.06$, $\eta^2_{partial}=.01$), and the interaction between stimulation and task ($F(1,67)=3.59$, $p=.062$, $MSE=0.65$, $\eta^2_{partial}=.05$). We repeated the same analysis while excluding the individual plateau from the analysis. The effect of stimulation remained significant ($F(1,68)=6.66$, $p=.012$, $MSE=1.20$, $\eta^2_{partial}=.08$). The effect of task and the interaction between stimulation and task remained not significant (task: $F(1,68)=0.26$, $p=.611$, $MSE=0.04$, $\eta^2_{partial}=.003$; stimulation X task: $F(1,68)=3.28$, $p=.074$, $MSE=0.59$, $\eta^2_{partial}=.04$).

To further explain the significant effect of stimulation, we plotted the aperiodic exponent change for each stimulation group separately (see **Figure 3** and **Figure S2** for individual data). The aperiodic exponent change of participants who received tRNS (i.e., more excitation induced) was lower (i.e., flatter) (M=-0.17, SEM=0.07) after stimulation compared to those who received sham stimulation (M=0.08, SEM=0.06). This corroborates with the excitatory effects of tRNS, leading to a lower aperiodic exponent, which reflects a higher E/I. However, it should be noted that in contrast to our expectations, type of task (learning/overlearning) did not influence the aperiodic exponent change from pre to post.

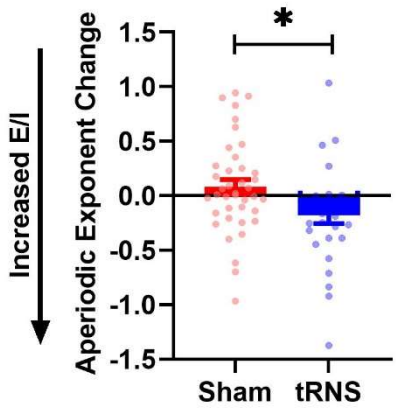

Figure 3| ANCOVA showing differences in aperiodic exponent for the stimulation groups (tRNS/sham) on the change in aperiodic exponent. Participants who received tRNS show an increase in E/I as indicated by the mean (±S.E.M.) decreased aperiodic exponent (change: post-pre exponent in $\mu V^2 Hz^{-1}$). Participants who received sham stimulation showed a mean (±S.E.M.) decrease in E/I as indicated by an increased exponent from pre to post. *p<.05.

Because a frequentist approach does not allow to accept the null result (i.e., no effect of task on aperiodic exponent), we reran the same ANCOVA using a Bayesian approach on the aperiodic exponent change. Our results, as presented in the Supplementary Information, strengthens the conclusion that tRNS impacts the aperiodic exponent, while task has no effect. These findings match the idea that tRNS leads to higher excitation and therefore a lower (i.e., flatter) aperiodic exponent and that such effect is independent of learning/overlearning.

The Aperiodic Exponent Moderates Response Times on a Learning and Overlearning Task

As shown in the previous paragraph, the aperiodic exponent was not influenced by the type of task. To investigate if tRNS efficacy on a learning/overlearning task depends on the individual baseline aperiodic exponent, we ran a Bayesian mixed effects model with the *brms* package to predict median RTs for each block during the learning and overlearning task. Note that we also evaluated the models for accuracy instead of RTs as dependent variable, but due to the emphasis on RTs in cognitive skill acquisition (Newell & Rosenbloom, 1981; Snowball

et al., 2013; Tzelgov et al., 2000) and participant instructions to avoid errors inducing a high accuracy (see Methods 'Baseline Ability Task'), we reported the accuracy results in the Supplementary Information.

Fixed effects entailed the aperiodic exponent at baseline, block (1-18), task (learning/overlearning) and stimulation (tRNS/sham). The model included a random intercept for block for all participants. Our effect of interest was the tRNS X block X baseline aperiodic exponent X task interaction, and therefore we compared the model with this interaction to models with lower order interactions. Model comparisons were made by means of leave-one-out cross-validation (LOO), including a basic learning model that contained median RTs as dependent variable and block and task as a fixed effect (see Supplementary Information for all model comparisons, caterpillar plots, and the posterior predictive check for this model, Rhat=1).

We checked the posterior distributions that captures the uncertainty surrounding the magnitude of an effect. Typically, a posterior distribution higher or equal to 75% (below or above zero) is chosen as a threshold to indicate that an effect is present. The choice for a certain cutoff criterion depends on the potential risks and benefits of the intervention (i.e., Ahn et al., 2018), and in this context it means that there is a 75% chance that the alternative hypothesis (i.e., the presence of an effect) is true. **Figure 4A** shows that there is a 90% probability that tRNS lowers median RTs on average during both tasks and thus improves performance (see **Figure S3** for all main effects). The most important effect is the three-way interaction between tRNS, task, and aperiodic exponent at baseline, which was the model with th best fit (see **Figure 4** and **Figure S3**). Notably, the posterior probability of the presence of a three-way interaction between tRNS X task X baseline aperiodic exponent is 82% (see **Figure 4B**).

To understand the source of this 3-way interaction we dissected it by running the model for learning and overlearning separately (see **Figure 4C**). For the learning task the posterior distribution for the interaction between stimulation and the baseline aperiodic exponent was 96%. We therefore further dissected the model for sham and tRNS separately for the main effect of the baseline aperiodic exponent in the learning task. We found that those with higher baseline aperiodic exponent performed worse than those with a lower exponent in the sham condition (posterior distribution=77%). However, this effect was reversed when tRNS was applied, showing better performance for those with a higher baseline aperiodic exponent (posterior distribution=88%).

Oppositely for the overlearning task, the posterior distribution was 56% indicating no support for an interaction between stimulation and baseline aperiodic exponent in this task. However, in the overlearning task the posterior distribution for the main effect of baseline aperiodic exponent (across stimulation conditions) was 87%, indicating a difference between performance for individuals with higher baseline aperiodic exponent. We did not find support for the main effect of stimulation (posterior distribution=65%).

Table 1| Fixed effects of the Bayesian mixed effects model for learning and overlearning related to the aperiodic exponent (n=75)

Predictors	Estimates	SE	95% CrI	Posterior Probability (%)
(Intercept)	7.87	0.15	[7.58 - 8.18]	100
Block	-0.38	.03	[-0.44 - -0.32]	100
Aperiodic Exponent	0.15	0.13	[-0.12 - 0.41]	87
Task	-0.84	0.23	[-1.30 - -0.41	100
tRNS	-0.33	0.24	[-0.82 - 0.13]	90
Aperiodic Exponent X Task	-0.43	0.27	[-0.94 - 0.10]	94
Aperiodic Exponent X tRNS	-0.38	0.21	[-0.79 - 0.02]	96
Task X tRNS	0.44	0.35	[-0.22 - 1.15]	89
Aperiodic Exponent X Task X tRNS	0.36	0.35	[-0.35 - 1.04]	82

Note. The categeorical variables task (learning=0 & overlearning=1) and stimulation (sham=0 & tRNS=1) were dummy coded.

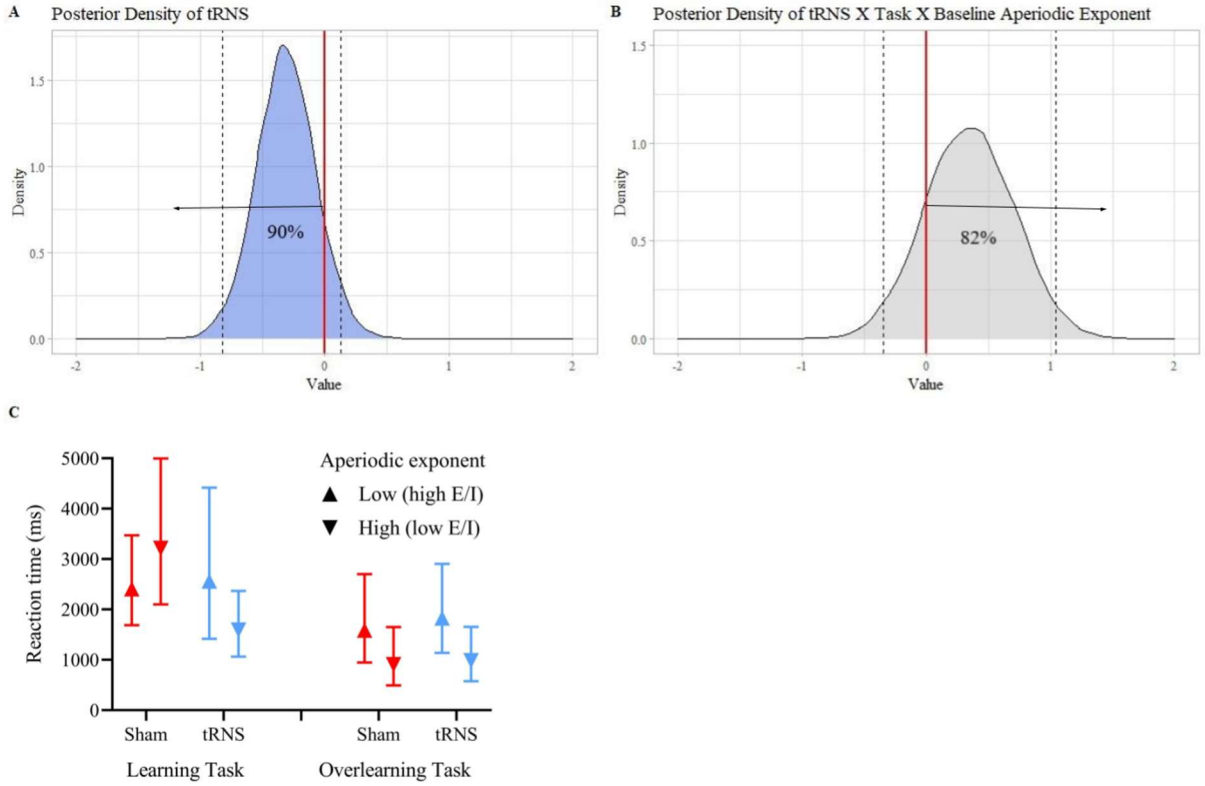

Figure 4| Posterior density of tRNS and the three-way interaction between tRNS, task, and baseline aperiodic exponent from the best fitted model. A) The posterior density of stimulation (tRNS) shows that 90% of the posterior distribution is below zero. Indicating that there is a 90% probability that tRNS lowers median RTs (ms) during the learning and overlearning task. **B)** Posterior distribution of the three-way interaction between tRNS, task, and baseline aperiodic exponent that shows that there is a 82% probability that this interaction increases median RTs (ms) during the learning and overlearning task. **C)** The left panel indicates the marginal effects of the learning task for low baseline aperiodic exponent values (mean -1 standard deviation (SD)) and high baseline aperiodic exponent values (mean +1 SD). Sham stimulation is indicated in red and tRNS in blue. The right panel indicates the marginal effects of the overlearning task. This plot shows that participants who had a high baseline aperiodic exponent and received tRNS during the learning task, performed better than participants with a lower baseline aperiodic exponent. No beneficial effects of tRNS were found for participants in the overlearning task. 95% CrI are indicated.

Sensations

No significant differences arose in terms of felt sensations between the tRNS and sham stimulation group (for statistical details see **Table S1**). Also, no difference was found between the groups in the impact of these sensations on their subjective performance.

Discussion

The aim of the present study was to impact E/I (measured by means of the aperiodic exponent) directly using tRNS, and indirectly by manipulating the level of skill acquisition (learning/overlearning). The aperiodic exponent decreased after tRNS, indicating an increased E/I, which corroborates with the working mechanisms of tRNS as a stimulation method that increases neuronal excitation. However, we found no effect of task manipulation on the aperiodic exponent, which indicates that overlearning a skill does not affect the aperiodic exponent or the E/I respectively. This was in contrast to our expectation formed by a previous MRS study (Shibata et al., 2017). We also showed that tRNS efficacy on learning depends on the baseline aperiodic exponent, but no beneficical effects were found for overlearning. To conclude, our results showed that the aperiodic exponent (i.e., E/I) can be altered by tRNS, and we showed a moderating effect of the baseline aperiodic exponent related to the effect of tRNS on skill acquisition.

In line with our expectations, we found that compared to sham stimulation, tRNS increased E/I levels. This result is in line with tRNS experiments in animals showing a reduction of GABAergic activity due to the tRNS excitatory effects (Sanchez-Leon et al., 2020). Our results, which were found using both frequentist and Bayesian approaches, show a decreased aperiodic exponent after applying tRNS related to an increased E/I. This strengthens the notion that delivering electrical random noise to the brain influences the underlying electrophysiological signal. It is thought that tRNS works by enhancing a signal with a near critical signal-to-noise ratio due to introducing noise in the system, described as the phenomenon of stochastic resonance. Previous studies related this increased signal-to-noise ratio from tRNS to enhanced learning, perception, and cognitive performance, which are linked to stochastic resonance (Antal & Herrmann, 2016; Cappelletti et al., 2013; Fertonani et al., 2011; Herpich et al., 2019; Snowball et al., 2013; Van der Groen & Wenderoth, 2016). Our findings suggest a working mechanism of tRNS efficacy, related to E/I. Whether this

mechanism is dependent or independent from stochastic resonance is a question for further research.

We did not find an effect of task manipulation (i.e., mathematical learning/overlearning) on the aperiodic exponent. It is likely that the aperiodic exponent was not strongly affected by our task manipulation. Manipulation on the electrophysiological level by means of increasing excitatory effects due to tRNS is a more direct approach to target the aperiodic exponent and is likely to yield a stronger neuronal effect than cognitive manipulation. This interpretation is in line with the view that brain stimulation can amplify the cognitive and neural effects of otherwise purely behavioral approaches (Cappelletti et al., 2013; Cohen Kadosh et al., 2012; Snowball et al., 2013). While another explanation can be attributed to the efficacy of our task manipulation paradigm, this is unlikely; participants in the learning task did not reach a plateau of performance improvement, while participants who completed the overlearning task clearly did show this plateau (see **Figure 2**). It is still possible that both mathematical learning and overlearning lead to a steeper aperiodic exponent (i.e., lower E/I). This explanation is in line with our finding that the exponent increased for participants in the sham stimulation group (see **Figure 3**). But this is in contrast to Shibata et al. (2017), who found that perceptual overlearning led to a reduction in E/I to protect a newly formed memory trace from subsequent new information. An alternative explanation, which we discuss later, is that E/I measures based on EEG and MRS reflect different aspects of E/I.

Previous studies have shown that the efficacy of tRNS depends on the individual baseline cognitive ability or neural activity (Evans et al., 2018; Frank et al., 2018; Harty & Cohen Kadosh, 2019). We have extended these findings showing that enhanced skill acquisition by tRNS is based on the participants' baseline E/I. First, our results show that the effect of tRNS is best explained when considering the moderating effects of baseline

aperiodic exponent and task manipulation. To illustrate, the posterior distribution of the three-way-interaction for the learning and overlearning data indicates the presence of an effect. In contrast to sham stimulation, which has shown better performance for those with a higher E/I (as reflected by a lower aperiodic exponent), tRNS improved the performance for those with lower E/I (as reflected by higher aperiodic exponent). This effect was present only in the learning task. In the overlearning task, tRNS had no effect, and better performance was characterised by lower E/I (higher aperiodic exponent) across stimulation condition. A possible explanation is that participants with low E/I levels benefit more from tRNS compared to participants with high E/I, indicating an optimum level depending on task difficulty (Krause et al., 2013; Shibata et al., 2017). This explanation fits also with the stochastic resonance framework, which predicts non-beneficial or even detrimental effects when random noise is introduced to an optimal system (McDonnell & Ward, 2011). This reveals that the baseline aperiodic exponent (i.e., E/I) is an important predictor of tRNS efficacy. Second, we found that tRNS, an excitatory form of neurostimulation, as supported also by our results, is more beneficial during the learning task (i.e., for low E/I participants) than during the overlearning task. As mentioned previously, Shibata et al. (2017) showed that overlearning relates to a shift from increased E/I, which occurs in learning, to a reduced E/I. While we did not find such a reduction, our results suggest that in the learning task those with higher E/I at baseline will perform better than those with lower E/I, unless intervening with tRNS, and in the overlearing task participants with lower E/I at baseline would perform better than those with higher E/I. These results suggest, similar to Shibata et al's work, that E/I is involved in learning and overlearning. However, our findings indicate that this involvement may not be due to E/I alterations relating to skill acquisition, but due to the participants' E/I level at baseline.

While at the beginning of our project some of our predictions were rooted in studies that used MRS-based E/I measures, our view is that there are some discrepancies between EEG-based E/I and MRS-based E/I that must be acknowledged and addressed in the future. First, we and others have found that EEG-based E/I increases with age (Cellier et al., 2021; Van Bueren et al., 2022), rather than a decrease as was found using MRS (Cohen Kadosh et al., 2015; Zacharopoulos et al., 2021b). Second, our lack of replication of the effect of learning and overlearning on E/I change between before and after task manipulation (Shibata et al., 2017) could be rooted in the different methodologies used to assess E/I, rather than other factors such as the cognitive domain. These discrepancies raise the question of whether E/I measures based on EEG and MRS reflect different aspects of E/I. Indeed, MRS-based E/I measure is likely to reflect intra- or extracellular activity, while EEG-based E/I is based on extracellular concentrations (Buzsáki et al., 2012; Dyke et al., 2017). To tentatively examine whether MRS-based E/I and EEG-based E/I reflect different aspects of E/I, the results are incidental, or if the two measures reflect a shared variance of E/I, we used an independent dataset that assessed the link between E/I measures derived by MRS and EEG in 20 young adults (see Supplementary Information). We found that higher glutamate/GABA measured with MRS (i.e., higher E/I) was significantly associated with an increased aperiodic exponent (i.e., lower E/I) over the left IPS. No relation was found for the left MFG (see **Figure S4**). This shows that MRS and EEG may measure different aspects of E/I. These preliminary results highlight the need to further examine the origin of E/I in MRS and EEG to progress our basic understanding as well as utilizing these measures for clinical applications.

Our results elucidate one of the underlying mechanisms of tRNS in cognitive and electrophysiological studies highlighting the role of aperiodic activity, and thus E/I balance. This study indicates the important role of baseline E/I in skill acquisition and tRNS efficacy. More specifically, participants with a higher aperiodic exponent (i.e., lower E/I) benefit more

from tRNS during a learning task compared to participants with a lower aperiodic exponent (i.e., higher E/I). The beneficial effect of tRNS was only found during learning and not during overlearning. This new understanding has important implications when considering to whom, when, and in the future what dose of tRNS should be delivered, and increase the importance of a personalized neurostimulation approach (Van Bueren et al., 2021).

Materials and Methods

Participants and Ethical Permission

One hundred and two right-handed participants participated in the study. None of the participants reported a history of psychiatric, neurological, or skin conditions and all met the safety criteria for tES participants. All volunteers were naïve to the aim of the study, and written informed consent was obtained. We ensured that all participants had no more than one cup of coffee or other sources of caffeine within 1 hour before the start of the study. We excluded seven participants who displayed an overall accuracy below 70% in the learning (Sham=4 and tRNS=3) or the overlearning task (Sham=1 and tRNS=1) as they were non-compliant with the task. Similarly, we excluded four participants because they showed no arithmetic facts learning in the learning or overlearning (Sham=2 and tRNS=2) tasks, as indexed by the lack of a significant negative linear regression coefficient of response times as a function of block. Five participants were excluded due to malfunction of the software (Sham=3 and tRNS=2). For the electrophysiological analysis, 11 participants were excluded due to artifacts during the pre or post resting state (rs)-EEG recording (more than 25% of their data were rejected) (see **Table 1** for demographic data). The final sample (n=75) was composed of 22 participants in the sham-learning condition, 21 in the sham-overlearning condition, 16 in the tRNS-learning condition, and 16 in the tRNS-overlearning condition. We excluded three participants (Sham=3) from the frequentist and Bayesian ANCOVA analyses as they were outliers on Cooks distance with RTs

as outcome variable. The study complied with the standards set by the Declaration of Helsinki and approved by the ethical advisory committee of the Faculty of Experimental Psychology at Oxford University (Protocol Number: IDREC, C2-2014-033). The methods of this study are on Open Science Framework (see https://osf.io/y4xar). However, the analyses (i.e., neuronal avalanches) presented in this preregistration did not yield significant results (see **Figure S6**). We later came across the work on the aperiodic exponent as a measure of E/I, which we used in this study.

Table 1| Demographic data of the stimulation conditions

Final Sample (N=75)		Stimulation Conditions				
		Sham-Learning (n=22)	tRNS-Learning (n=16)	Sham-Overlearning (n=21)	tRNS-Overlearning (n=16)	
	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	p*
Age (years)	23.40(4.27)	23.00(3.87)	25.00(5.54)	23.00(2.39)	24.17(5.33)	.45
Aperiodic Baseline	1.43(0.45)	1.38(.53)	1.63(.49)	1.38(.29)	1.37(0.46)	.29
Aperiodic Post	1.38(0.41)	1.39(.45)	1.32(0.21)	1.46(.50)	1.32(.41)	.88
Sex	44 females : 31 males	16 females : 6 males	7 females : 9 males	15 females : 6 males	6 females : 10 males	

*p-value of a between-groups ANOVA to compare stimulation groups

Baseline Matching

We investigated whether the participants in the four conditions (i.e., sham-learning, tRNS-learning, sham-overlearning, tRNS-overlearning) differed in median reaction times (RTs) and accuracy in the baseline task. A univariate ANOVA with condition as between-participants factors showed no significant differences for accuracy ($F(3,98)=1.73$, $p=.166$). Subsequently, all incorrect responses were removed from the baseline task (16% of all trials), and median RTs for each subject were calculated. Another univariate ANOVA showed no significant differences for median RTs ($F(3,98)=.11$, $p=.951$) at baseline between the different groups. Furthermore, there were no differences between the groups regarding subjective levels of sleepiness before the start of the experiment ($F(3,98)=.58$, $p=.629$). In addition, we ran an exploratory univariate ANOVA to determine if there were any differences regarding baseline aperiodic activity values before applying tRNS. We found no significant differences between the groups at baseline for aperiodic activity ($F(3,71)=1.25$, $p=.297$) after outlier removal for the ANCOVA. These results suggest similar baseline values across active and sham stimulation groups.

Tasks

Baseline Ability Task

At the beginning of the session, participants solved four multiplication problems to become familiar with the testing procedure. Afterwards, participants solved 10 new multiplication problems to evaluate their baseline ability (see **Table S2**). Every multiplication problem presented consisted of two-digit times one-digit operands with a two-digit answer (e.g., 16 x 3=48). None of the one-digit operands involved the digits 0 or 1 to minimize variations in difficulty. Furthermore, the two-digit operand was larger than 15 and not a multiple of 10.

At the beginning of the task, participants pressed the spacebar when ready to solve an arithmetic problem. Then, each trial started with a fixation screen (**Figure 6A**) after which a symbol of a headphone set appeared in the middle of the screen, and the arithmetic problem was presented auditorily. A symbol of a microphone appeared immediately after the arithetmic problem, and participants could say aloud the response. A noise-sensitive microphone captured the participant's responses through a Chronos box (Science Plus Group). Lastly, the words "Retrieve" and "Calculate" appeared on the left and right side of the screen; Participants indicated whether they had used a retrieval or calculation strategy when solving the arithmetic problem by pressing the left or right mouse button, respectively.

Participants were instructed to wear a headphone to cancel out any surrounding noise, and to speak clearly and loudly in the microphone without mumbling or clearing the throat (e.g., saying "eh-em", which would be registered as a response). Lastly, participants were informed that there was no time limit for answering, and they were urged to avoid errors.

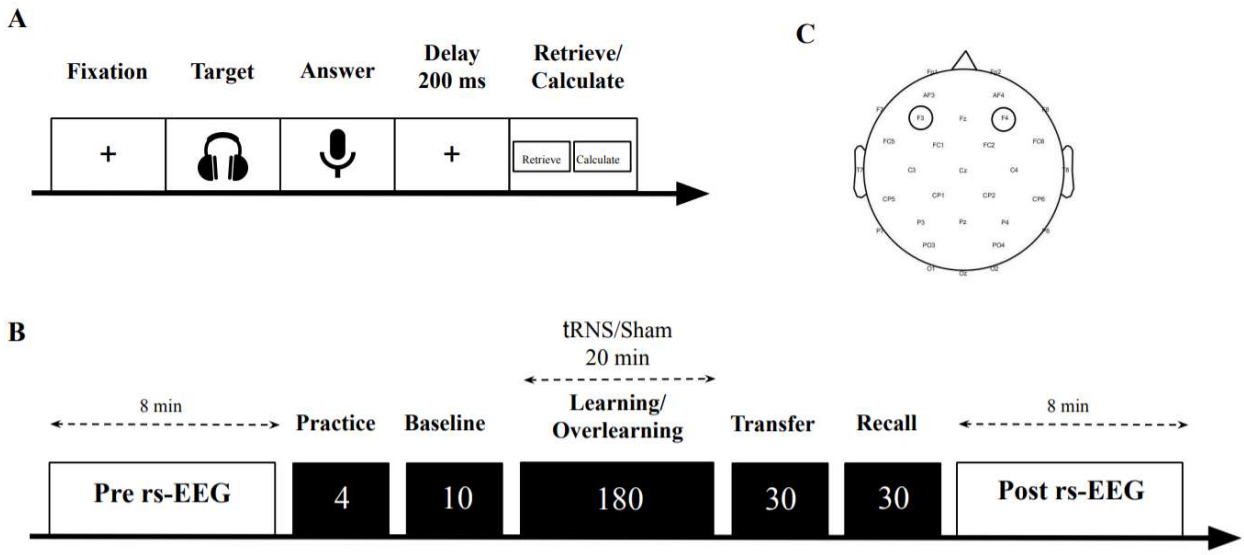

Figure 5| A schematic overview of the task structure and experimental protocol. A) First, a fixation screen was shown. Subsequently, a multiplication was presented by voice recording through a headphone. Hereafter, participants were shown a microphone symbol to indicate that they could say the answer into the microphone. This was followed by a 200 ms delay period. Lastly, participants indicated by clicking the left or right mousepad on the keyboard whether they retrieved or calculated the answer. **B)** First, a pre rs-EEG was measured of 8 minutes. Subsequently, a training was presented that contained 4 different multiplication problems. Based on baseline performance, participants either completed the learning or the overlearning task. One block in both the learning and overlearning task consisted of 10 multiplications with 18 blocks, and 180 trials in total. Participants received 20 minutes, 1 mA tRNS during either the learning or overlearning task or sham stimulation. Next, the transfer task was presented with new arithmetic problems containing 10 multiplication repeated three times. The recall task contained the identical multiplications as either the learning or the overlearning task and was repeated three times. Lastly, another post rs-EEG measurement of 8 minutes was assessed. **C)** Placement of the stimulation electrodes over F3 and F4.

Learning and Overlearning Condition

In total, 180 multiplication problems were administered in both the overlearning and the learning condition (see **Table S3**). The structure of the tasks was identical to the baseline task (see **Figure 5A**). Both conditions consisted of 18 blocks, comprised of the same number of trials and were presented in a fixed order. After three blocks, participants had a one-minute break. Therefore, in the learning condition, a subset of ten problems was presented once in each block. In the overlearning condition, a subset of five problems was selected, which was

presented twice in each block (i.e., less information to learn in comparison to the learning condition). This manipulation allowed us to use the same task and duration yet influencing the stage of skill acquisition that the participants reached. The design was based on a small pilot study (n=4) in which six multiplication problems were repeated four times. A plateau in performance improvement was visible after block four.

Transcranial Random Noise Stimulation

tRNS was applied over the bilateral dorsolateral prefrontal (dlPFC; F3 and F4) cortices, as defined by the international 10-20 system for EEG recording (see **Figure 5C**). Two Pistim Ag/AgCl electrodes were used with a 1 cm radius and a surface area of 3.14 cm^2 each. A current was delivered through these electrodes in the form of high frequency noise (100-500 Hz) by a multichannel transcranial current stimulator (Starstim 8 device, Neuroelectrics, Barcelona). The impedances of the Pistim electrodes were held at < 10 kΩ and intensity of the current was 1 mA peak-to-peak which has been shown to be safe and painless (Ambrus, Paulus, & Antal, 2010; Fertonani, Pirulli, & Miniussi, 2011). Duration of the stimulation was set to 20 minutes after onset of the task for the stimulation condition and 30 s for the sham condition with a 15 s ramp-up and a 15 s ramp-down. This provided the initial skin sensations experienced during stimulation. Both the participants and the experimenter were blinded to the stimulation condition. After completing the experiment, all participants filled out a questionnaire in which they were asked whether they felt any sensations during stimulation (i.e., itchiness, pain, burning, warmth/heat, pinching, iron taste, and fatigue) and if these sensations affected their performance. Unfortunately, due to an experimental error, we did not ask them whether they think they received sham or active stimulation. A follow up study that used the same parameters and a similar paradigm to this one (Sheffield et al., 2020), on a similar population, participants in both groups reported being in the stimulation condition at approximately the same rate (sham:

78%; active tRNS: 79%; $\chi(1)=0.03$, $p=1$). This independent data is supported by our data, which did not find differences in sensations between both groups (see Results section).

Electrophysiological Data

Rs-EEG recordings were made before baseline allocation and at the end of the experiment as stated in our preregistration (see **Figure 5B**). Electrophysiological data were obtained with 32 Ag/AgCl electrodes according to the international 10/20 EEG system using the wireless ENOBIO 32 sensor system (Neuroelectrics, Barcelona) at 500 Hz with no online filters. Note that we also used recorded rs-EEG from the two stimulation NG Pistim Ag/AgCl electrodes (F3 and F4). The impedances of the electrodes were held below 5 kΩ. The ground consisted of the active common mode sense (CMS) and passive driven right leg (DRL) electrode which were positioned on the right mastoid and connected by adhesive electrodes. Both the pre rs-EEG and the post rs-EEG had a duration of eight minutes, in which the participants had their eyes open while watching a fixation point in the middle of the screen in order to avoid mental and muscular activity.

Data Pre-processing

EEG data were pre-processed using EEGlab toolbox (v14.1.0) (Delorme & Makeig, 2004) in Matlab software (R2020b). A high-pass filter of 0.1 Hz was applied to minimize slow drifts and a notch filter at 50 Hz was applied to minimize line noise interference with the signal, and any data recorded before the presentation of the fixation point was removed. Every data file was manually checked and high-amplitude artefacts due to muscle movement, sweating or electrode malfunction were rejected. After pre-processing, Independent Component Analysis (ICA) was performed to remove stereotyped artefacts such as eye movements (e.g., blinks), heart rate activity and muscular activity. A maximum of six components per data file were removed, and a maximum of five bad channels were interpolated. EEG segments that contained artefacts that could not be removed by ICA were visually inspected and rejected from the

analysis (Delorme et al., 2007). If more than 25 percent of the rs-EEG data were rejected after pre-processing and ICA, data of the subject were discarded from analysis.

Aperiodic Activity Computation

The rs-EEG data of the remaining participants were separated in 2-second segments with an overlap of 1 second and windowed with a Hann window. Subsequently, data were transformed into the frequency domain via Fast Fourier Transformation (FFT). The FFT was exported from Matlab and important in Python (v.3.7.0; Van Rossum & Drake, 1995), and subsequently analyzed with the FOOOF package (v 1.0.0; Donoghue et al., 2020) over the 1-40 Hz range. This package allows for the decomposition between periodic and aperiodic components of the FFT. The aperiodic activity was calculated for the midline frontal electrode Fz which is the closest electrode to our stimulation electrodes F3 and F4.

Experimental Design and Statistical Analyses

First, participants completed the Stanford sleepiness scale (SSS), which is an introspective measure of subjective sleepiness and the Multidimensional Mood Questionnaire (MDBF), to assess alertness, good-bad mood, tiredness, calmness, and restlessness.

Then, participants completed an rs-EEG pre-measurement of eight minutes where they were informed to sit as still as possible (see **Figure 5B**). Then, a training was presented that consisted of four different arithmetic multiplications. Hereafter, the baseline task was started and a variance minimization procedure (based on response times) followed the baseline task in a double-blind fashion to determine which participants would be allocated to which group (see https://osf.io/y4xar for a detailed explanation of this procedure). This procedure is superior to random assignment for assigning participants to groups before an intervention (Sella et al., 2021), as it results in better matching. The stimulation started together with the learning or the overlearning task. Subsequently, the participants completed a transfer task and lastly a recall task. More information about the procedure of these tasks, which is beyond the scope of the

present manuscript, can be found on https://osf.io/y4xar. At the end of the behavioral tasks, an 8 minute rs-EEG measurement was recorded.

Behavioral Data Cleaning

We excluded responses below 200 ms due to possible noises picked up by the microphone or mumbling of the subject (0.89% for the baseline task, 2.74% for the learning task, and 7.07% for the overlearning task). We also excluded wrong responses from the baseline ability task (16.32%), the learning task (10.65%), and the overlearning task (7.7%). We calculated the median RTs for each participant in the baseline task and in each block of the learning and overlearning tasks.

Calculation of the Amount of Learning: Plateau of Performance Improvement

A plateau in performance improvement was computed following the next procedure: the distribution of RTs from the first block was compared to the distribution of RTs from the next block using the Wilcoxon test. When no significant difference was found in RTs between the actual block and the remaining blocks, the actual block was considered as the plateau point. Therefore, the plateau point is a number between 2 and 18 and an earlier plateau point indicates a higher amount of overlearning.

Statistical Analyses

All numerical independent variables were standardized to avoid multicollinearity issues. All inferential statistics reported in the present study were obtained with RStudio version 4.1.1 using the the *wilcox.test* function for the Mann-Whitney U test, the chisq.test for the Chi-Square Test, the *aov* function for ANCOVA and Univariate ANOVA, the *lm* function for the exploratory regression, and the *brms* package for the Bayesian mixed effect models (Bürkner, 2017) which are robust to normality violation and can deal with complex models. We used the open-source project JASP to run the Bayesian ANCOVA (Version 0.14.1.0; JASP Team, 2021). We originally used *glmer* for our analysis but due to model complexity we revert to *brms*. All

Bayesian models were ran with 5000 iterations and 4 chains each, and used dummy coding. We made the decision to not look at the RTs on trial level in our Bayesian models due to the high amount of introduced noise (i.e., variance between trials) and the lack of computational power. Due the right skewness of the median response time, the lognormal family was used. Also, all continuous independent variables were centered to prevent multicollinearity.

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Competing Interests

All authors declare no competing interests.

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