Improvement in visual perception after high-frequency transcranial random noise stimulation (hf-tRNS) in those with migraine: An Equivalent Noise approach

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Abstract

Migraine is a common neurological disorder with strong links to vision. Interictal migraine is thought to be characterised by internal noise in the brain, possibly due to increased variability in neural firing, which can be estimated using equivalent noise tasks. High-frequency transcranial random noise stimulation (hf-tRNS) can be used to modulate levels of internal noise in the brain, and so presents a possible therapy to redress noise levels in the migraine brain. This is a case-control study using a 2-alternative forced choice (2AFC) design. hf-tRNS and Sham control stimulation were used alongside a global motion direction discrimination task and visually based equivalent noise tasks. The migraine group demonstrated increased baseline internal noise levels compared to the control group. Internal noise levels, and sampling, were reduced using hf-tRNS but not Sham stimulation. However, there were no differences in terms of coherence thresholds, slopes, and lapse rate for global motion discrimination between the two groups. This is the first demonstration of the possibility of decreasing internal noise levels in migraine using hf-tRNS. Future work could explore the possibility of neurostimulation as a therapy for migraine.

Keywords: Global motion perception, internal neural noise, sampling factor, neurostimulation, Sham control

Highlights

- Equivalent noise task allows estimation of internal noise in the visual system.
- Internal noise levels increased in migraine on motion-based perception task.
- Internal noise can be reduced by hf-tRNS.
- Possible application of hf-tRNS after research into stimulation protocols.

Introduction

Migraine has strong associations with sensory systems, especially vision. Around 80% of migraine aura is in the visual modality (Lipton et al., 2001). It has been argued that visual stimuli can also trigger migraine attacks (Kelman, 2007). Additionally, there are several reports of interictal differences in basic visual performance in migraine compared to control groups (for a review, see O'Hare and Hibbard, 2016). In particular, poorer performance on global motion tasks (McKendrick et al., 2004; Antal et al., 2005; Ditchfield et al., 2006; McKendrick et al., 2006; Webster et al., 2011a ; Shepherd et al., 2012; Tibber et al., 2014).

It has been suggested that internal noise could be the source of poorer performance on visual tasks in migraine (Wagner et al., 2010). Internal noise can be estimated using an equivalent noise task (Dakin et al., 2005). In order to achieve this, performance in two conditions is estimated: the zero-noise condition estimates the limit of observer performance in the absence of external noise, the high noise condition estimates the limit of the observer's performance under high external noise conditions. This technique is used to reduce the effect of other sources of response variability unrelated to the perceptual system, for example correspondence noise from the display (Barlow and Tripathy, 1997). Additionally, performance under high noise conditions can be used to estimate the sampling factor of the system. Sampling increases under high noise conditions as a strategy to stabilise estimates of motion direction (Allard and Cavanagh, 2011). Using regression analysis, Tibber and colleagues (Tibber et al., 2014) found both group (migraine and control) and sampling predicted performance on the global motion task. From this, the authors concluded that poorer performance in migraine on the motion coherence task is due to an inability to exclude external noise.

Shepherd and colleagues (2012) demonstrated poorer performance on a global motion task in the migraine compared to the control group, irrespective of contrast, density, and duration of the display. However, the addition of dynamic "twinkling" noise improved performance compared to static noise in the migraine group, whereas the difference between the dynamic and static noise conditions was negligible for the control group. This might be interpreted as evidence for stochastic resonance in those with migraine. Stochastic resonance is a process whereby the likelihood of detecting a subthreshold stimulus is increased by adding a small amount of noise to the system (Treviño et al., 2016). Stochastic resonance has been demonstrated in physical systems, but also in biological systems, and is thought to be the mode of action of high frequency transcranial random noise stimulation (hf-tRNS) (Ghin et al., 2018; Miniussi et al., 2013; Pavan et al., 2019; van der Groen et al., 2018; van der Groen and Wenderoth, 2016; Ward, 2009).

Transcranial random noise stimulation is thought to increase cortical excitation (Terney et al., 2008), and is thought to increase performance through stochastic resonance (Miniussi et al., 2013; Pavan et al., 2019; Ward, 2009), depending on initial levels of internal noise and the strength of the stimulus. Stochastic resonance depends on the specific relationship between the threshold for perception for a particular stimulus and the noise levels. The perception threshold relates to the action potentials of neurons. In general, a stimulus needs to be greater than a particular threshold level to be perceived – the input stimulus must excite the neurons sufficiently otherwise the action potential is not generated. However, in biological systems there is noise, for instance the spontaneous random firing of neurons (McDonnell and Ward, 2011). It may be the case that those with migraine have an excitable visual system (Aurora and Wilkinson, 2007) characterised by additional random firing of neurons unrelated to the stimulus, resulting in a small signal-to-noise ratio. If the stimulus level is very close to the perception threshold (but not quite over it) then the

spontaneous firing may increase the level to over the threshold and therefore the stimulus is perceived, even though it is a sub-threshold stimulus. Hf-tRNS stimulation can be used to increase the excitability of the cortex, increasing the spontaneous firing rate of the neurons. And so, although increasing the excitability through neurostimulation results in increased noise, this can paradoxically improve the perception of an otherwise subthreshold stimulus (Pavan et al., 2019; Miniussi et al., 2013; Ward, 2009). It has been suggested that stochastic facilitation may be a better term when referring to biological systems, as true stochastic resonance has a much narrower definition (McDonnell and Ward, 2011). However, as stochastic resonance in its broader sense is used widely (McDonnell and Ward, 2011), we will continue with this terminology here. Critically, adding a small amount of noise to the subthreshold stimulus can reduce the signal-to-noise ratio, increasing the neural gain of the system and increase performance (e.g., Hauser et al., 2016). Neural gain in the case of the logistic can be represented by the following equation, following Servan-Schreiber et al., (1990), see equation 1:

$$f_G(x) = \frac{1}{1 + e^{-(Gx+B)}}$$

Equation 1

Where $f_G(x)$ is the typical neural response to the input x, where x is between 0 and 1. The gain is represented by G. Servan-Schreiber et al., (1990) show mathematically how increases in G are proportional to changes in the signal to noise ratio. Importantly, Servan-Schreiber et al., (1990) make the point that increasing the gain G will not increase the maximum performance, merely change the threshold at which the best performance is reached.

There are several different possible stimulation parameters for tRNS, which are important to the efficacy of the neurostimulation (Moret et al., 2019). Previous research has shown hf-tRNS (100-640Hz) to have demonstrable facilitatory effects on behaviour with stimulation over motor (Terney et al., 2008; Moret et al., 2019), and visual areas (Campana et al., 2016; Fertonani et al., 2011). Specifically, in the case of equivalent noise tasks, high frequency tRNS has been shown to increase the sampling factor (Ghin et al., 2018). This is what would be expected with an increase of noise to the stimulus, a switch to increased pooling to stabilise the estimate of the direction of motion (Allard and Cavanagh, 2011). As there is a relationship between sampling and global motion task performance in those with migraine (Tibber et al., 2014), and there is evidence of potential stochastic resonance processes in those with migraine (Shepherd et al., 2012), this is worthy of investigation using neurostimulation. Here we conduct an equivalent noise (EN) task to see if hf-tRNS increases the sampling factor in the migraine group, and therefore improves performance on global motion tasks. In addition, we conducted a global motion task to replicate the previous results of (Shepherd et al., 2012).

Method

Participants

This research was conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki (2013), and was approved by the University of Lincoln, School of Psychology Research Ethics Committee (protocol number: PSY1718481). Participants were recruited from the students and staff of the University of Lincoln between July 2018 and August 2019. Written informed consent was obtained from all participants. Participants were screened for the general exclusion criteria to minimise any potential risk from hf-tRNS, including medical conditions such as epilepsy and acute eczema (Nitsche et

al., 2008). Sixteen individuals with migraine were recruited to the study, based on fulfilling the International Headache Society Diagnostic criteria (International Headache Society, 2018) according to self-report. 62.5% had a professional diagnosis, which is not unrepresentative of migraine in the general population (around 50% with professional diagnosis, McGregor et al., 2003). Those with headaches in the two days before the testing sessions were asked to reschedule the appointment, in the case of one observer with very frequent headaches this was not possible. This observer was excluded from the analysis. The median time since headache compared to first testing sessions was 14 days. One observer did not wish to report their age in the migraine group, therefore the mean age of the migraine group without this individual was 30.93 (SD = 10.85), 11 female, 4 male. The mean age of the control group was 31.7 (SD = 11.35), 12 female, 4 male. Characteristics of the migraine group can be seen in Table 1. The final sample consisted of 15 migraine and 16 control participants, based on sample size estimates conducted using G*Power, (Faul et al., 2007; Faul et al., 2009), based on the Equivalent Noise task combined with neurostimulation conducted by Ghin and colleagues (2018). Please see *Supplementary Information 1*.

Table 1. Characteristics of the migraine group.

Visual disturbances[1]	Professional Diagnosis[2]	Sex	Age[3]	Onset[4]	Freq[5]	Last[6]
Yes	No	Female	20	17	1-3	3
Yes	MA	Female	29	15	<1	7
Yes	MO	Female	23	7	1-3	14
Yes	No	Female	19	17	<1	140
Yes	M	Female	23	12	1-3	14
Yes	No	Female	57	40	1-3	84
Yes	MA	Female	-	30	<1	912.5
Yes	MO	Male	28	15	3-10	3
Yes	MA	Male	32	14-15	<1	14
Yes	M	Female	38	13	1-3	20
No	No	Male	44	16	1-3	140
Yes	MA	Female	39	4	1-3	10
Yes	M	Female	41	14	1-3	3
Yes	No	Male	25	14	<1	35

No	No	Female	26	14	1-3	14

[1]Answer to the question: "Do you experience visual disturbances during the attack?" [2]M = migraine, MA = migraine with aura, MO = migraine without aura, No = no diagnosis from a medical professional. [3]One participant did not wish to report their age. [4]Self-reported age at time of onset of migraine. [5]Estimated number of attacks per month (based on self-report). [6] Last migraine attack (based on self-report) in days. One of the participants reported a migraine attack in the last 20 hours due to very frequent migraine attacks and was excluded from data analysis. None of the participants reported a migraine attack in the 3 days after testing, established at follow-up.

Auxiliary screening measures

Auxiliary measures were used to assess the participant's vision and clinical characteristics. All observers had normal or corrected-to-normal vision (>20/30, criterion as Wagner et al., 2012), verified using the 8AFC version of the Landolt-C test in the Freiburg Acuity Test (FrACT) (Bach, 1996; 2007).

An adapted version of the Pattern Glare Test (Wilkins and Evans, 2001) was administered to investigate visual discomfort in response to a series of striped patterns (see Figure 1). The participants rated on a 5-point Likert Scale whether they saw movement, bending, colours, blurring, shimmer, flicker, fading, shadowy shapes and were asked if they experienced anything else. For further details, please see *Supplementary Information 2*.

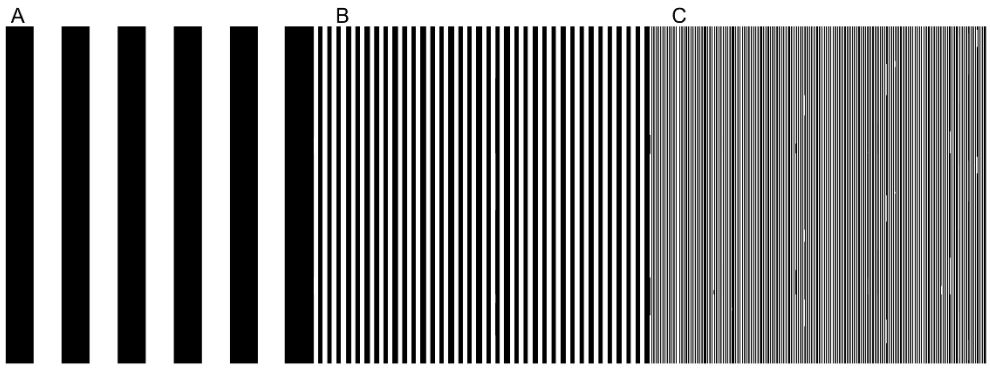

Figure 1. The square wave gratings used to estimate susceptibility to visual discomfort, with spatial frequencies of (A) 0.5 c/deg, (B) 3.0 c/deg, and (C) 12.0 c/deg.

Apparatus

The experiment took place in a darkened room. Stimuli were presented on a 20-inch HP p1230 monitor with a refresh rate of 85 Hz. The display resolution was 1280 x 1024 pixels, with each pixel subtending approximately 1.6 arcmin. The minimum and maximum luminance values of the screen were 0.08 and 74.6 cd/m^2 respectively, and the mean luminance was 37.5 cd/m^2. A gamma-corrected lookup table (LUT) was used so that luminance was a linear function of the digital representation of the image. The tasks were presented to the participant at a viewing distance of 57 cm.

Stimuli

Stimuli were created and presented using MATLAB (The Mathworks, Natick) and the Psychtoolbox extensions (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007). Stimuli were global motion random dot kinematograms (RDKs) made up by 150 white dots (diameter: 0.12 deg) presented within a circular aperture (diameter: 8 deg; density: 2.98 dots/deg^2). The luminance of all dots was set to 74.6 cd/m^2 (Weber contrast: 0.99) and moved on a grey background (mean luminance). For complete details of the stimuli design, please see *Supplementary Information 3*.

For all three motion tasks, a black fixation point (diameter 0.3 deg) was always present in the centre of the screen. Figure 2 shows a schematic representation of the global motion task and the Equivalent Noise task.

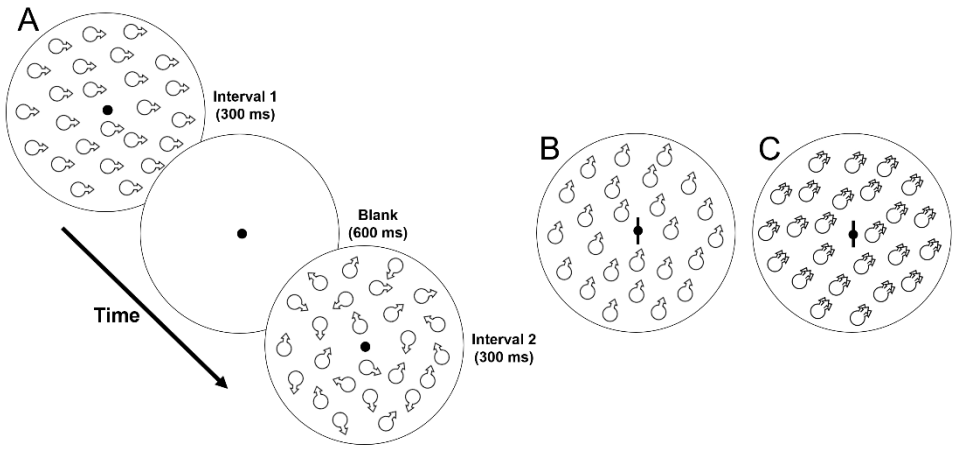

Figure 2: Schematic representation of stimuli and procedures. A: motion coherence task, consisting of two intervals of 300 ms each, with a 600 ms break between them. B: Internal noise task of the equivalent noise procedure, consisting of one interval only. All elements move in a coherent direction, either to the left or right of vertical. The angle of the motion with respect to vertical is reduced increasing the difficulty of the task. This finds the minimum angle that can be detected by the observer with no external noise. C: Sampling task of the equivalent noise procedure, consisting of one interval only. The average direction of motion is always 45 degrees either to the left or to the right (in the example only the right part is shown), however the standard deviation of the trajectory of the elements (represented here by the small arrows) is increased to increase difficulty of the task. This finds the maximum performance of the observer under high external noise conditions.

Stimulation technique

Stimulation was delivered by a battery driven stimulator (BrainSTIM, EMS; http://www.brainstim.it/index.php?lang=en) through a pair of saline–soaked sponge electrodes. To carry out the stimulation, BrainSTIM v1.0 was used. Bilateral stimulation over the temporal-occipital poles was administered. For details see *Supplementary Information 4*. The hf-tRNS consisted of an alternating current delivered at 1.5 mA with zero offset and applied with random frequencies ranging from 100 to 600 Hz (Ghin et al., 2018). The most appropriate intensity varies with the type of stimulus and task demands, as well as the stimulated area (van der Groen and Wenderoth, 2016; van der Groen et al., 2018). Previous

work has shown that 1.5mA can elicit the strongest effects on motion direction discrimination compared to lower stimulation levels (e.g., Pavan et al., 2019), whilst being well within current density safety parameters, given the size of the electrodes. The noise stimulation is full band coloured noise (BrainSTIM Transcranial Stimulator Operating Manual). In the experimental session participants received 20 minutes of hf-tRNS, which was delivered during the experimental task (online stimulation). During the Sham condition participants received 30 seconds of stimulation.

Procedure

All participants (migraine = 15, controls = 16) carried out all 3 motion tasks in both Sham and hf-tRNS conditions. The order of the three motion tasks was counterbalanced between participants, but each participant completed the motion tasks in the same order for both the stimulation and Sham conditions. Head movements were stabilised with a chinrest, and the main experiment took place in a darkened room. Participants took part in two sessions on separate days lasting around one and a half hours each. Participants completed the auxiliary measures. After this, the training tasks were carried out to make sure the participants understood the tasks.

The main experiment consisted of three different motion tasks. The first estimated motion coherence, the second and third tasks were devised to estimate *internal noise* and *sampling factor* for the *Equivalent Noise* analysis.

Coherence Threshold

An initial training block consisting of 20 trials was used to familiarise the participants with the stimuli and task. In the training block one of the two presented RDK had always a motion coherence of 100% and was presented either in the first or second temporal interval.

For the main motion coherence task, RDKs were presented twice for 300 ms each with a short interval of 600 ms between them (Figure 2A). In one of the intervals, the dots would move coherently either to the left, or to the right, in the other, dots would not show coherent motion (noise). The task of the observer was a two-interval forced-choice (2IFC) procedure to indicate whether the first or second interval contained the coherent motion using the keys "K" to indicate the first temporal interval, and "M" to indicate the second temporal interval, on a standard UK computer keyboard. An Updated Maximum-Likelihood (UML) staircase procedure was used with a 1 up – 2 down rule to estimate participants' parameters of the psychometric function (Shen and Richards, 2012; Shen et al., 2015). In this case the threshold corresponds to a coherence level for which participants were at 70.7% correct performance. For further details of the UML procedure, please see *Supplementary Information 5*.

Equivalent Noise Analysis

The aim of the two additional motion tasks was to investigate the neural mechanisms involved in global motion processing modulated by online hf-tRNS in migraine and control participants. To this purpose we implemented the same EN paradigm used in Ghin and colleagues (2018). In an EN paradigm, directions are drawn from a circular Gaussian distribution of dot directions, having a specific mean direction and standard deviation. In this case, all dots are signal dots, but directional noise can be achieved by increasing the standard deviation. Consequently, higher motion sensitivity depends on the ability to integrate all dot directions (Dakin et al., 2005; Tibber et al., 2014; Ghin et al., 2018). There are two necessary points of performance to estimate the Equivalent Noise, high- and zero-noise (Dakin et al., 2005).

In the zero-noise condition (Figure 2B), a simple 1 up – 1 down staircase tracked the minimum directional offset from the vertical direction that was perceivable in the complete absence of directional noise (all the dots had the same direction – 100% coherence). In the high-noise condition (Figure 2C), a 1 up – 2 down staircase with constant mean direction (either 45° clockwise or 45° counter-clockwise) tracked the standard deviation of the circular Gaussian distribution of directions that produced a direction discrimination performance of 70.7%. In both conditions, a vertical reference was provided at fixation, by means of a black vertical line (4 deg length, 0.1 deg width) crossing the fixation point.

For further details of the EN task and analysis, please see *Supplementary Information 6*. As a general caveat, it is worth noting that the EN task and analysis are the same as (Ghin et al., 2018).

Follow-up

One week after the final session of the study, participants were contacted via email. One participant reported a non-migraine headache the evening after the testing session. Three participants reported headache; however, this was at least 2 days after the testing session. One of the headaches was following the hf-tRNS session, the other two were following the Sham session.

Results

Auxiliary Screening Measures

There was no statistically significant difference in acuity between the two groups (t_{28} = -1.55, p = 0.17). There was an increased discomfort score for the 0.5 c/deg control pattern for the migraine group (t_{28} = 2.45, p = 0.021, Cohen's d = 0.89). There was a marginal (but non-significant) increased discomfort score for the 3.0 c/deg pattern for migraine compared

to controls (t_{28} = 2.02, p = 0.053, Cohen's d = 0.74). There was no difference between migraine and control for the 12.0 c/deg control pattern (t_{28} = 1.77, p = 0.088, Cohen's d = 0.65).

Motion Coherence task

Figure 3 shows mean coherence thresholds, slopes, and lapse rate of the global motion coherence task for migraine and control participants and for the two stimulation conditions. Where residuals were not normally distributed (Shapiro-Wilk test), data were analyzed using the aligned rank transform for non-parametric factorial analysis (Wobbrock et al., 2011). See *Supplementary Information 7* for further details and results of the normality tests. The analysis was performed using *R* (v4.0.2) in RStudio (v1.3.1073) (R Core Team, 2020). After the rank assignment, we performed a mixed effects model using the *lme4* package for *R* (Bates et al., 2015) with Group (i.e., Migraine vs. Controls) as between-subjects factor, and Stimulation Type (Sham vs. hf-tRNS) as within-subjects factor, and with random intercept across subjects.

For thresholds, the analysis did not report any significant main effect or interaction: Group ($F_{1, 28}$ = 0.34, p = 0.56, d = 0.22), Stimulation Type ($F_{1, 28}$ = 0.018, p = 0.89, d = 0.05), interaction between Group and Stimulation Type ($F_{1, 28}$ = 0.006, p = 0.94, d = 0.03).

For slopes, there was no significant main effect or interaction: Group ($F_{1, 28}$ = 0.03, p = 0.85, d = 0.07), Stimulation Type ($F_{1, 28}$ = 1.98, p = 0.17, d = 0.52), interaction between Group and Stimulation Type ($F_{1, 28}$ = 1.29, p = 0.26, d = 0.42).

For the lapse rate, there was no significant main effect or interaction: Group ($F_{1, 28}$ = 0.67, p = 0.42, d = 0.30), Stimulation Type ($F_{1, 28}$ = 0.11, p = 0.74, d = 0.12), interaction between Group and Stimulation Type ($F_{1, 28}$ = 2.43, p = 0.13, d = 0.58).

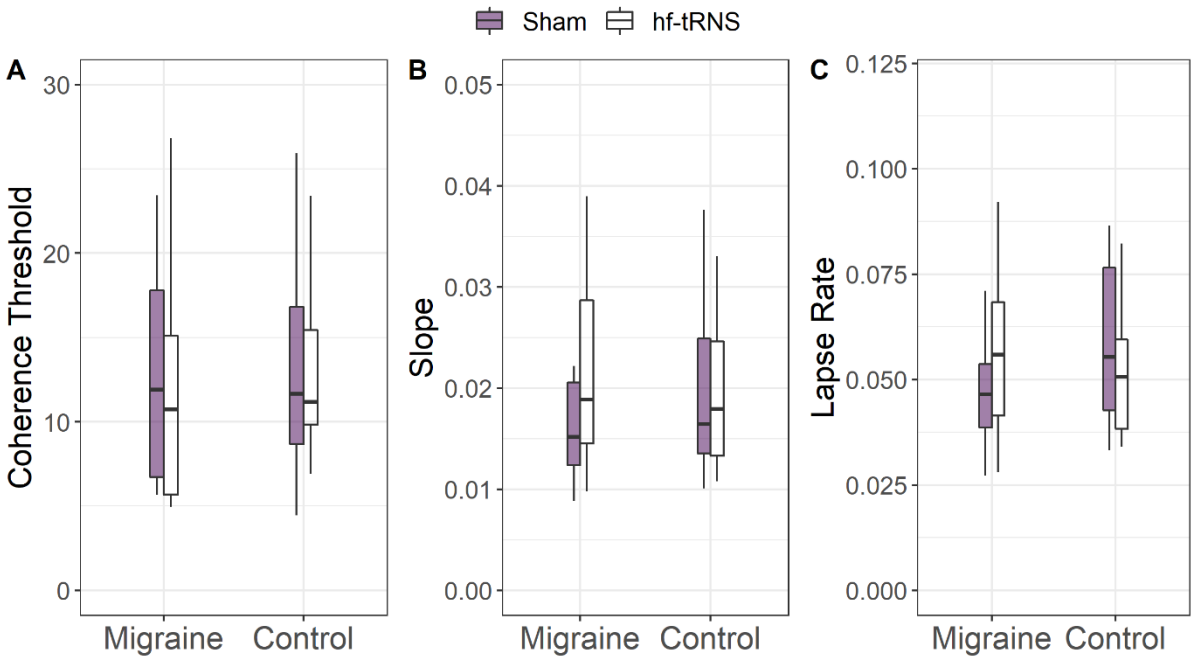

Figure 3. Boxplots of motion coherence threshold (A), slope (B) and lapse rate (C) for each stimulation condition (Sham and hf-tRNS) and for the two groups (migraineurs and controls). For each boxplot, the horizontal thick black line indicates the median, the lower and upper hinges correspond to the first and third quartiles (i.e., the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR of the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge.

Equivalent Noise Analysis

Figure 4 shows the result of the *Equivalent Noise* analysis. Data were analysed using a Generalised Linear Model (GLM) (Fox, 2003). A GLM was used to analyse *internal noise* and *sampling factor* estimated with the EN analysis and weighted for their uncertainty values, as reported in (Ghin et al., 2018). See *Supplementary Information 7* for further details about the GLM analysis.

For *internal noise*, Group (migraine vs. control participants), Stimulation Type (hf-tRNS vs. Sham), and interaction between Group and Stimulation Type were the predictors.

The regression analysis reported a significant effect of the Group (χ^2 = 24.7, *df* = 1, *p* < 0.0001, η^2 = 0.80), a significant effect of the Stimulation Type (χ^2 = 35.17, *df* = 1, *p* < 0.0001, η^2 = 0.99), but not a significant interaction between Group and Stimulation Type (χ^2 = 1.26, *df* = 1, *p* = 0.26, η^2 = 0.04). In general, controls exhibited lower *internal noise* than migraineurs, and hf-tRNS had the effect of reducing *internal noise* in both groups (Figure 4A). Table 2 reports the coefficients of the regression analysis.

Table 2. Estimated coefficients of the GLM fitted on *internal noise* data with weights. Standard error, *t*- and *p*-values for model intercept, Group, Stimulation, and Group x Stimulation predictors are reported.

Predictors	**Estimate**	**Std. Error**	***t-value***	**Pr(>| *t* |)**
(Intercept)	0.13	0.03	4.35	<0.0001
Group	0.23	0.056	3.93	0.00023
Stimulation	0.30	0.06	4.97	<0.0001
Group * Stimulation	0.12	0.104	1.13	0.263

Though the interaction was not significant and given the main effect of the Group, we performed the same regression analysis separately for migraine and control participants in order to test the effects of hf-tRNS on *internal noise*. For both groups there was a significant effect of the stimulation (χ^2 = 17.37, *df* = 1, *p* < 0.0001, η^2 = 0.56; χ^2 = 18.97, *df* = 1, *p* < 0.0001, η^2 = 0.61, for control and migraine participants, respectively). The same analysis was conducted separately for the two stimulation conditions (Sham and hf-tRNS) in order to test for differences in terms of *internal noise* between migraine and control participants in the two stimulation conditions. The regression analysis reported a significant difference between migraine and control participants in both stimulation conditions (χ^2 = 10.34, *df* = 1, *p* =

0.0013, $\eta^2 = 0.33$; $\chi^2 = 18.78$, $df = 1$, $p < 0.0001$, $\eta^2 = 0.61$, for Sham and hf-tRNS, respectively).

For the *sampling factor* (Figure 4B) we used the same GLM model as for the *internal noise*. The regression analysis only showed a significant effect of the Stimulation Type ($\chi^2 = 6.65$, $df = 1$, $p = 0.0099$, $\eta^2 = 0.21$), not an effect of the Group ($\chi^2 = 2.03$, $df = 1$, $p = 0.15$, $\eta^2 = 0.66$) or a significant interaction between Group and Stimulation Type ($\chi^2 = 0.089$, $df = 1$, $p = 0.765$, $\eta^2 = 0.09$). For the stimulation type, a post-hoc comparison showed that hf-tRNS reduced the *sampling factor* with respect to the Sham condition (Sham: 5.74 dots, SE: 0.37; hf-tRNS: 4.43, SE: 0.33). These results suggest that there is no difference between migraine and control participants in terms of *sampling factor*. Table 3 reports the coefficients of the regression analysis.

Table 3. Estimated coefficients of the GLM fitted on *sampling* data with weights. Standard error, *t*- and *p*-values for model intercept, Group, Stimulation, and Group x Stimulation predictors are reported.

Predictors	**Estimate**	**Std. Error**	***t-value***	**Pr(>| *t* |)**
(Intercept)	4.15	0.46	9.05	< 0.0001
Group	0.58	0.66	0.87	0.39
Stimulation	1.16	0.68	1.69	0.069
Group * Stimulation	0.297	0.99	0.298	0.77

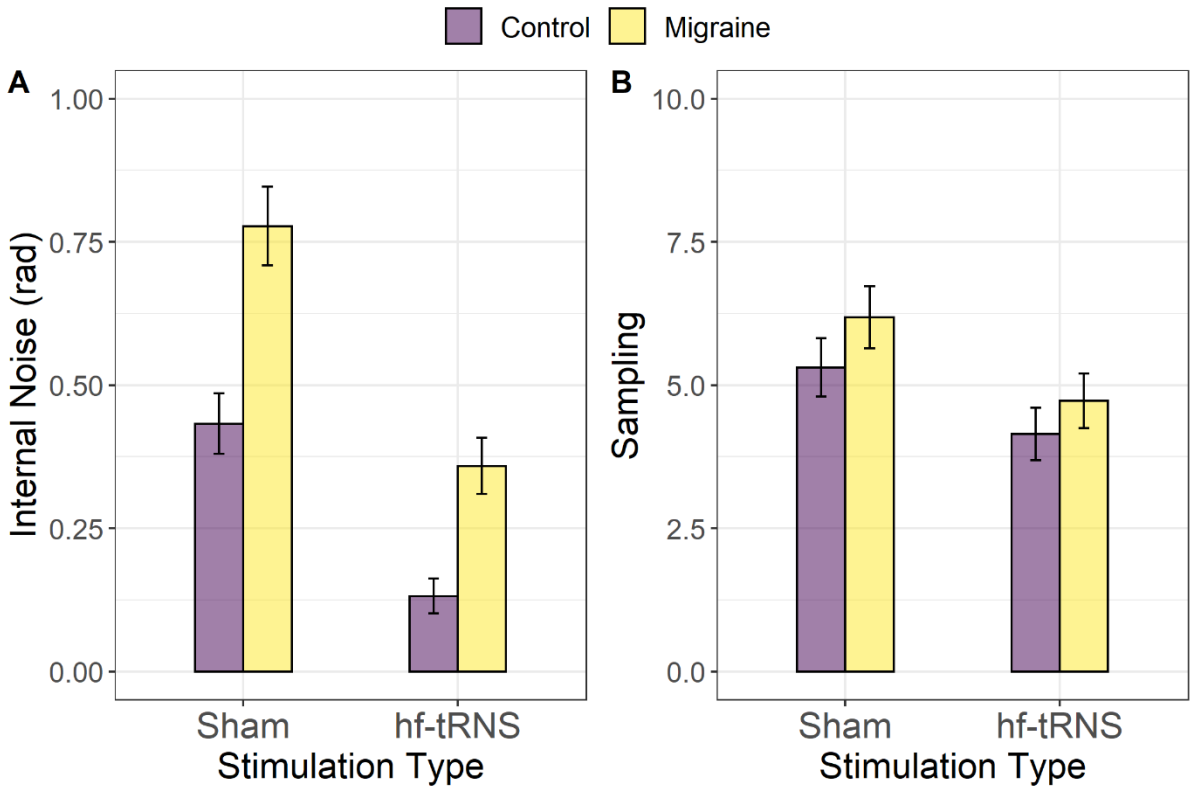

Figure 4. Results of the equivalent noise analysis. The mean values and standard errors correspond to the output of the regression analysis with weights. (A) *Internal noise* estimates (in radians) for migraine and control participants and for Sham and hf-tRNS conditions. (B) *Sampling* estimates for migraine and control participants and for Sham and hf-tRNS. Error bars ±SE.

Discussion

This research is the first to investigate motion processing in combination with hf-tRNS in those with migraine, in order investigate the underlying mechanisms of both internal noise and sampling factor using an equivalent noise task. To limit the effect of bias, placebo control was used (Sham condition), and also a control group comparison (matched for age and gender as far as possible). Linear mixed effects models and generalized linear models

were used to analyse the data, as these can better account for individual variability compared to traditional ANOVA procedures (Kristensen and Hansen, 2004).

In line with published literature, the migraine group showed increased visual discomfort compared to the control group (Marcus and Soso, 1989; Harle et al., 2006; Shepherd, 2000). All participants met the required criterion for normal visual acuity, using the FRACT test. This is a reasonable, portable measure of visual acuity, showing good agreement with other estimates (Bach, 1996; 2007).

In contrast to previous research, there was no difference in the basic motion coherence thresholds between the migraine and control group, which is unusual as this been a relatively robust finding (McKendrick et al., 2004; Antal et al., 2005; Ditchfield et al., 2006; McKendrick et al., 2006; Webster et al., 2011a ; Shepherd et al., 2012; Tibber et al., 2014). There are slight methodological differences in the exact staircase procedure used, it has been suggested that UML used in the current study could provide a more reliable estimation of the parameters (Shen and Richards, 2011; Shen et al., 2015) (see *Supplementary Information 5* for a discussion). Finally, it is possible authors who do not replicate the motion coherence deficit simply do not report it, and therefore the picture is less coherent than it might seem (Fanelli, 2012).

We found increased internal noise estimates in the migraine group compared to the control group. Other studies using different methodologies have also found internal noise estimates to be larger in those with migraine in contrast (Wagner et al., 2010; Webster et al., 2011b) and shape processing tasks (Webster et al., 2011b; Wagner et al., 2013). However, on motion-based tasks, previous work has found no differences in internal noise estimates between migraine and control groups (Webster et al., 2011a; Tibber et al., 2014).

One possible cause of the difference in results is the inclusion of subtypes of migraine. Previous work (e.g., Webster et al., 2011a; Tibber et al., 2014) combined MA and

MO groups, as there was no statistically significant difference between the groups. However, as there were non-significant trends towards greater internal noise estimates in the migraine group, it is possible that combining the two groups masked a potential effect specific to MA. The majority in the current study reported visual disturbances around the time of the attack, although not all of them had a professional diagnosis, as is typically the case in migraine (Dowson and Jagger, 1999; McGregor et al., 2003). Although clinical interview is best practice for diagnosing migraine, self-administered questionnaires based on the International Headache Society criteria are an effective method of identifying those with migraine (Samaan et al., 2010).

The exact stimuli used in the various studies could be a reason for the mixed findings. As stochastic resonance depends on a particular set of conditions, specifically signal strength combined with response threshold, the required level of accuracy could potentially be a very important experimental parameter. Previous work (Tibber et al., 2014) required a different level of accuracy from participants (82%) compared to the 70% threshold required in the current study. It is not yet clear if the phenomenon of stochastic resonance can explain the effects, but there is tentative evidence for stochastic resonance effects in those with migraine (Shepherd et al., 2012). It is also worth noting that (Tibber et al., 2014) showed a non-significant trend (when corrected for multiple comparisons, critical p-value 0.0167) towards increased internal noise estimates in the migraine group on a motion-based task ($t(33.02) = -2.33$, $p = 0.03$, Cohen's $d = 0.02$).

We found that high frequency tRNS reduced internal noise estimates in both groups. Adding a small "boost" to the signal through hf-tRNS may have been sufficient to reach threshold firing for the cells and therefore increase the likelihood of a response (stochastic resonance). As the migraine group showed a higher baseline internal noise level than the

control group, it is possible that hf-tRNS could be used to boost the probability of a response, and so mitigate the effects of the baseline internal noise level in this group.

Internal noise could be the result of more variable neural firing (Tolhurst et al., 1981), which has been associated with hyperexcitability in those with migraine (Wagner et al., 2010). However, it has been debated whether neuronal variability is the source of internal noise (Hartmann et al., 2015).

In the current study, there was no main effect of group on sampling, as in previous research (Tibber et al., 2014). However, high frequency tRNS reduced sampling in both migraine and control groups. Allard and Cavanagh (2011) suggested that pooling motion signals over a larger area is a strategy to mitigate the effects of noisier signals. Previous research (Ghin et al., 2018) has also demonstrated that hf-tRNS is able to modulate sampling, although this study demonstrated an increase of sampling after hf-tRNS. It is possible that hf-tRNS affects the global pooling strategy, but the exact direction may depend on the specific effect of stochastic resonance. The effects of stochastic resonance depend on *both* the levels of internal noise and task threshold - the level of internal noise must be just sufficient to raise the performance above threshold in order to see the effect of stochastic resonance. Too much and there will be a detrimental effect of noise, too little and this will be insufficient to affect performance as the level will still be below threshold. In addition, any changes in threshold will also affect the balance – the optimum level of noise is relative to the task threshold. Depending on the relative levels of internal noise and task threshold, the added hf-tRNS may act either to decrease performance or to have a paradoxical beneficial effect, however, it should be highlighted that the two-point version of the equivalent noise task (zero and high noise) has been used effectively previously (Tibber et al., 2014; Ghin et al., 2018; Pavan et al., 2019). However, in order to see the full stochastic resonance effect, it would be beneficial to estimate performance using several levels of noise, rather than just the two points, as this

will allow us to see the classic "dipper" shape (e.g., Vilidaite and Baker, 2017). It is possible that this may highlight an interaction effect between the migraine and control group in the current study. As this would make the experiment much longer, there are ethical implications of performing this as a neurostimulation experiment, however, this could be conducted in future in a purely behavioural experiment.

Motion coherence thresholds have shown robust deficits in those with migraine compared to controls in the past (e.g., McKendrick et al., 2004; Antal et al., 2005; Ditchfield et al., 2006; McKendrick et al., 2006; Webster et al., 2011a; Shepherd et al., 2012; Tibber et al., 2014). Motion coherence thresholds have also been used as a paradigm to show the effects of hf-tRNS over the visual areas (e.g., Pavan et al., 2019). The current study showed there was no difference in motion coherence thresholds, slopes and lapse rate between the migraine and control groups with or without hf-tRNS stimulation. Previous research has shown differences in performance on equivalent noise tasks specifically using hf-tRNS (Ghin et al., 2018; Pavan et al., 2019). Motion-based equivalent noise tasks have previously shown a non-significant trend towards differences in migraine and control groups (Tibber et al., 2014). The equivalent noise task in the current study did show an effect of hf-tRNS, but this was in both groups. Therefore, a better method for future studies into hf-tRNS in migraine may be to use the equivalent noise tasks, rather than traditional motion coherence thresholds. It is possible that stronger effects may be seen of hf-tRNS with repeated stimulation sessions, for example, Moret et al. (2018) showed improvement in those with amblyopia using repeated hf-tRNS sessions. As this is one of the first studies to investigate the possibility of hf-tRNS stimulation improving performance on equivalent noise tasks in those with migraine, there is much that remains for future research.

Limitations

The sample size of the current study was relatively small in comparison to other techniques, however sample sizes in neurostimulation studies tend to be around this number (e.g., Ghin et al., 2018; Moret et al., 2019; Pavan et al., 2019). Previous work by Pavan et al., (2019) comparing Sham vs hf-tRNS at 1.5mA, for performance on a motion discrimination task, showing effect size r = 0.59, meaning an achieved power of 0.96. Power analysis using G*Power (Faul et al., 2007; Faul et al., 2009) based on the effect sizes reported by Pavan et al. (2019) for 1.5mA hf-tRNS stimulation on a motion discrimination task showed that 7 observers would be sufficient. Based on the Equivalent Noise task (Ghin et al., 2018), power analysis indicated that our current sample of 15 would be sufficient to show effects of hf-tRNS. However, it should be acknowledged that migraine may represent a more diverse population and so this may not apply. Additionally, there was only a single migraine group, combining subtypes. Several studies into visual perception have shown no difference between the two main migraine subtypes, i.e., those with and without migraine aura (e.g., McKendrick and Badcock, 2004; McKendrick et al., 2006). Importantly, this includes the previous work on equivalent noise in those with migraine (Tibber et al., 2014). However, other researchers have suggested that migraine with and without aura are separate disorders, and so should be considered separately (Russell et al., 1996), although this has been debated (e.g., Blau, 1995). Future studies may separate migraine participants with and without aura.

Another limitation is that several participants did not have a clinical diagnosis. It is common for those with migraine not to seek a clinical diagnosis (Lipton et al., 2001; MacGregor et al., 2003; Vetvik and McGregor, 2017; Song et al., 2019), despite evidence showing the impact of headache to be similar for those with and without a formal diagnosis (Oliveria et al., 2011). It might be the case that by recruiting from a specialist headache clinic, more severe cases of migraine would show differences. However, this group may not be representative of the majority with migraine, which was the focus of the current study.

One individual in the current study had also reported a long time interval since their last attack, potentially raising the question of remission from their episodic migraine. The International Headache Society does not list a time-limit to define a period of remission from episodic migraine (IHS 2018). Dent et al. (2011) reported on average 18.4 attacks per year, with a standard deviation of 47.4, meaning there were some participants experiencing less than one attack per year. It is possible that this individual was in remission from migraine. Indeed, as there was no long-term follow-up, any of the participants could potentially be in remission, and this cannot be known. However, as are several environmental factors that can precipitate migraine (e.g., Hauge et al., 2011; Petrouka et al., 2014), it is also possible that these have reduced, rather than any change in the state of the brain.

As well as migraine subtype, professional diagnosis, and time since last attack, the migraine group were also heterogeneous in several other aspects, including the number of years experiencing migraine, headache frequency, and migraine triggers. Although this is not uncommon in migraine research (e.g., Stewart et al., 1994; Dowson, 2001) it must be considered when drawing conclusions. Ideally, a large-scale, longitudinal study such as the work by Shepherd (2020) would be required to capture these differences in the migraine population and draw firmer conclusions. As a proof-of-concept study, this was beyond the scope of the current research, but would be very beneficial in future work.

Conclusion

To conclude, internal noise estimates on a motion-based task were found to be higher in those with migraine compared to control groups. Estimates of internal noise and sampling could be reduced using high-frequency transcranial random noise stimulation. With the right

stimulation protocol and training, neurostimulation could potentially be therapeutic, however more research is needed into clinical outcomes.

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

Raw Data

Raw data can be found at the Open Science Framework:

https://osf.io/vjrey/?view_only=09ee4009b7174302a329df3b20c76c8f

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