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## Transcranial magnetic stimulation for migraine: clinical effects

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**Abstract** The objective was to assess the impact of transcranial magnetic stimulation (TMS) on pain and the autonomic nervous system (ANS) in migraine. Forty-two people [mean age  $41.43 \pm 11.69$  (SD) years, 36 females] were randomised into high vs. low TMS stimulation groups and received 2 brief pulses of TMS. Thirty-three (33/42) individuals had heart-rate variability assessed, before and after stimulation. No group effects were found. Pain decreased by 75%; 32% of people after 1 treatment reported no headache after 24 h. Mean heart rate decreased from  $79.05 \pm 10.27$  to  $72.89 \pm 11.35$

beats/min. The low-frequency (LF) and the high-frequency (HF) areas derived from power spectral analyses increased [mean  $6522 \pm 1277$  to  $8315 \pm 1009$  beats/min<sup>2</sup> (LF) ( $p=0.001$ ) and mean  $5600 \pm 1568$  to  $8755 \pm 3071$  beats/min<sup>2</sup> (HF) ( $p=0.001$ )]. The LF:HF ratio decreased from mean  $1.31 \pm 0.51$  to  $1.13 \pm 0.48$  (NS). TMS produces immediate, sustained reductions in pain and modification of the ANS.

**Keywords** Migraine • Transcranial magnetic stimulation • Pain

### Introduction

Burden of illness and patient satisfaction reports in migraine headache show that current treatment regimes are incomplete [1, 2]. The main patient concerns are that (a) relief of pain is not immediate or sustained, (b) potential drug side effects are worrisome, and (c) the frequency of headache recurrence is not abolished or significantly diminished. As at least 10% of the population worldwide suffers from migraine headache, the impact of these problems is significant [3]. More effective treatment regimes and a complete understanding of the pathophysiology of migraine are needed.

Controversial theories about the cause and mechanisms of migraine range from experiments that show

impaired brain energy metabolism [4], autonomic nervous system (ANS) hypofunction [5, 6], brain cell hyperexcitability to low intracellular brain magnesium [7–15]. Once considered solely a vascular event, current research supports a combination of both neural and vascular causes [16–20]. Many studies report the biochemical reaction and clinical effects of medications in migraine [21].

Despite considerable study, a unified theory of the pathophysiology of migraine does not exist. The most current cortical depression theories argue that the spreading depression of Leão is related to glutamate changes within the brain. This mechanism may not apply to all forms of migraine, and studies of cortical excitability of migraine done between migraine attacks yield conflicting results concerning the hypo- and hyperexcitability of the cortex [22–33]. Because

both pharmacological and non-pharmacological treatment interventions only partly address patient concerns, a novel treatment method using single-pulse transcranial magnetic stimulation (TMS) was evaluated.

### Justification for the application of TMS

TMS involves the application of a large brief current that is passed through an insulated coil placed on the scalp. The current sets up a magnetic field that penetrates the skull producing a secondary current that stimulates the cerebral cortex as well as trigeminal nerve fibres. This secondary current alters the cortical excitability.

Theoretical mechanisms of the relationship between migraine headache with aura and TMS are that just before the headache begins, brain cells become overly active and form a wave of increased neuronal activity. The travelling wave of hyperactive cells spreads across the cortex followed by an area of depressed neuronal activity. The effect of this process may be the occurrence of an aura, pain, sensory changes in the face and/or limbs, and/or nausea and dizziness, through activation of the trigeminal-vascular system and the trigeminal-cervical complex [34]. It is hypothesised that if very short pulses (1 ms) of TMS are applied to the scalp just as the headache begins, these pulses stop the travelling wave of hyperactive brain cells and subsequent neuronal depression. The headache either stops or it is less severe. Repeated applications may result in a decrease in headache frequency or complete cessation of headache.

Safety data indicate that single-pulse transcranial stimulation is a safe, useful tool for investigating neurophysiological mechanisms in human studies. No adverse side effects with single-pulse stimulation have been reported [35, 36].

We report the results of a study to assess the efficacy of TMS on pain intensity and heart-rate variability (HRV) in individuals with migraine headache.

This project was approved by the Research Ethics Committee of the Hamilton Health Sciences Centre, Hamilton, Ontario, Canada. An information package was provided and informed consent was obtained from all participants, and the study adhered to the principles established in Helsinki.

### Patients and methods

#### Sample

Eighty (80) people from the community-at-large were screened for admission to the study. All individuals had been previously diagnosed with migraine and were re-assessed at intake.

Forty-two (42) individuals with migraine (ICHD-II classification) met the inclusion criteria [37]. One of the criterion was that individuals must live and/or work within 30 min of our laboratory. This factor was important because it was necessary to apply the stimulation as soon as possible. Exclusion criteria were metal in the cranium, cardiac/neuro pacemakers, previous seizure activity, neurosurgery or head injury. Ten (10) people had migraine with aura, 25 without aura and 6 had headache with migraine components. The average headache duration was  $8.84 \pm 14.65$  (SD) h. Headache pain persisted, on average, from 20 min to 10 days. The shortest episode was 10 min and the longest 31 days. Headache frequency ranged from 1/day to 4/year. In 25 patients precipitating factors were unknown. In the remaining patients (n=17), hormonal changes (n=6), stress (n=2), head injury (n=3) and food sensitivities (n=2) were thought to be precipitating factors for migraine. Fourteen people reported onset of headache in the morning, 11 people reported the afternoon as time of occurrence and 17 were unable to define a pattern of onset. Patients (mean age of  $41.42 \pm 11.69$  years, 36/42 females) were randomised into either the high stimulation (50% of the maximum output) or low stimulation (30% maximum output) group. Of those individuals who received stimulation, five people had an aura and three of the five had pain with an aura. There were 19 complaints of pain in the temporal region, 24 in the occipital area and 8 in the frontal area of the brain. Nine out of 51 complaints were in more than one area. Other signs and symptoms were nausea, double vision, photophobia, aura and dizziness. Headache diaries were kept pre- and post-stimulation. There were no restrictions on medications, which consisted of analgesics, narcotics, antiemetics and/or sedatives.

#### Measurements

##### *Stimulation parameters*

TMS was applied using a Caldwell Stimulator, model #MES-10. The stimulator was programmed to deliver a pulse of 70  $\mu$ sec width. The coil radius was 9.5 cm. Peak induced voltage was 187 V. The magnetic intensity in the middle of the coil was 2.3 T. TMS was applied as soon as possible on arrival in the laboratory. Each person received two brief pulses, 5 s apart, over the area of perceived pain or over the area of the brain generating the aura. Patients and examiners were blinded as to the intensity of the stimulation (high vs. low). Forty-two people received 1 trial, 22/42 had 2 trials and 11/42 people had 3 trials. No person received more than 3 impulses of TMS at any given time. Repeat trials remained at the initial stimulation intensities. Follow-up calls were made to individuals 24 h after stimulation.

##### *Pain and suffering measures*

Pain intensity was measured using a 5-point Likert-type scale in which 5 was the worst response. Pain levels were recorded pre-stimulation, and at post-stimulation at 5-min intervals for 20 min. Suffering was assessed using the Measuring and Assessing Suffering Questionnaire (MASQ) on intake to identify the suffering component [38].

##### *Heart-rate variability measures*

Thirty-three (33/42) individuals were assessed for ANS effects using HRV measures. Nine people who were part of the pilot

study were not assessed for HRV. HRV was measured 5 min before stimulation and for 20 min post-stimulation. The HRV signal was computed from the electrocardiogram (ECG) and subjected to spectral analyses. Areas under the low-frequency (LF) and high-frequency (HF) components of the HRV were determined and a ratio of the powers (LF:HF area) was calculated.

#### Signal processing of heart rate variability

Processing the HRV was done as follows. A continuous ECG signal was obtained from the lead II electrodes, amplified and sampled at 500 times/s and stored on a hard disk [39]. The stimulation did not generate any ectopic beats. Off-line analysis of the power spectra of the heart rate (HR) was performed. Following QRS detection, the HR signals of 128 s were interpolated using linear interpolation every 0.5 s. The re-sampled HRV signal was passed through a 4th-order high-pass IIR filter with a cut-off frequency of 0.02 Hz to remove the very low frequency components. Subsequently, an 11th-order autoregressive model was fitted to the signal and power spectra were computed using the autoregressive modelling method. Following normalisation, percentage areas in the LF band and the HF band were computed. The LF band was from 0.02 to 0.15 Hz while the HF band extended from 0.15 to 0.4 Hz. The LF band is predominantly sympathetic and the HF band is vagally modulated [40]. A ratio of the LF:HF ratio was computed before and after stimulation. All results are expressed as mean $\pm$ SD.

#### Statistical analyses

Analyses of variance techniques were applied to determine whether there were differences between the high- and low-stimulation groups. A repeated measures of covariance design was used to assess the mean difference in a Likert scale pain "score". The 4 paired observations for each study participant high vs. low (minute 5, 10, 15, 20) could effectively use each subject as his/her own control. A further specification (that of a covariate which remained constant across trials) was used to adjust for pre-intervention pain. The repeated measures ANOVA also originally included a between-subjects grouping factor of stimulation group (high vs. low intensity). The mean HR and indices derived from the power spectrum of the HRV were subjected to Student's t-test to determine if there was a significant difference before and after stimulation. A minimum level of significance was set at  $p < 0.05$ .

## Results

### High vs. low stimulation

The mean differences between the low-stimulation and high-stimulation groups were found to be slight, even after adjusting for baseline (pre-intervention) pain. The interaction term for stimulation group by time (minute 5 to minute 20 post-stimulation) was not statistically significant. An apparent (albeit non-significant) linear trend was

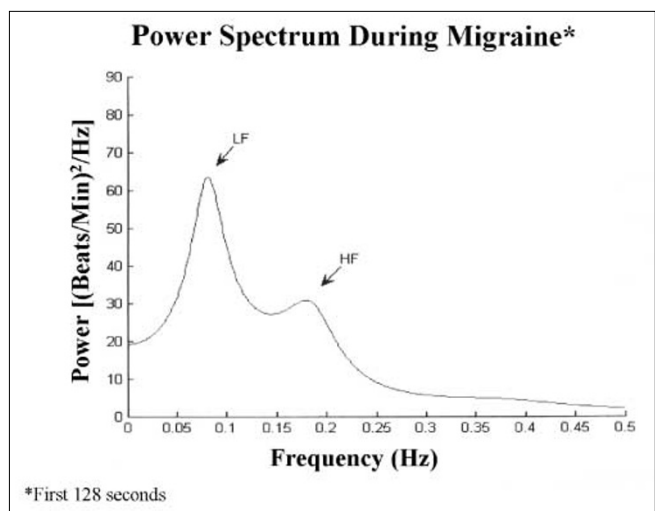
still found for a main reduction in pain from minute 5 to minute 20 post-stimulation. Further, data exploration revealed few outliers in either stimulation group. Subsequently, the high- and low-stimulation groups were combined into one group for further comparisons.

### Pain and suffering

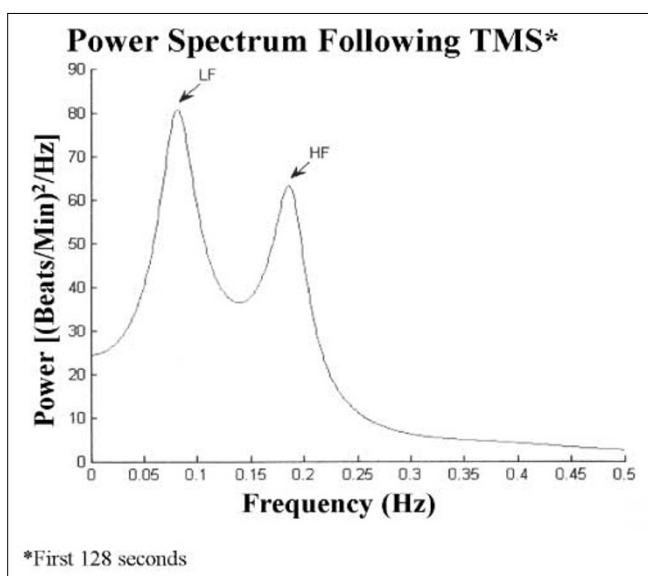
There was an overall mean decrease in pain intensity of 75% which was calculated based on the change between the pre-stimulation mean of pain intensity,  $3.30 \pm 0.74$ , and the post-stimulation value,  $2.49 \pm 1.01$  ( $p < 0.05$ ). At the intake assessment there were no significant differences in total suffering scores between those persons with pain ( $n=19$ ) and those without ( $n=23$ ). In the pain group, mean values for total suffering were  $2.24 \pm 0.54$  vs.  $2.36 \pm 0.573$  SD for the no-pain group.

### Autonomic nervous system effects

ANS effects were significant. Mean HR decreased from  $79.05 \pm 10.27$  to  $72.89 \pm 11.35$  beats/min. The LF area increased from  $6522 \pm 1277$  to  $8315 \pm 1009$  beats/min<sup>2</sup> ( $p < 0.001$ ), and the HF area increased from  $5600 \pm 1568$  to  $8755 \pm 3071$  beats/min<sup>2</sup> ( $p < 0.001$ ). The LF:HF ratio decreased from  $1.31 \pm 0.51$  to  $1.13 \pm 0.48$  (NS). An example of the power spectrum before and immediately after TMS, in one subject, is shown in Figures 1 and 2.



**Fig. 1** A segment of the continuous heart-rate variability data of a patient during migraine. The length of the recorded HRV is approximately 300 s and the power spectrum of the first 128 s of the signal is plotted



**Fig. 2** Depicts the heart-rate variability signal of a patient following transcranial magnetic stimulation. The power spectrum of the first 128 s of the HRV signal is plotted. The mean heart rate shows a slight downward trend. However, note the increase in power in both LF and HF bands of the power spectrum

**Table 1** TMS and headache recurrence after 24 h

Trials	Headache recurrence			
	None	Mild	Moderate	Severe
1 (n=42)	32%	24%	11%	33%
2 (n=22)	29%	16%	8%	46%
3 (n=11)	40%	30%	0%	30%

Results suggest that the effects of TMS may be cumulative

### Efficacy

Sixty-nine percent of the people showed improvement with 1 trial, 87% improved in those persons who had 2 trials and 82% got better after 3 trials. In individuals with an aura, relief was 100% and immediate. The mean time to show improvement was  $15.46 \pm 6.82$  min. Improvement was defined as a decrease in perception of pain of at least 1 level on a 5-point Likert-type scale, and as a decrease in the number of headaches occurring after TMS.

Of those persons who received 1 trial (n=42), 32% reported no further headache after 24 h. After 2 trials (n=22), 29% were headache free the next day and in those persons (n=11) who had 3 trials, 40% reported no further headaches after 24 h (see Table 1). Of those persons without an aura who received 1 trial, 6 patients were headache free, of those who had 2 trials, 8 were headache free and after 3 trials, 1 was headache free after 20 min.

Seventy-six percent of patients who received 1 trial did not take medications before stimulation. Twenty-four percent did not take medication in the following 24 h. In the 2-trials group, 52% did not take medication prior to stimulation and 35% did not take rescue medication for 24 h. For the group who received 3 trials, 55% did not take medication pre-stimulation and 60% did not take it for 24 h.

### Side effects

No adverse side effects were reported either immediately post-treatment or after 24 h. Only 1 person reported slight unsustained dizziness and 1 person was a little drowsy. Several people reported feeling more energetic while others reported longer than usual times between headache onset. Two people said they felt tired after treatment. For those who did not receive immediate benefit with only 1 trial, reports were that there was difficulty controlling the persisting headache with their usual treatments. None of these effects were recurring or required medical attention.

### Discussion

TMS is an important adjunct treatment for migraine headache. Pain relief is often immediate and frequency of headache recurrence decreased by 48% after 1 trial with no adverse side effects. Reports of improvement after more than 1 trial may be due to a cumulative effect of TMS. Further studies are needed.

Processing the HRV signals makes a significant contribution to the understanding of the role of the ANS in migraine. During the study we observed that TMS provided reduction in the pain. Our goal was to assess the effect of such changes objectively using PS/HRV. If one reduces the pain, there may be changes in the sympathetic-vagal balance of the ANS. Future studies are needed to compare the effects on the ANS between TMS and other interventions such as pharmacological agents.

Further, Appel et al. [40] report an enhancement of LF power and suggest that this finding is due to vagal nerve overflow to the sinus node, indicating that patients with migraine have sympathetic system instability. Our study shows that TMS produces perturbations of the ANS, which results in a balancing of the sympathetic and parasympathetic components. TMS may "normalise" the ANS and subsequently modify the vasodilatation of the meningeal blood vessels. These observations support the work of Silberstein [17], Goadsby [19] and Matharu et al. [13], who argue that balancing the ANS may not only prevent abnormal sensory neuron activation in the trigeminal

nucleus caudalis, a process thought to be the cause of the phenomenon of cutaneous allodynia, but it may also have a damping effect on central nervous system hyperactivity and thereby abort the headache.

The relationship between TMS and headache medications also requires further investigation. Although 76% of individuals who received TMS did not take medication prior to treatment and 24% did not take medications post-treatment, the relationship between TMS and specific drug regimes must be rigorously delineated [41, 42].

One limitation of the study is that it was hypothesised that the low stimulation group would show no effect and as a result would act as a control group. As there is an effect in both groups, stimulation/sham stimulation studies are being done. Optimal stimulation intensities are now possible with the advent of newer stimulation devices. Patients and investigators are blind as to whether stimulation is being delivered or not. To explore the issue of placebo more rigorously, patients are initially asked whether they think they are in the stimulation or non-stimulation group and are questioned again after the intervention is applied. Results are pending.

A second limitation to the study is that patients were required to come to the laboratory and sometimes, by the time they arrived, the aura had disappeared and the headache was well established. A portable device has been

developed to overcome this problem and it is currently being tested. We believe that further episodes of stimulation could have achieved better control of headache. Availability of the portable device will allow testing of this hypothesis.

Preliminary intake results also provide evidence that the phenomenon of suffering, in association with migraine headache, is separate from pain. These results confirm findings in other chronic illnesses (arthritis) [38]. Suffering is an issue to be addressed if optimal care in migraine is to be achieved. Perceptions of suffering were the same for those who had pain as those who did not. Follow-up measures of suffering, post-stimulation, would be useful and are incorporated into our new protocol.

To date, our initial results provide evidence that TMS can prevent headache and is an effective adjunct treatment for migraine headache pain. TMS meets the criteria of immediate, sustained pain relief with no known side effects. TMS produces a balancing of the sympathetic and parasympathetic components of the ANS.

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