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Review article

Using noise for the better: The effects of transcranial random noise stimulation on the brain and behavior

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ABSTRACT

Van der Groen, O., Potok, W., Wenderoth, N., Edwards, G., Mattingley, J.B. and Edwards, D. Using noise for the better: The effects of transcranial random noise stimulation on the brain and behavior. NEUROSCI BIOBEHAV REV X (X) XXX-XXX 2021.- Transcranial random noise stimulation (tRNS) is a non-invasive electrical brain stimulation method that is increasingly employed in studies of human brain function and behavior, in health and disease. tRNS is effective in modulating perception acutely and can improve learning. By contrast, its effectiveness for modulating higher cognitive processes is variable. Prolonged stimulation with tRNS, either as one longer application, or multiple shorter applications, may engage plasticity mechanisms that can result in long-term benefits. Here we provide an overview of the current understanding of the effects of tRNS on the brain and behavior and provide some specific recommendations for future research.

1. Introduction

Transcranial random noise stimulation (tRNS) is a specific form of transcranial electrical stimulation (tES), which is itself one of several types of non-invasive brain stimulation (NIBS). tES involves the application of weak currents to superficial cortical regions through electrodes attached to the scalp. Various types of tES have been used to influence human behavior, including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). There are several key papers that give an overview of NIBS, focused on transcranial magnetic stimulation (TMS), tDCS and tACS, in relation to cognition (Miniussi et al., 2013; Parkin et al., 2015), social processing (Penton et al., 2020) and clinical conditions (Miniussi and Vallar, 2011; Perera et al., 2016). Over the last 13 years there has been an increase in publications employing tRNS (Pubmed search: 'Transcranial Random Noise Stimulation' in title/abstract), with 1 publication in 2008 and 32 in 2019. tRNS has benefits relative to other tES methods. For example, tRNS induces less discomfort which is helpful for blinding (Ambrus et al., 2010), and could increase comfort when stimulating over extended periods. Several studies have shown that tRNS has a larger neuromodulating influence when compared with other tES methods, reflected in larger neurophysiological and behavioral after effects (Inukai et al., 2016; Moliadze et al., 2014; Prete et al., 2018), making it a promising method for enhancing human behavior. tRNS is also less affected by cortical folding, thus reducing variability in outcomes due to anatomical differences between participants. tRNS also allows for stimulation of a larger population of neurons (both excitatory and inhibitory). For example with tDCS, tangential DC-currents applied to a symmetrical dendritic arbor will cancel each other out at the axon hill, whereas with tRNS the cell would be depolarized regardless of current flow orientation (Terney et al., 2008). Previous tES reviews have included sections on tRNS (Parkin et al., 2015; Reed and Cohen Kadosh,

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2018; Veniero et al., 2019) but this is the first narrative review that focusses solely on tRNS. In particular, it provides an overview of the effects of tRNS on human perception, cognition and learning, and explores the mechanisms that might underlie the effects of tRNS on these functions. In addition, we review studies that have used tRNS to enhance rehabilitation outcomes. We first discuss the underlying mechanisms of tRNS, which is critical for the effective use of this technique. We then provide an overview of domains in which tRNS has been effective and ineffective, followed with suggestions of avenues for progression in the use of tRNS as a clinical and research tool.

1.1. tRNS properties

tRNS involves the application of alternating currents at a mix of frequencies, between 0.1 and 100 Hz for "low" frequency stimulation, and between 101 Hz and 640 Hz for "high" frequency stimulation. The arbitrary division of "low" and "high" frequencies is based on one of the early tRNS papers (Terney et al., 2008), with 640 Hz being at the high end of physiologically measured human brain oscillations (Gobbelé et al., 2000). tRNS generates a random level of current for each sample of the signal. These random current levels are normally distributed (see Fig. 1) and result in zero-mean Gaussian white noise. Therefore, tRNS is a biphasic stimulus and is not considered directional. The absence of a direct current (DC) field means that tRNS might not induce a homeostatic effect since the electrical field is constantly changing (Fertonani et al., 2011). However, it is possible to add directionality by adding a DC field (that is, combining tRNS with tDCS), which allows the neuronal membrane response to adapt to the field over time and induce a homeostatic effect. One study found preliminary evidence that 10 min of offline tRNS involving a DC offset (anodal stimulation) is more likely to increase cortical excitability (Ho et al., 2015) compared with tRNS alone, although the apparent difference was not statistically significant. It is speculated that tRNS with a DC offset combines characteristics of direct current stimulation (polarizing the resting membrane potential) and random noise stimulation (potentially introducing noise into the system), to induce changes in cortical excitability (Ho et al., 2015).

A key characteristic of tRNS is that it is polarity independent, i.e., it is neither anodal nor cathodal (Miniussi et al., 2013). In one study which demonstrated this polarity independence (Pirulli et al., 2016), the authors asked three groups of participants – those receiving tRNS, those receiving tRNS with reversed electrodes, and those receiving sham stimulation – to undertake a visual perceptual learning task during which stimulation was applied (online; intensity: 1.5 mA, 100–640 Hz) over the occipital cortex, with the second electrode placed on the right upper arm. Reversing the cable connections between the groups showed that tRNS improved learning performance irrespective of its polarity. The polarity independence and absence of a uniform electrical field direction mean that it is possible to use both electrodes to simultaneously stimulate different cortical areas. Polarity independence can be of benefit when targeting multiple nodes in a specific brain network or networks. However, electrode placement should be considered carefully to avoid stimulation of unwanted sites. Whether tRNS enhances excitability under both electrodes equally is yet to be evaluated. For example, excitability changes under both electrodes could be tested by applying transcranial magnetic stimulation (TMS) over the primary motor cortex in each hemisphere to elicit motor evoked potentials (MEPs), before and after stimulation with tRNS.

A large fraction of the tES current shunts across the scalp (Vöröslakos

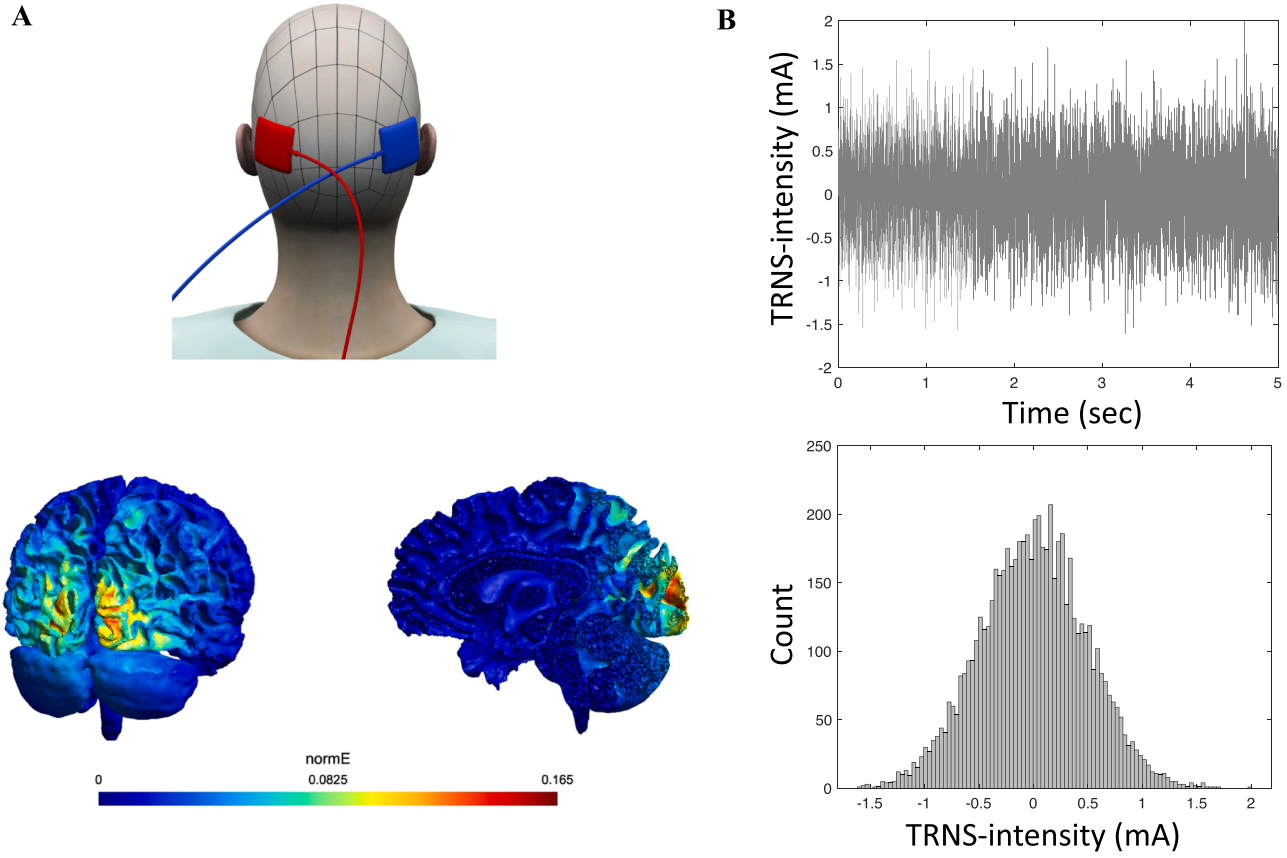

Fig. 1. Transcranial random noise stimulation (tRNS). A) An example of a tRNS electrode montage and its modeled electrical field strength (normE) targeting the visual cortex. B) A random level of current is generated for every sample (sampling rate 1280 Hz). The random numbers are from a normal distribution and the average current applied is 0. This image shows a signal which is 2 mA peak-to-peak, i.e., with 99% of all generated amplitude values between −1 and 1 mA. The histogram shows the normal distribution with a zero-mean.

et al., 2018). Several independent modeling studies have demonstrated that, due to resistive properties of the skull and tissue, tES applied at 2 mA peak-to-peak generates < 0.5 V/m electric fields in the human brain. This is sufficient to generate 0.1–0.2 mV changes in membrane potential of stimulated cells (Liu et al., 2018). This is too small to induce action potentials, but large enough to bias activity via alterations in the resting membrane potential. Importantly for tRNS, the human brain, skull and soft tissue have ohmic properties, i.e., induced fields are independent of stimulation frequency (Vöröslakos et al., 2018). This means that all applied frequencies can in principle reach the cortex. However, neuronal membranes might act as a low-pass filter (Esmaeilpour et al., 2021). Thus, even though all frequencies reach the brain, the induced change in membrane potential might be smaller than estimated. Moreover, the cut-off frequency is dependent on the type of neuron. For example, layer-4 stellate neurons have a higher cut-off frequency than layer-5 pyramidal neurons (Draguhn and Buzsáki, 2004; Lindén et al., 2010). Therefore, neuronal elements could be affected differently depending on the stimulation frequency. In this context, computational modeling could be beneficial to generate testable hypotheses concerning which neuronal populations respond to tRNS. One such model applied to tDCS found that including pyramidal cells and interneurons resulted in a more accurate simulation of the results of an in-vivo tDCS experiment (Molaee-Ardekani et al., 2013).

1.2. The neurophysiological basis of offline tRNS effects

Prolonged stimulation with tRNS can induce neurophysiological after-effects. Offline tRNS refers to experiments in which participants are not engaged in a specific task during stimulation. The impact of tRNS on cortical excitability was first demonstrated by Terney et al. (Terney et al., 2008). They stimulated the left motor cortex with high-frequency tRNS (HF-tRNS, 10 min, 1 mA peak-to-peak) and tested cortical excitability using TMS delivered over the primary motor cortex to induce MEPs. They found increased MEP amplitudes (increased excitability) after tRNS when subjects were sitting passively during the stimulation, and this effect lasted 60 min post-stimulation (Terney et al., 2008). In a separate study, Herpich et al. (2018) found that HF-tRNS (20 min, 1 mA, offline) produced increased cortical excitability in the visual cortex, and this effect lasted 60 min post-stimulation, demonstrated by a lower TMS intensity needed to elicit phosphenes. Various factors can influence the effect of tRNS on cortical excitability, including intensity and current density, stimulation duration and frequency range. For example, a single study showed that 10 min' of stimulation (0.1 – 640 Hz, offline) targeting the primary motor cortex with low intensity tRNS (0.4 mA) reduced cortical excitability, higher intensity tRNS (1 mA) increased excitability, while stimulation intensities of between 0.6 mA and 0.8 mA did not influence excitability (Moliadze et al., 2012). The inhibitory effect did not emerge until 20 min after stimulation, whereas the increase in excitation with 1 mA occurred immediately after stimulation. The authors suggest that their results could stem from different sensitivities of excitatory and inhibitory synapses to different stimulation intensities, and that inhibitory mechanisms may have a delayed onset when compared with excitatory protocols. It is therefore important to assess cortical changes at various timepoints to prevent missing any possible tRNS effects. These results show that stimulation intensity is critical in determining the effect of tRNS on excitability. Similar intensity effects have been observed for other tES methods, such as tDCS. For example, tDCS can have either facilitatory or inhibitory effects depending on stimulation intensity (Batsikadze et al., 2013; Chew et al., 2015). It has been suggested that increasing stimulation intensity while keeping its duration constant might activate counter-regulatory mechanisms to prevent excessive brain excitation (Hassanzahraee et al., 2020).

Individual differences in brain anatomy could explain some of the variation in the effects of tRNS intensity on excitability and behavior, because the electrical field induced at a target location can vary greatly as a function of skull thickness and cerebrospinal fluid depth (Laakso et al., 2015). Current-modeling could be used to determine the electrical field strength at the target location, for example by combining an individual's MRI with toolboxes such as SimNIBS (Saturnino et al., 2019), ROAST (Huang et al., 2019) or SCIrun (Dannhauer et al., 2012). Direct physiological validation of these models is currently limited (de Berker et al., 2013), but some studies have shown that individual current modeling can be useful (Antonenko et al., 2019; Edwards et al., 2013; Mosayebi-Samani et al., 2021). A recent study used modeling of individual induced electric field (EF) strengths to shed light on inter-individual variability in response to 15 min of tDCS targeting the primary motor cortex (Mosayebi-Samani et al., 2021). That study found that induced EFs positively correlated with tDCS induced physiological changes assessed by TMS and by MRI measures of cerebral blood flow. Another study used modeling to predict the amount of current necessary to evoke a muscle twitch with strong transcranial electrical stimulation (Edwards et al., 2013). One caveat is that most software packages model electric fields for direct current stimulation, which produces different current strengths relative to random noise stimulation, because the latter is by definition weaker in its power. This is because tRNS applies a distribution of different intensities (applied with different frequencies) where the peak intensity occurs least often, in contrast to tDCS which always applies a single intensity value.

As it may not always be possible to create individual head models, it is important to report tRNS intensity and electrode size in order to determine current density. tRNS intensities have been reported as peak-to-peak and peak-to-baseline. For example, on the peak-to-peak definition, an intensity of 1 mA indicates that 99% of all generated samples lie between 0.5 mA and − 0.5 mA. In contrast, in the peak-to-baseline definition, 99% of all generated samples lie between 1 mA and − 1 mA. Published tRNS papers often fail to specify whether the reported intensities are peak-to-peak or peak-to-baseline, which complicates the comparison of results between studies. In this article we indicate which measure was used whenever it is reported in the paper.

Electrical fields can influence subcutaneous nerves that signal to the brain, and thus can indirectly affect brain circuits even when subjects are not aware of the stimulation (Liu et al., 2018). Current modeling allows for the evaluation of potential stimulation effects on peripheral elements such as the trigeminal nerve branch, occipital nerve, retina, and vestibular organ. Stimulation of a control brain region which equally affects subcutaneous nerves would help dissociate cortical versus peripheral effects of stimulation. For example, tACS has been suggested to induce phosphenes via modulating neural activity in the visual cortex (Kanai et al., 2008), although these effects could be explained by retinal stimulation (Kar and Krekelberg, 2012; note, however, that such effects have not previously been reported for tRNS).

Stimulation duration is another parameter that modulates aftereffects on cortical excitability. A minimum stimulation duration of 5 min (HF-tRNS, 1 mA) is considered necessary to induce aftereffects on corticospinal excitability in the motor system (Chaieb et al., 2011), while the minimum duration for aftereffects in sensory or other systems has yet to be examined. In relation to stimulation duration, several tDCS studies have demonstrated the influence of the break duration on neuroplastic changes between repeated rounds of stimulation. For example, 5 min of anodal tDCS increases neuronal excitability for 3 min; however, if two 5 min periods of tDCS are applied, separated by a 3 min break, then the second session has an inhibitory effect (Fricke et al., 2011). Several other tDCS and TMS studies have also demonstrated that the effect of stimulation depends on stimulation history, formalized in a model of homeostatic plasticity (Gamboa et al., 2010; Siebner, 2004). How repeated applications of tRNS are influenced by homeostatic plasticity is important to inform the timing of stimulation sessions when these are used to enhance performance spanning multiple training sessions.

The range of frequencies applied is important in determining the aftereffects of stimulation. tRNS applied at 100–700 Hz (1.5 mA for

10 min) has been found to increase MEP amplitudes at 10 min and 20 min after stimulation, though this change was not evident immediately after stimulation (Moret et al., 2019). Other frequency bands (100–400 Hz; 400–700 Hz; sham) did not influence cortical excitability. These results suggest that large spectrum stimulation is necessary to induce aftereffects.

Despite these neurophysiological aftereffects, the exact physiological mechanism of offline tRNS effects is unknown. Pharmacological evidence (in vivo) has suggested that sodium (Na+) channel blockers reduce tRNS-induced changes in cortical excitability (Chaieb et al., 2015). This sodium dependence is consistent with evidence showing that adding noise to cell slices (in vitro) causes an acute repetitive opening of sodium channels (Bromm, 1968; Remedios et al., 2019; Schoen and Fromherz, 2008) and can enhance action potential generation in mouse sensory neurons (Onorato et al., 2016). Continuous opening of sodium channels would lead to membrane depolarization, which could result in long-term potentiation (LTP)-like changes. tDCS research suggests that LTP-like mechanisms occur after more than 3 min of stimulation (Chaieb et al., 2015; Terney et al., 2008). tRNS-induced plasticity is also $GABA_a$ receptor sensitive (Chaieb et al., 2015), and a recent study has suggested that GABA levels can be reduced after prolonged stimulation with tRNS in juvenile mice (Sánchez-León et al., 2021). It is unknown if similar effects occur in the human brain, but this could plausibly be tested by measuring GABA levels following tRNS with magnetic resonance spectroscopy (MRS) (Puts and Edden, 2012). To understand the different parameters of tRNS (e.g., stimulation frequency, duration), cellular and neuronal population level effects need to be evaluated systematically. A better understanding of the neurophysiological mechanisms that underlie tRNS induced effects will allow for optimization of stimulation protocols. For example, knowledge of the neural elements that are sensitive to tRNS as well as the role of homeostatic effects should allow for optimized stimulation protocols. Future studies should also develop and validate specific current modeling tools in order to optimize the delivery of tRNS.

In summary, the effects of offline tRNS on cortical excitability depend on a range of stimulation parameters, complicating comparisons between studies. Current modeling should be used to determine the electrical field strength at the target location.

1.3. The neurophysiological basis of acute online tRNS effects

Recently, it has been shown that tRNS (2 mA peak-to-baseline amplitude) can cause an acute online increase in cortical responsiveness, assessed with TMS, during the application of tRNS over the motor cortex (Potok et al., 2021). In that study, tRNS was applied in short bursts of 3 s, and cortical excitability was evaluated with single-pulse TMS between 1.3 and 1.7 s during the stimulation. There was a small but reliable decrease in resting motor threshold (RMT) acutely. The observed effects were not likely due to neuroplastic changes since tRNS conditions were always interleaved with no noise or other active control conditions, thereby minimizing the influence of long-term excitability changes. Moreover, there was no systematic change in excitability over time for trials without tRNS, making it unlikely that these results were affected by long-term neuroplasticity. The underlying neurophysiological mechanism of online excitability modulation with tES is unclear, but Liu and colleagues have proposed several hypotheses (see Liu et al., 2018), including but not limited to, entrainment of network patterns and stochastic resonance. Entrainment is unlikely to result from adding noise, but might be achieved using other tES protocols. For example, 10 Hz tACS (1 mA) over the visual cortex is able to entrain intrinsic alpha oscillations (Helfrich et al., 2014).

Stochastic resonance has been proposed by several authors as a potential working mechanism of tRNS (van der Groen and Wenderoth, 2016). Stochastic resonance is a phenomenon whereby small amounts of noise can be of benefit to the output of a system (Moss et al., 2004), i.e., where noisy electrical fluctuations actually boost neural signals and enhance detectability of weak events (see Fig. 2). Stochastic resonance occurs when an optimal level of noise is added to a weak signal. At a neuronal level stochastic resonance can occur when physiological (excitatory postsynaptic potentials (EPSP) and inhibitory postsynaptic potentials (IPSP)) and exogenous (tES) polarizing mechanisms are added. An EPSP is a depolarization of a postsynaptic cell following the influx of positively charged ions (such as Na^+), whereas an IPSP is a hyperpolarization due to an influx of negative ions (e.g. Cl^-) or efflux of positive ions (e.g. K^+). tRNS might cause an acute repetitive opening of sodium channels (Bromm, 1968; Remedios et al., 2019; Schoen and Fromherz, 2008). A small amount of noise can then bias the probability or timing of neuronal firing when a cell is close to threshold. At a behavioral level, the stochastic resonance hypothesis has been tested by presenting weak stimuli (visual, auditory, or tactile), to bring neurons close to firing threshold, and then applying tRNS as a way of adding neural noise. An optimal amount of noise results in improved behavioral performance, whereas too little or too much noise results in no performance enhancement or even a reduction of performance. Such outcomes yield the characteristic inverted-U relationship between noise intensity and performance (Ward et al., 2002). Of note is that much of the SR work has been conducted when noise is applied to the peripheral nervous system (e.g., visual or auditory white noise). Whether peripheral and central noise (e.g., induced with tRNS) are treated equally by the brain remains unknown. Some tRNS studies have demonstrated an inverted U-relationship between tRNS intensity and behavioral performance (van der Groen and Wenderoth, 2016), but some have not shown this relationship (Rufener et al., 2020). A potential idea is to test whether, and how, peripheral noise and central noise interact.

Related to stochastic resonance is the hypothesis of temporal summation of neural activity. tRNS might lead to the membrane potential of stimulated neurons approaching their response threshold due to induction of direct temporal summation (Terney et al., 2008). That is, tRNS might repeatedly open sodium channels and cause a second sodium influx, resulting in further depolarization of the neuron; due to the polarity independence of tRNS this should occur at both electrodes. Such effects might be expected when the time it takes to change the membrane potential of a neuron is sufficiently long to permit the summation of two tRNS stimuli delivered in close succession. This temporal summation would interact with neurons that are activated by a task, which could result in the strengthening of activity-dependent processes and thus potentially behavioral improvements (Pirulli et al., 2013). Comparative studies of the effects of tRNS in humans and non-human animal models could shed light on the underlying mechanisms in order to optimize stimulation protocols. For example, using intracranial recordings it should be possible to develop a better understanding of the physiological impact of tRNS in vivo (Jamil and Nitsche, 2017). Moreover, tDCS has been shown to induce after-effects on the glial and vascular systems; whether tRNS can influence these as well is unknown and requires further investigation (Jamil and Nitsche, 2017).

2. tRNS effects on perception and learning

2.1. tRNS acutely influences perception

tRNS can have online effects on visual processing of weak stimuli (Battaglini et al., 2019; Campana et al., 2016; Fertonani et al., 2019; van der Groen and Wenderoth, 2016). For example, we have shown that an optimal intensity of HF-tRNS over the primary visual cortex (V1) improves visual detection performance, but only when targets are subthreshold (van der Groen and Wenderoth, 2016). A more recent study, which investigated the effect of tRNS on contrast detection, also found that tRNS (100–640 Hz, 1.5 mA) enhances the detection of low contrast stimuli (Gabors), but only for oblique orientations with a high spatial frequency (12 cycles per degree visual angle, (Battaglini et al., 2020)). These results suggest that tRNS can improve performance when sensory processing is sub-optimal.

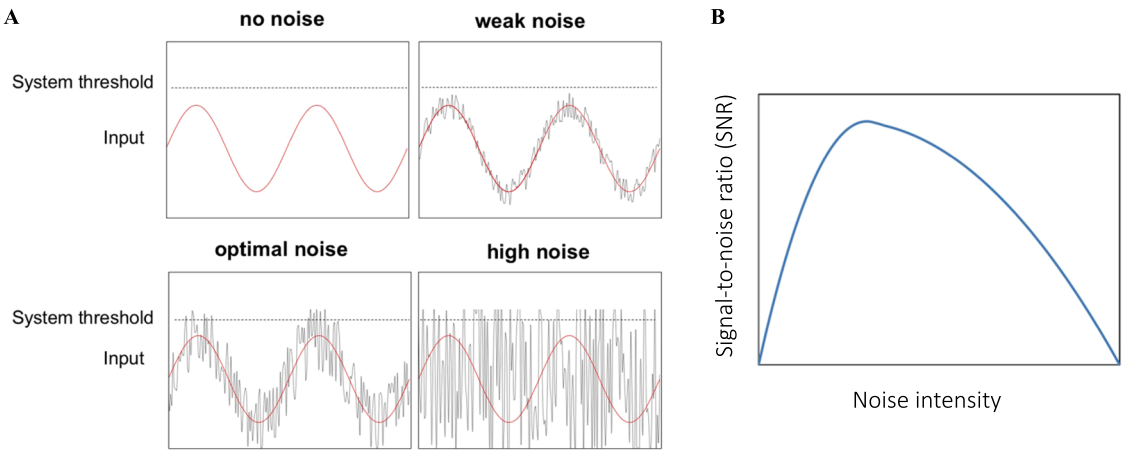

Fig. 2. Overview of the stochastic resonance concept. A) An optimal level of noise can allow a weak subthreshold signal to cross a threshold for detection. When too much noise is added the signal will be masked by the excessive noise (from Miniussi et al. (2013)). B) This image shows how the output signal-to-noise ratio (SNR) changes with increasing noise levels. The dose-response relationship between noise level and SNR is characterized by an inverted-U shape function.

We recently conducted a combined behavioral and computational modeling study to shed light on the possible mechanism by which tRNS influences visual perception in a dot-motion coherence discrimination task (van der Groen et al., 2018). We found an online improvement in behavioral performance, resulting in a characteristic inverted-U shape relationship between noise intensity and behavioral performance. Behavioral responses were characterized with a drift diffusion model (DDM) (Ratcliff and McKoon, 2008). The modeling showed that the drift-rate was higher when an optimal level of tRNS was applied. The drift rate is thought to reflect evidence accumulation (Ratcliff and McKoon, 2008), suggesting that tRNS can increase the signal-to-noise ratio (SNR) of weak visual stimuli. Modeling studies by other groups have also shown that tRNS can modulate neural SNR (Ghin et al., 2018; Pavan et al., 2019) in motion coherence discrimination tasks. These studies suggest that tRNS does not modulate the amount of internal noise, but instead increases the amount of sampling in a motion detection task. Internal noise influences the precision with which each dot's direction can be estimated, while sampling determines the number of dots involved in the computation of coherent directions. This means that effectiveness of signal processing can be increased when the stimulus is near threshold. tRNS might affect neuronal populations by increasing the probability of firing through a non-linear amplification of subthreshold neural oscillatory activity (Miniussi et al., 2013), potentially resulting in higher signal processing effectiveness.

These data show that tRNS can have a direct, online effect on behavioral performance, likely by boosting the SNR of information represented in the brain. Online effects of tRNS have also been observed in the auditory system (Prete et al., 2018, 2017; Rufener et al., 2018, 2017). In contrast to the studies above, the results of a separate study questioned the existence of stochastic resonance in human auditory perception (Rufener et al., 2020). In that study the authors applied varying degrees of auditory and tRNS noise during which participants were required to detect an auditory stimulus at threshold. The results revealed that subjects did not benefit from noise. The authors state that in the literature the reported benefits of noise are small, most studies are based on underpowered sample sizes, and most do not report a consistent decrease in performance when noise intensities increase, which is a characteristic of stochastic resonance.

In summary, most published studies suggest that tRNS can boost perception, and others have built on these findings by using tRNS as a tool in supporting perceptual learning, discussed in detail below. Our broad knowledge of sensory systems can be used to test specific effects of tRNS. For example, knowledge of the spatial tuning of neurons in the visual cortex and the temporal frequency channels in the auditory system have been used to test specific hypotheses regarding the impact of tRNS (Battaglini et al., 2020; Van Doren et al., 2014). When combined with computational modeling of cognitive and perceptual functions, it should be possible to expand knowledge of the mechanisms of tRNS. To date, the exact mechanisms of observed tRNS effects on perception remain unknown. Several hypotheses have been developed around the working mechanisms of tRNS, including stochastic resonance and the hypothesis of temporal summation. While these can explain some tRNS effects, there is at present no unifying hypothesis on the mechanisms of action of tRNS.

2.2. *tRNS improves learning*

Several studies have investigated the effects of tRNS paired with learning tasks (Brem et al., 2018; Cappelletti et al., 2013; Contemori et al., 2019), focusing in particular on designs in which tRNS is applied during learning and performance is tested after learning. One study focused on visual perceptual learning (Fertonani et al., 2011). In this study, participants performed 7 blocks of a perceptual learning task involving visual orientation discrimination while they received 1.5 mA tRNS over the occipital lobe. HF-tRNS significantly increased accuracy compared with sham and tDCS. The learning rate was higher – reflected in a steeper learning curve – when participants received tRNS. A follow-up study showed that tRNS improves learning only when it is provided *during* training but not when it is applied *before* a learning task (Pirulli et al., 2013). Of note is that the design of these studies included one day of learning, whereas typical perceptual learning studies span multiple days. One study, however, showed that HF-tRNS (1.5 mA amplitude, no DC-offset) during perceptual learning (crowding--reduction training implemented over four days) led to increased learning rates compared with sham stimulation in healthy subjects (Contemori et al., 2019). This result suggests that tRNS may be beneficial for enhancing the rate of perceptual learning over multiple days.

Several other studies have applied tRNS over multiple training sessions during perceptual and arithmetic learning, and have shown increases in the slope of the learning curve (Popescu et al., 2016; Terney et al., 2008), suggesting faster learning. Herpich and colleagues applied tRNS to the visual cortex by placing electrodes over the occipital lobe (Herpich et al., 2019). Participants performed 10 days' of global-direction discrimination training for 20 min a day while receiving 1 mA HF-tRNS (101 – 640 Hz) targeting the visual cortex. Ten days of training resulted in significant improvements in motion discrimination performance, with effects lasting at least 6 months after training ceased. These effects did not occur in control groups that received sham stimulation, no-stimulation or tRNS over the parietal cortex. This suggests that tRNS can have lasting effects on perceptual

performance.

During perceptual learning in cats and humans, performance improvements have been related to increased SNR at a neural level (Gilbert et al., 2001; Ren et al., 2016). Moreover, psychophysical studies have suggested that boosting sub-threshold, stimulus-related cortical activity can promote perceptual learning (Seitz and Dinse, 2007). Signals could be boosted, for example, by multisensory integration and potentially non-invasive brain stimulation, such as tRNS. When perceptual learning is combined with tRNS, learning might accelerate via acutely increased SNR. However, this hypothesis should be tested, for example by applying the drift diffusion model during a learning task. Collectively, these studies demonstrate that tRNS can be effectively used for improving learning in healthy participants.

3. tRNS effects on higher cognitive functions

3.1. tRNS can influence attention

tRNS has been successfully used to modulate human attention (Lema et al., 2021; Tyler et al., 2015, 2018; van Koningsbruggen et al., 2016). One study used a spatial priming protocol in combination with HF-tRNS (1 mA) delivered bilaterally over the left and right posterior parietal cortex (Shalev et al., 2017). In this task, participants pressed a button when they saw a target image in a stream of distractors, presented to the left and right of a central fixation cross. Participants received tRNS or sham stimulation while either detecting targets that were more frequent to the right (right spatial priming) or without any priming. The authors modeled aspects of attentional processing that changed (based on the theory of visual attention (TVA) (Bundesen, 1990)). Their protocol could bias attention toward the right hemifield, but tRNS did not further increase this spatial bias. However, the TVA model showed an increase in the parameter representing selectivity. That is, tRNS enhanced individuals' capacity to select targets over irrelevant distractors. Applying tRNS without any priming did not influence selective attention. This suggests that tRNS can have an online effect, but applying tRNS without a specific task does not have a generalized impact on attention.

The neurophysiological effects of tRNS on sustained attention have been studied using EEG before and after an attention task (Harty and Cohen Kadosh, 2019). At a behavioral level, the application of 1 mA tRNS (peak-to-peak) over the right dorsolateral prefrontal cortex (DLPFC) and right inferior parietal lobe (IPL) was associated with improved sustained attention. At a neurophysiological level this resulted in a reduction in the theta:beta ratio measured with EEG, which is thought to reflect increased control of top-down attention (Angelidis et al., 2016). The effect of 1 mA tRNS on sustained attention was modulated by an individual's theta:beta ratio at baseline. The authors suggested that individuals with a high theta:beta ratio may have had neural oscillations in the theta range that did not reach threshold for signal transmission, and that these were enhanced by tRNS, possibly via stochastic resonance. In contrast, they found that tRNS with a 2 mA intensity (peak-to-peak) had no impact on behavior or the EEG signal. Another study applied 1.5 mA of tRNS for 20 min targeting visual motion area V5 and showed that off-line tRNS induced moderate aftereffects in gamma oscillatory activity measured with EEG (Ghin et al., 2021). How tRNS might influence synchronization between different brain areas has not been well investigated, but has been proposed as a possible effect of tRNS (Antal and Herrmann, 2016; Keiichi et al., 2004; Kitajo et al., 2007; Ward, 2009; Ward et al., 2010). In theory, noise can increase the regularity of neuronal spiking, causing neurons to fire in a more clock-like fashion (Ermentrout et al., 2008). Future research should explore the idea that tRNS can influence neuronal synchronization. If this proves possible, it would open a new avenue for exploration in the clinical sphere, since a number of brain disorders have been associated with abnormal neuronal synchronization (Uhlhaas and Singer, 2006). Taken together, the studies reviewed in this section suggest that tRNS can modulate and improve human attentional processes.

3.2. Variable effects of tRNS on working memory

The effects of tRNS on working memory (WM) are unclear. One study, in which tRNS (1 mA peak-to-peak) was applied to the left DLPFC while participants performed an N-back task for 10 min (Mulquiney et al., 2011), yielded no effect of stimulation on WM performance. A randomized controlled trial also found no benefit of tRNS on WM when applied over 10 sessions of WM-training (Holmes et al., 2016). In that study the authors applied tRNS (1 mA peak-to-peak, no DC offset) bilaterally to the DLPFC. Other studies added a DC offset to the tRNS, (i.e., where tRNS is superimposed on a fixed current). This makes the signal directional, resulting in either anodal (positive) or cathodal (negative) stimulation. One study (Murphy et al., 2020) applied 1 mA tRNS, with a 1 mA DC offset, over the left DLPFC (anode over F3 – cathode over contralateral supraorbital) while participants completed the Paced Auditory Serial Addition Task (PASAT), which engages fronto-parietal regions involved in WM processing. tRNS (with a 1 mA DC offset) was more beneficial than tDCS in improving WM function, potentially because the 'noise' introduced by tRNS would be expected to amplify WM-related oscillatory activity in a manner consistent with a stochastic resonance effect. However, relatively little is known about the neurophysiological effects of tRNS with a DC-offset. However, without a DC-offset, tRNS did not seem to be beneficial for improving WM (Holmes et al., 2016); therefore, a DC-offset might be necessary in order to improve WM with tRNS. The anodal DC component may shift the resting membrane potential closer to the firing threshold, and the added noise may more effectively influence a larger population of neurons toward threshold. This hypothesis could be tested by applying tRNS with either an anodal or cathodal offset over the motor cortex, and assessing how this changes cortical excitability measured via TMS-induced MEPs, both online and offline. At present, there are a limited number of studies and no comparative meta-analyses, and it therefore remains unclear whether tRNS can influence WM.

3.3. tRNS effect on higher order cognitive functions and social perception

The application of tRNS extends to modulating higher order cognitive functions including social perception. While some studies have shown a positive effect of tRNS on higher level cognitive function (Moret et al., 2021; Pasqualotto, 2016; Popescu et al., 2016; Snowball et al., 2013), there is probably an upper limit for cognitive enhancement using tRNS. Moreover, individual differences could play an important role in the effectiveness of tRNS in influencing performance. For example, a single-subject study investigated whether tRNS applied bilaterally over the DLPFC could enhance arithmetic skills in a world-champion mental calculator (Krause et al., 2019). His arithmetic skills were not improved by applying tRNS during the task, and in fact deteriorated somewhat during tRNS, although not significantly. A more recent study did not find a modulatory effect of online HF-tRNS (either 1 mA or 0.705 mA) on cognitive training in adults, but in some tasks older adults did benefit more from tRNS (1 mA) than younger participants (Brambilla et al., 2021). Another study investigated the interaction between the effects of tRNS on face memory performance and found that 1.5 mA tRNS (10 min before and 10 min during the task) targeting the ventrolateral prefrontal cortices (VLPFC) could enhance performance in young adults (Penton et al., 2018). However, a follow-up within-subject study with older adults found a reduction in performance, with a larger reduction in participants with a better baseline performance. 20 min of tRNS targeting the inferior frontal cortex (IFC) improved performance on an emotion perception task, but not an identity perception task, especially in participants with a low baseline performance (Penton et al., 2017).

These findings highlight that tRNS is not a one-size-fits-all stimulation method. Several neurophysiological factors could underlie the different responses of individuals to tRNS. For example, it has been

suggested that high-performers might benefit less from tRNS since their activated networks are already at an optimal level (Krause et al., 2019; Penton et al., 2017). Furthermore, high-performers have been shown to recruit different brain networks (Desco et al., 2011; O'Boyle et al., 2005). Therefore, targeting the same regions for high- and low-performance individuals might not result in similar modulations at a network level. Relatedly, older adults often rely more on bilateral network activation due to a reduction in activation of task-specific hemispheric specialization, and these network changes have been linked to age-related differences in responses to tDCS (Zimerman and Hummel, 2010). Therefore, network-wide effects of tRNS in different populations must be evaluated in order to optimize stimulation protocols. Functional magnetic resonance imaging (fMRI) might reveal the network nodes an individual recruits for a specific task, which could in turn be used to determine a stimulation target. Similarly, neuroimaging pre- and post-stimulation may elucidate how tRNS extends to network-wide modulation.

Two tDCS studies have demonstrated that adjusting the stimulation locations according to age-related network changes can lead to improved effectiveness of tDCS in enhancing performance (Arciniega et al., 2018; Meinzer et al., 2013). Moreover, the homeostatic set-point hypothesis states that there will be a set point of firing rates in order to maintain homeostatic stability in the brain (Turrigiano and Nelson, 2004), and this set point poses a potential limit on the effect size of tRNS. For example, after prolonged stimulation homeostatic mechanisms might become active in order to prevent 'runaway' neural activity or quiescence.

4. Neural correlates of behavioral effects

Several neuroimaging studies have shed light on the neural correlates of the impact of tRNS on behavior (Contò et al., 2021; Rufener et al., 2017; Saiote et al., 2013; Snowball et al., 2013). One study investigated the behavioral effects and EEG markers of tRNS on the resolution of participants' temporal and spectral perception using gap-detection and pitch-discrimination tasks, respectively (Rufener et al., 2017). tRNS increased the detection rate of near-threshold stimuli in the temporal domain. This behavioral improvement coincided with a reduction in peak latency of early responses of auditory event related potentials (ERPs). The latency is thought to reflect neural conduction time. Therefore, tRNS might facilitate the firing of neurons involved in this task rather than increase the number of neurons recruited. The authors suggest that tRNS increases neural SNR, potentially via a stochastic resonance mechanism.

Another experiment studied the impact of 1 mA tRNS over the primary motor cortex during the first 10 min of a visuomotor tracking task (Saiote et al., 2013). At a behavioral level, they found that HF-tRNS improved learning marginally, but not significantly. At a neurophysiological level, they found a reduction in motor-task related activity bilaterally in the frontal cortex and precuneus measured with BOLD fMRI, thought to reflect greater neural efficacy. Snowball et al. (2013) applied tRNS bilaterally to the DLPFC during cognitive training (complex arithmetic tasks) for five consecutive days. They found an increased learning rate in two learning tasks, and this was associated with more efficient neurovascular coupling, determined with near infrared spectroscopy, in brain regions involved in the mental arithmetic task. More recently, Contò et al. (2021) found high-frequency tRNS over parietal cortex paired with training in two attentional tasks resulted in increased functional connectivity between dorsal and ventral attention network. Connectivity increased positively with behavioral improvement in one of the tasks, indicating tRNS can strength task relevant networks. Stimulation of hMT+, the active control site, did not elicit such behavioral or neural effect. As hMT+ is also a node of the dorsal attention network, and a close anatomical neighbor to the parietal stimulation, this demonstrates networks should be carefully targeted through specific nodes (Contò et al., 2021). These results suggest that tRNS effects can be captured by neuroimaging methods, and that such effects might influence behavior by providing more efficient neuronal processing.

5. Implications for investigation and potential treatment of neurological conditions

tRNS has been used to target different clinical populations and can improve function in atypical development. One pilot study (n = 4) in stroke patients demonstrated that tRNS during reaching training did not provide a benefit, but found that patients wore the electrodes comfortably, indicating feasibility of the method (Hayward et al., 2017). A larger study (n = 18) applied tRNS over the motor cortex during a grasp training program in patients 1–6 weeks after ischemic stroke, and found significant improvement in the Fugl-Meyer score directly, and sustained 30 days after intervention, compared with a sham control (Arnao et al., 2019). The Fugl-Meyer score is a performance based motor impairment index, with a higher score representing less impairment (Page et al., 2012). Although the difference in improvement was less than the minimal 'clinically important' difference of 6 points on this scale, the results are nevertheless a first encouraging step.

tRNS has also been used in clinical populations to boost visual perception (Camilleri et al., 2016, 2014; Campana et al., 2014; Donkor et al., 2021). Patients with cortical blindness following stroke impacting the occipital cortex can regain visual processing in the blind visual field with perceptual training (Huxlin et al., 2009; Melnick et al., 2016). In one study, perceptual learning combined with tRNS applied to early visual brain areas in patients with chronic cortical blindness yielded a significant improvement in visual motion processing after 10 days of training (Herpich et al., 2019). The authors tailored the difficulty of the task to each participant, ensuring the task was highly engaging, which is thought to boost the effectiveness of non-invasive brain stimulation (Edwards et al., 2019). Visual acuity has also been significantly improved following tRNS in patients with neurodevelopmental disorders such as amblyopia (Moret et al., 2018).

tRNS targeting the auditory cortices has been found to improve phoneme processing in developmental dyslexia by modulating sensory processing in the auditory cortex (Rufener et al., 2019). Another study found that tRNS (0.1 – 500 Hz) delivered over bilateral DLPFC, a key area in numerical processing, coupled with cognitive training, improved learning in children with mathematical learning disabilities at school (Looi et al., 2017). In that study, the authors found a steeper learning rate than a sham stimulation control condition. tRNS has also been successfully used in the treatment of tinnitus targeting the auditory and prefrontal cortex, with effectiveness depending on the stimulation frequency (Joos et al., 2015; Kreuzer et al., 2019, 2017; Mohsen et al., 2019, 2018; To et al., 2017; Vanneste et al., 2013), chronic pain (Alm and Dreimanis, 2013; Curatolo et al., 2017; Palm et al., 2016), fatigue in multiple sclerosis (MS) (Salemi et al., 2019), improvement in visual perception in migraine (O'Hare et al., 2021) and in attention-deficit/hyperactivity disorder (Berger et al., 2021).

The studies reviewed above show promise for the use of tRNS in treating a range of clinical conditions. Despite a promising boost in performance, tRNS targeting higher order brain processes are inconsistent. For example, one randomized controlled trial used tRNS, with a 2 mA DC-offset while participants were not engaged in any task, as an acute treatment for depression (Nikolin et al., 2020). In that trial, individuals with depression received 20 sessions of tRNS targeting the left DLPFC, with no significant improvement. Another study applied 2 mA tRNS over bilateral prefrontal cortex, without a DC offset, as an adjunct to in-patient treatment in depression, but failed to find a significant benefit (Schecklmann et al., 2021). Patients received a range of treatments, including psychotherapy, group therapies, pharmacotherapy and occupational therapy, which were not kept stable between participants. Therefore, potential null results could be due to the lack of an interaction between ongoing brain activity and tRNS effects. Moreover, tRNS

might not have been effective at a group level since a separate study showed an interaction between the effects of tRNS, subjects' age and trait mood (Evans et al., 2018). Older adults often rely more on bilateral network activation due to a reduction in activation of task-specific hemispheric specialization, and these network changes have been linked to age-related differences in response to tDCS (Zimerman and Hummel, 2010). Therefore, network wide effects of tRNS in different populations must be evaluated in order to optimize stimulation protocols.

Other studies targeting frontal brain areas (including the DLPFC) aimed at treating MS pain and attention (Palm et al., 2016), and treating vegetative state (Mancuso et al., 2017), did not find a benefit of tRNS. For the latter study, the authors suggest the lack of effect may have been because tRNS relies heavily on propagation of weak ongoing endogenous neuronal signals, which may be insufficient in this population. In summary, these studies suggest that tRNS has the potential to be used in neurological conditions to promote recovery, but a lack of understanding around the working mechanisms of tRNS complicates the application of tRNS in clinical populations.

6. Concluding remarks

tRNS is a promising tool that can have direct online effects on perception and cognition and can improve learning in health and disease. tRNS can have online effects on brain processing, potentially by increasing the SNR of incoming information. This could result in improved behavioral performance, since the information to be decoded has an enhanced SNR. In addition, long-term neuroplastic effects of tRNS also contribute to behavioral improvements. The exact neurophysiological mechanisms of tRNS remain unclear. It has been suggested that tRNS can influence neuronal synchronization between different brain areas and might also alter GABA levels. If and how tRNS influences neuronal synchronization and GABA levels is an important avenue for future research, since many cognitive functions are dependent on neuronal synchronization, and GABA plays a major role in learning (Stagg et al., 2011; Ziemann et al., 2001). Comparative studies on tRNS between humans and animals could shed light on the underlying mechanisms in order to optimize stimulation protocols. For example, using intracranial recordings it should be possible to develop a better understanding of the physiological impact of tRNS in vivo. Moreover, MRS could shed light on changes in GABA levels in vivo. To further develop the field of tRNS, studies should include modeling of induced electrical fields to allow for more targeted stimulation and comparison of induced electric fields between and within studies. If this is not possible then it should be clearly stated that stimulation intensities were peak-to-peak or peak-to-baseline, and current densities should be reported. Most studies to date have employed relatively small sample sizes, which is especially problematic when the induced electrical field is variable between individuals. Therefore, larger sample sizes with individualized stimulation protocols are warranted. Moreover, the prevalence of positive effects of tRNS could to some extent reflect a publication bias. Pre-registration of trials is therefore recommended, which is already common practice in clinical trials. Currently, there are also no meta-analyses of the effects of tRNS, which makes it difficult to determine its overall efficacy, despite the encouraging studies that have been published so far.

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