Can Magnets Make Us Happy?

Investigating the Role of Dopamine in Putative Antidepressant Low-Intensity Magnetic Stimulation

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Abstract

Major depression poses one of the greatest disease burdens to modern society and conventional treatments lack efficacy despite a steadily increasing prevalence. A new intervention method using low-intensity magnetic stimulation of the brain has shown promising results, also regarding “treatment-resistant” patients. Magnetic stimulation therapy may therefore become a key treatment for depression in the future. However, its influence on brain physiology is still poorly understood. In order to investigate the involvement of dopamine in the observed antidepressant effects, twenty volunteers underwent low-intensity magnetic stimulation in a double-blind, sham-controlled, within-subject measurements experiment. The degree of negative bias in facial expression recognition which is indicative of depression as well as handwriting size and finger-tapping speed which positively correlate with dopamine levels were assessed at different magnetic stimulation frequencies and compared with sham treatment. The antidepressant effect found in previous studies could be partially reproduced and has been observed to increase with stimulation frequency. However, no evidence of dopamine as a mediating factor has been found. An involvement of the noradrenergic network instead seems more probable. Potential limitations of this study include varying time intervals between repeated measures and a narrow range of different stimulation frequencies. Nonetheless, our findings are in line with previous research and highlight the importance to further investigate the influence of weak magnetic fields on the human nervous system, also outside of clinical applications.

Keywords: Low-intensity magnetic stimulation, PEMF, micro-TMS, depression, dopamine, antidepressant

Can Magnets Make Us Happy? Investigating the Role of Dopamine in Putative Antidepressant Low-Intensity Magnetic Stimulation

Electricity is an essential force of neuronal communication. Every instance of signal transmission in the brain relies on electrochemical impulses caused by changes in electric charge. Not surprisingly, electromagnetic activity radiating through the brain influences cellular components and neuronal circuits and can cause changes in perception, emotion, cognition, motor function and behavior (e.g., Pascual-Leone, Davey, Rothwell, Wassermann & Puri, 2002; Rossi, Hallett, Rossini & Pascual-Leone, 2009). In recent years also antidepressant effects of magnetic brain stimulation have been observed. Symptoms of bipolar and major depression could be substantially reduced by the administration of low-intensity magnetic stimulation (Martiny, Lunde & Bech, 2010; Rohan et al., 2004; Rohan et al., 2014). Given the high prevalence of mood disorders and the limited efficacy of conventional treatments, the development of new intervention methods is a dire necessity. However, the underlying mechanisms of the magnetically induced therapeutic effect still remain unclear. This study aims to gain a better understanding of the magnetic influences on mood disorders by attempting to magnetically modulate dopaminergic activity levels.

In 1985, Barker, Jalinous and Freeston described that hand muscle contractions can be triggered involuntarily by applying magnetic pulses to the motor cortex. This technique became known as transcranial magnetic stimulation (TMS) and has since been used to induce a variety of temporal alterations of brain functioning, e.g. regarding visual perception (Amassian et al., 1989), speech production (Epstein et al., 1996) and learning ability (Boyd & Linsdell, 2009). TMS is utilizing a high magnetic field strength (1-3 T) and therefore can cause a variety of side effects reaching from temporary neck pain and headaches to syncope and even seizures (Rossi et al., 2009). However, effects of magnetic stimulation at much lower field strengths (1-2500 µT) have been shown as well while side effects are virtually never observed: In 2004, Shupak, Prato and Thomas measured an increased pain threshold after a brief exposure to weak pulsating magnetic fields. This magnetically induced analgesic effect was replicated by Kortekaas et al. in 2013. fMRI studies provide further evidence of reduced activity in pain relevant brain areas (Robertson et al., 2010b) and suggest a dose-response relationship between magnetic field strength of the stimulation and pain processing in these areas (Robertson et al., 2010a). In contrast to induced analgesia after a brief exposure (15-30 min), prolonged exposure (>2 h) to weak pulsating magnetic fields has been shown to induce the opposite effect: subjects exhibit a reduced pain threshold after stimulation, i.e. hyperalgesia (Ghione, Del Seppia, Mezzasalma & Bonfiglio, 2005; Ghione, Del Seppia, Mezzasalma, Emdin & Luschi, 2004; Papi, Ghione, Rosa, Del Seppia & Luschi, 1995; Sartucci et al., 1997). This exposure time dependent change in pain perception is one of the most robust effects of low-intensity magnetic stimulation and has also been validated in animal studies (for a review, see Del Seppia et al., 2007). Furthermore, magnetically induced alterations of mood have also been found. In 2004, Rohan et al. observed for the first time mood improvements in patients with bipolar depression after exposure to weak pulsating magnetic fields. Following this initial finding, Martiny et al. (2010) conducted a double-blind, sham-controlled study in which they administered low-intensity magnetic stimulation to 50 patients with treatment-resistant major depression. After six weeks of treatment they concluded that the size of the antidepressant effect was “above what is usually found for any antidepressant” (*d* = .62). A “substantial improvement (>10% of baseline) in mood” was also observed by Rohan et al. (2014) in a similar study conducted with 41 patients with bipolar depression and 22 patients with major depression.

As promising as the antidepressant findings of low-intensity magnetic stimulation are, the neurophysiological mechanism underlying these effects still remains unclear. Robertson et al. (2010b) describe three potential methods of magnetoreception in the human brain,

a) detection by magnetic dipoles within cells and tissue

b) detection of an induced current

c) detection via the different chemical reaction rates when the electron spins of free radicals are affected by a magnetic field

and regard an induced current mechanism as the most probable to explain their observation of magnetically altered activation of pain processing areas. They argue that even though the induced currents are weak they may still be detected by neural networks as they are more sensitive than single neurons (Francis, Gluckman & Schiff, 2003) and support their claim with the finding of a dose-response relationship “which would not necessarily be present for a resonance-based mechanism” (Robertson et al., 2010a). An induced current mechanism is further supported by the observation that exposure to weak pulsating magnetic fields alters subsequent electroencephalograms (Bell, Marino & Chesson, 1992; Ghione et al., 2005; Marino, Nilsen, Chesson & Frilot, 2004). If the induction of currents in neural circuits by exogenous magnetic field changes is indeed responsible for the observed antidepressant effects of low-intensity magnetic stimulation, an involvement of the dopaminergic network may be possible. Even though the exact function of dopamine in mood disorders is yet to be clarified, a considerable amount of evidence links reduced dopaminergic activity to depressive symptoms (for a review, see Dunlop & Nemeroff, 2007). The observed antidepressant effects may therefore involve increased dopamine levels caused by magnetic influences on the dopaminergic network. For one, there is substantial evidence that dopamine neurons are sensitive to magnetic fields (e.g., Chung et al., 2015; Shin, X. Nguyen, T. Nguyen, Pham & Kim, 2011; Sieroń et al., 2004). Also, dopaminergic pathways extend through large portions of the brain involving cortical and subcortical regions (see Figure 1) and may therefore be particularly sensitive to induced currents by magnetic field changes. The firing frequencies of dopamine neurons may thus be influenced by the frequency of the stimulation applied and higher dopamine levels may be caused by high frequencies of magnetic stimulation. The putative antidepressant quality of low-intensity magnetic stimulation may therefore be mediated by an up-regulation of dopaminergic activity through magnetically induced currents of high frequency.

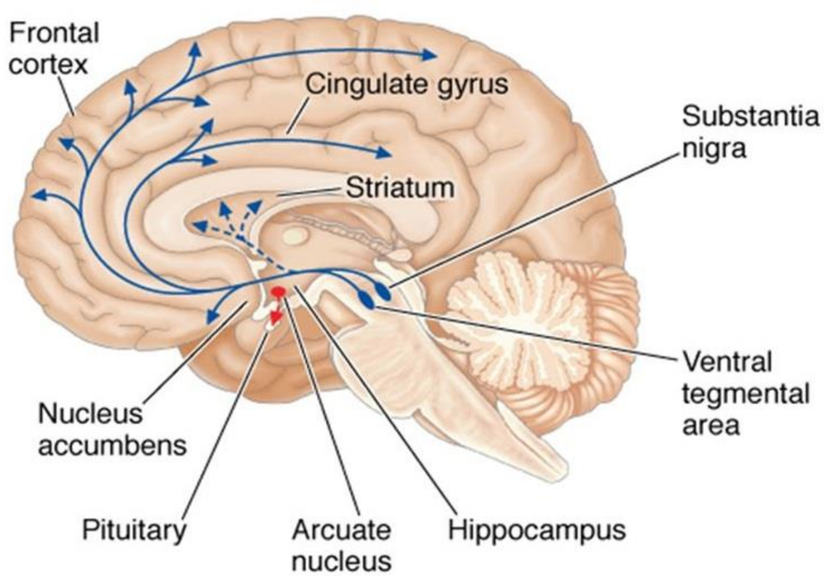

Figure 1. Dopaminergic pathways (Bunton, Chabner & Knollmann, 2011).

Most dopaminergic projections originate within two midbrain structures: the ventral tegmental area and the substantia nigra pars compacta. Midbrain dopamine neurons are known to have tonic firing frequencies between 1-5 Hz (Oleson & Cheer, 2012). We therefore expect that magnetic stimulation with a frequency of 5 Hz will lead to more dopaminergic activity than stimulation at 1 Hz while a frequency of 3 Hz will have an intermediate effect. Direct measurements of dopamine concentration are only possible in an invasive manner and are therefore unsuited for research with healthy human subjects. However, dopamine levels can also be assessed indirectly: finger tapping speed (Volkow et al., 1998) and handwriting size (Kuenstler, Juhnhold, Knapp & Gertz, 1999) have both been shown to correlate well with dopaminergic activity ($r(27) = .56$, $p < .005$ and $r(16) = .90$, $p < .001$, respectively). On the other hand, depression is strongly associated with a processing bias towards negative emotions in facial expressions (Bourke, Douglas & Porter, 2010). Hence, depressed individuals rate the emotional content of faces more negatively than healthy controls. We will therefore utilize measures of facial expression processing bias, handwriting size and finger tapping speed as approximations of depression and dopaminergic activity, respectively. In sum, we hypothesize that higher frequencies of low-intensity magnetic stimulation will lead to (1, main hypothesis) a more positive rating of facial expressions, (2) a larger handwriting size and (3) faster finger tapping than lower frequencies.

Method

Participants and Design

Twenty volunteers (nine female, eleven male) participated in the study. The age ranged from 19 to 26 ($M = 22.70$, $SD = 1.69$). Fourteen of the participants were

Dutch, four were German, one was Italian, one was Indonesian and all acquired English as a secondary language. Exclusion criteria were: brain implants, epilepsy and self-reported states of intense emotion or other influential factors on mood at the time of measurement. The data regarding the handwriting task of one participant was removed due to poorly understood task instructions. This study utilized a double-blind, true-experimental, within-subjects research design. The performance of the participant was measured during two identical experimental sessions, separated by at least 23 hours. One of the sessions involved magnetic stimulation, the other sham stimulation. Stimulation condition was being assigned randomly and blind to the participant and the experimenter. The within-subjects factor for each of the three tasks was the frequency of stimulation (1 Hz, 3 Hz and 5 Hz) and the dependent measurement was the difference in task performance between real and sham stimulation.

Materials

Magnetic stimulation set-up and signal generation. Audacity 2.0.2 for Windows was used to create an audio file featuring bursts of random white noise with durations of 100 ms which alternate with silent intervals of varying durations. During the first eight minutes of the track the silent intervals were set to 900 ms, generating a frequency output of 1 Hz. During the ninth minute of the track the silent intervals were set to 400 ms, generating a 2 Hz output, as shown in Figure 2a. In this manner, the frequency was then set to 3 Hz for eight minutes, to 4 Hz for one minute, to 5 Hz for seventeen (eight plus one plus eight) minutes, to 4 Hz for one minute, to 3 Hz for eight minutes, to 2 Hz for one minute and finally to 1 Hz for eight minutes, resulting in a total track length of 53 min, as shown in Figure 2b. A second audio file was created featuring 53 min of mere silence.

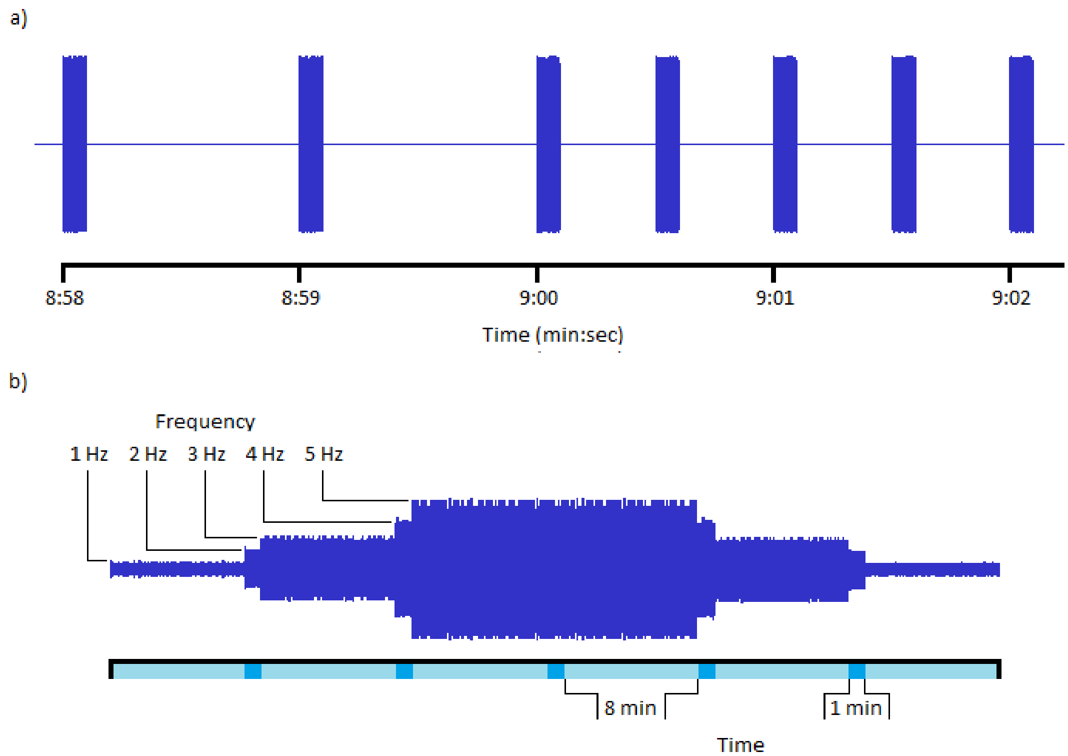

Figure 2. Experimental audio file. a) Frequency change from 1 Hz to 2 Hz. b) Frequency changes across the entire track.

A personal computer (Intel Pentium 4 processor 2.40 GHz, 512 kB RAM) was used to play the audio files from a USB stick using XMMS 1.2.10 audio player. The computer was equipped with an Intel Corporation 82801DB/DBL/DBM (ICH4/ICH4-L/ICH4-M) AC'97 Audio Controller sound card (driver: snd-intel8x0) and Knoppix 5.1 (Linux kernel 2.6.19) was booted from CD-ROM as operating system. The audio player, Knoppix master and Knoppix headphone volume controls were set to 66%, 66% and 70%, respectively.

Nineteen electromagnets were attached to an EEG recording head cap (Easycap, size: 58) in accordance with the 10-20 system. The set-up of the electromagnets was adopted from Kortekaas et al. (2013):

> The electromagnets consisted of 25 mm long, 9 mm thick reed relays (Reed Relay 275–232, Radio Shack, Fort Worth, TX, USA) of which the reed switch was replaced (Richards, Persinger & Koren, 1993) by an M2×30 mm grade 2 steel bolt, transforming them into iron core electromagnets.

All magnets were wired in parallel and the head cap was connected directly to the computer via the 3.5 mm headphone socket of the sound card. A test signal of 1 kHz resulted in a voltage of 118 mV measured at the cap. Furthermore, a resistance of 19.3 Ω was measured, determining a current of 6.1 mA and thus of 0.32 mA per electromagnet.

Experimental task set-up and stimulus generation. Eprime 2.0.10.353 was used in order to create a Wall of Faces (WOF) task paradigm (Simmons, Stein, Matthews, Feinstein & Paulus, 2006). Photographs of male and female faces with different expressions were used in order to generate arrays each displaying 32 faces against a black background, as shown in Figure 3. Each array contained faces with happy expressions and faces with angry expressions either in a 26/6, 16/16 or 6/26 ratio. A laptop (15-inch diagonal screen size) running Windows XP Professional was used to present the WOF and a computer mouse was used as a participant response device. Furthermore, an ABS hand tally counter (UIC1300) and a stopwatch were used.

Figure 3. An array of faces used in the WOF task. In this array, happy and angry expressions are present in a 16/16 ratio.

Procedure

Prior to the beginning of the experiment the participant was informed that the study assesses the effects of low-intensity magnetic stimulation on the activity level of the reward system and that one of the two experimental sessions involves real magnetic stimulation and the other a sham stimulation, even though both the participant and experimenter are blind to the condition. The participant provided informed consent after exclusion criteria were checked and was required to switch off any cell phones, to detach all objects from the hair that could interfere with the head cap and to remove food and chewing gum from the mouth, if necessary.

Furthermore, age and sex of the participant were recorded and a quick practice session for the WOF task was administered. Depending on the randomly assigned condition, real or sham stimulation was then induced via the head cap by playing one of the two audio files. During the stimulation the participant was first instructed to perform the finger tapping task which required pressing the button of the tally counter as often as possible during a one minute interval which was started and stopped by verbal indication of the experimenter. Performance was measured by the number of button presses generated within this interval. Secondly, the participant was instructed to copy the first verse of a printed version of the six verse poem *Ghost House* by Robert Frost on a sheet of plain A4 paper by handwriting. Performance was measured by the distance between the headline of the first word in the first line and the baseline of the first word in the last line of the verse in millimeters. Thirdly, the participant was requested to perform the WOF task while sitting in an approximate distance of 50 cm between the eyes and the display of the laptop. After the presentation of a fixation cross for 500 ms an array of faces was shown for 1500 ms. The participant subsequently had to indicate in a two-alternative forced-choice manner whether the facial expressions presented in this array predominantly appeared to be either positive or negative by clicking either the right or the left mouse button, respectively. The task required the participant to respond to 32 arrays of faces in succession (8 primarily negative, 8 primarily positive, 16 ambiguous) and performance was measured by the sum of right mouse button clicks (positive response) and left mouse button clicks (negative response) after they were assigned the values 2 and 1, respectively. The sequence of these three tasks took about seven to eight minutes to complete and was repeated every nine minutes of the stimulation, thus six times during the experimental session. The tasks were thus only performed at stimulation frequencies of 1 Hz, 3 Hz and 5 Hz and the participant was allowed to rest during stimulations with 2 Hz and 4 Hz and during the ninth minute of stimulation with 5 Hz, as shown in Figure 4. Note that at each of the six task repetitions the presentation order of WOF stimuli was changed and the subsequent verse of the poem was used for the handwriting task. The participant received a full debriefing and the experimental results after the end of the study.

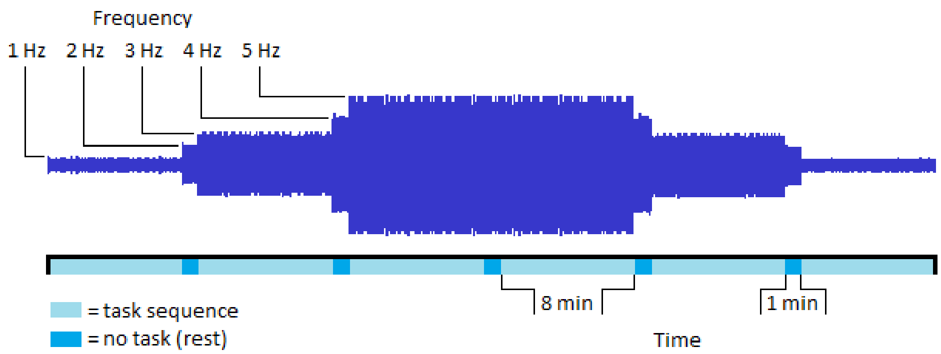

Figure 4. Periods of task administration and rest in relation to stimulation time and frequency.

Results

The main hypothesis stated that higher frequencies of low-intensity magnetic stimulation would lead to a more positive rating of facial expressions than lower frequencies. As shown in Figure 5, the mean WOF difference score increased with stimulation frequency, indicating a more positive rating at higher than at lower frequencies. Note that difference scores were obtained by a subtraction of WOF ratings during sham stimulation from WOF ratings during real stimulation. A repeated measures analysis of variance was conducted to compare the effect of stimulation frequency (1 Hz, 3 Hz and 5 Hz) on WOF performance difference scores. Mauchley's sphericity test showed that the assumption of sphericity was not violated,

$\chi^2(2) = 2.38$, $p = .30$. No significant effect of stimulation frequency was found, $F(2, 38) = 1.84$, $p = .17$. A paired-samples t-test was conducted to compare the difference scores between 1 Hz and 5 Hz stimulation frequencies. A trend level effect was found, $t(19) = -1.65$, one-sided $p = .057$; ratings at 5 Hz were more positive than ratings at 1 Hz.

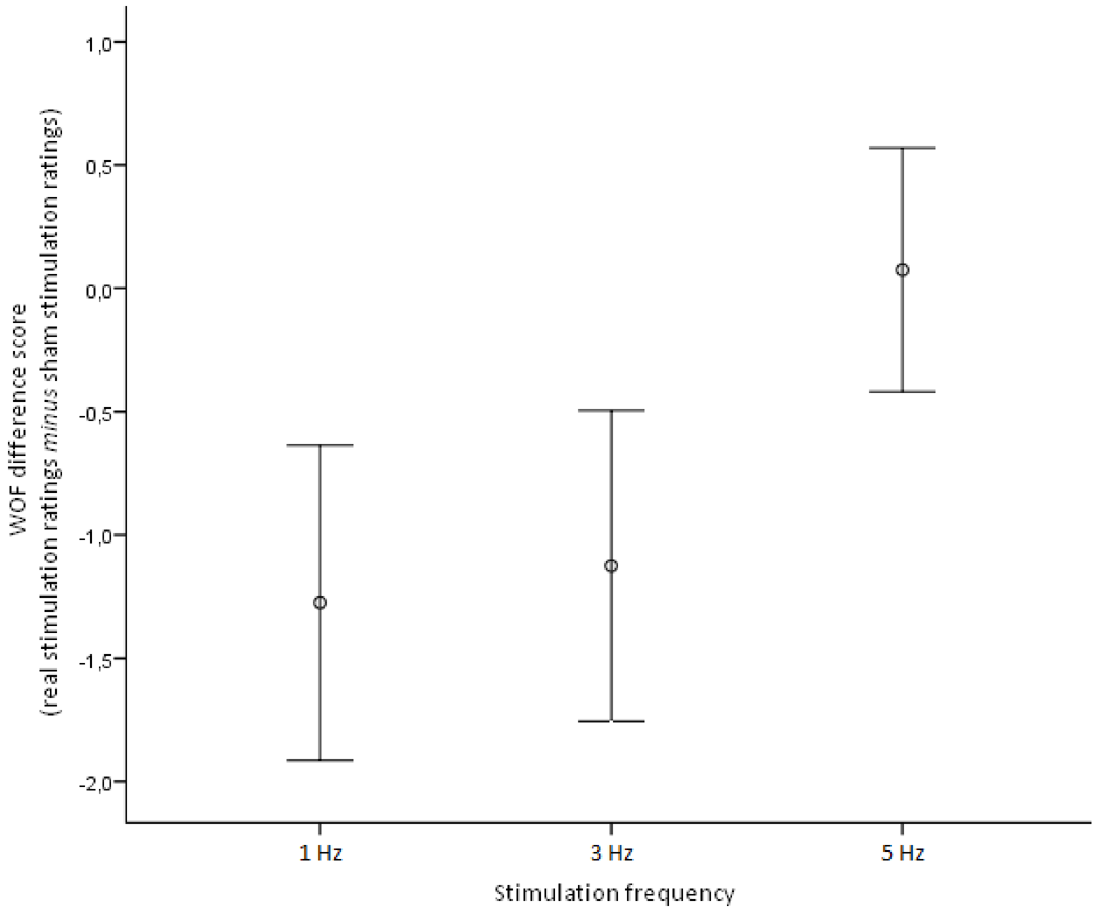

Figure 5. Means and standard errors of the mean for WOF difference scores at the three different stimulation frequencies. Higher scores indicate a more positive rating of facial expressions.

The second hypothesis stated that higher frequencies of low-intensity magnetic stimulation would lead to a larger handwriting size than lower frequencies. The mean handwriting size difference score (real vs. sham stimulation) did not systematically increase with stimulation frequency. A repeated measures analysis of variance was conducted to compare the effect of stimulation frequency (1 Hz, 3 Hz and 5 Hz) on handwriting size difference scores. Mauchley's sphericity test showed that the assumption of sphericity was not violated, $\chi^2(2) = 1.71$, $p = .42$. No significant effect of stimulation frequency was found, $F(2, 38) = 0.94$, $p = .40$.

The third hypothesis stated that higher frequencies of low-intensity magnetic stimulation would lead to faster finger tapping than lower frequencies. The mean finger tapping difference score (real vs. sham stimulation) did not systematically increase with stimulation frequency. A repeated measures analysis of variance was conducted to compare the effect of stimulation frequency (1 Hz, 3 Hz and 5 Hz) on finger tapping difference scores. Mauchley's sphericity test showed that the assumption of sphericity was not violated, $\chi^2(2) = 1.18$, $p = .56$. No significant effect of stimulation frequency was found, $F(2, 38) = 0.22$, $p = .81$.

Discussion

It was hypothesized that higher frequencies of low-intensity magnetic stimulation would lead to (1, main hypothesis) a more positive rating of facial expressions, (2) a larger handwriting size and (3) faster finger-tapping than lower frequencies. The positivity of facial expression ratings showed a strong tendency to increase with stimulation frequency. Therefore, our main hypothesis was partially confirmed. Handwriting size and finger tapping speed did not increase with stimulation frequency. Therefore, our second and third hypotheses were not confirmed.

The almost significant increase in positive ratings of facial expressions adds further support to the putative antidepressant quality of low-intensity magnetic stimulation. This research is thus in line with previous findings of Rohan et al. (2004), Martiny et al. (2010) and Rohan et al. (2014). Our observed effect suggests that magnetic field changes are indeed able to induce currents in neural networks and thereby to alter their activity. It is unclear, however, which neural network mediated the change in perceptual bias. It may be that increased dopamine levels were responsible for this effect. Handwriting size and finger tapping speed, though, are indicative of dopaminergic activity and were both highly insignificant. It may therefore be that the magnetic stimulation modulated activity in other networks. According to the widely accepted monoamine hypothesis, dopamine is not the only neurotransmitter involved in depression but serotonin and noradrenaline play a role as well (Schildkraut, 1965). Serotoninergic neurons have a typical firing frequency range of 0.5-3 Hz (Heinrich, Cromarty, Hörner, Edwards & Kravitz, 1999). Considering that the ratings of facial expressions primarily differed between stimulations at 3 and 5 Hz and almost no differences were observed between 1 and 3 Hz, it seems unlikely that serotonin mediated this effect. Noradrenergic neurons, however, exhibit tonic firing frequencies between 0.1-5 Hz which are similar to those of dopaminergic neurons (Devilbiss & Waterhouse, 2011). Noradrenaline may therefore be the factor mediating the influence of magnetic stimulation on the ratings of facial expressions while not affecting finger-tapping speed and handwriting size. Further investigations are needed in order to clarify this question.

Higher stimulation frequencies lead to more positive ratings of facial expressions. It should be noted, however, that magnetic stimulation *per se* did not increase the positivity of the ratings but rather decreased it (see Figure 5). Overall, the ratings during magnetic stimulation were more negative compared to sham stimulation while the largest decrease has been observed at 1 Hz. Sham stimulation levels were being approached at 5 Hz, suggesting that higher frequencies may be needed in order to actually increase the positivity of ratings during magnetic stimulation. It is unclear which neural network mediated the magnetic stimulation effects. However, noradrenergic and dopaminergic neurons exhibit similar phasic firing frequencies of up to 20 Hz and even more (Devilbiss & Waterhouse, 2011; Zhang, Doyon, Clark, Phillips & Dani, 2009) and direct electrical stimulation studies with dopaminergic neurons conclude that frequencies of at least 10-20 Hz must be applied in order to produce a measurable increase in extracellular dopamine levels (Grace, 1991). Even though induced currents on a network scale may be more potent than the stimulation of single neurons, magnetic stimulation may also have a stronger influence at 20 Hz or more. A replication of this study with higher stimulation frequencies is thus needed in order to clarify whether the positivity of facial expressions ratings can actually be increased beyond sham stimulation levels and whether the insignificance regarding handwriting size and finger tapping speed can truly be attributed to dopamine not mediating this effect (or to too low stimulation frequencies). Utilizing a stimulation frequency range of 20 Hz instead of 5 Hz may additionally increase the ability to observe effects. A further limitation of this study may also be the timing of the measurements. The number of days between the two experimental sessions varied considerably between participants and the second session often took place at a different time during the day than the first. These fluctuations may have increased variance in the measurements, reducing the significance of the results. We therefore advise researchers attempting to replicate this study to utilize a stimulation frequency range of 1-20 Hz and to perform repeated measures with a constant measurement timepoint per subject and with a constant time interval between measurement sessions.

The initial observations of an antidepressant effect made low-intensity magnetic stimulation a promising candidate for a new treatment of mood disorders. Our study which partially validates earlier findings demonstrates that this direction of research is worth further investigating. But the implications of these findings extend beyond the clinical area. In urban surroundings we are constantly surrounded by electromagnetic fields with different strengths and properties generated by computers, phones, radios, televisions – even by power lines and light bulbs. Given that already weak magnetic stimulation has repeatedly shown to alter pain perception and to induce mood changes in humans it may be necessary to reassess whether we handle sources of electromagnetic radiation and our exposure to them with sufficient care.

Summing up, the findings of our study are in line with previous research. We were able to partially confirm earlier observations of magnetically induced antidepressant effects. Still, the exact neural mechanism underlying these effects remains a topic of investigation and will challenge future researchers in this field. Our study demonstrates that very minor changes in electromagnetic fields are sufficient to manipulate the activity of our nervous system. Perception, emotion and even behavior have shown to be subject to magnetic influence which we readily encounter countless times every day.

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