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High-frequency repetitive transcranial magnetic stimulation to the cerebellum and implicit processing of happy facial expressions

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Introduction

The concept that the cerebellum is implicated in the experience and regulation of emotions and mood was posited more than half a century ago. The first empirical report of cerebellar involvement in the experience of emotions

Background: Previous research has demonstrated that the cerebellum is involved in emotive and cognitive processes. Furthermore, recent findings suggest high-frequency repetitive transcranial magnetic stimulation (rTMS) to the cerebellum has mood-improving properties. We sought to further explore the effects of cerebellar high-frequency rTMS on implicit processing of emotional stimuli and mood. Methods: In a double-blind, crossover study, 15 healthy volunteers received 15 minutes of 20 Hz (5 s on, 5 s off) rTMS over the medial cerebellum, occipital cortex or sham in a randomized counterbalanced order on 3 consecutive days. A masked emotional faces response task measured implicit emotional processing of happy, fearful and neutral facial expressions. We used positive and negative affect scales to evaluate rTMS-related changes in mood. Results: High-frequency rTMS over the cerebellum was associated with significant increases in masked emotional responses to happy facial expressions only. We observed no changes in consciously experienced mood. Limitations: Although the sham rTMS served as our baseline measurement, additional pre-rTMS data showing that reaction time increases immediately after cerebellar rTMS would have made our results more compelling. Conclusion: The results replicate and extend previous findings by establishing a direct relation between the cerebellum and emotive information-processing. The parallel between the present effects of high-frequency cerebellar rTMS and short-term antidepressant therapy regarding the change in implicit processing of positive stimuli in the absence of mood changes is notable and warrants further research.

Contexte : Des recherches antérieures ont démontré que le cervelet joue un rôle dans les processus émotionnels et cognitifs. De récentes découvertes permettent également de penser que la stimulation magnétique transcrânienne répétitive (SMTr) de haute fréquence appliquée au cervelet exercerait des effets positifs sur l’humeur. Nous avons voulu explorer plus en profondeur les effets de la SMTr sur le cervelet, sur le traitement implicite des stimuli émotionnels et sur l’humeur. Méthodes : Dans le cadre d’une étude à double insu avec permutation des groupes, 15 volontaires en bonne santé ont reçu 15 minutes de SMTr à 20 Hz (stimulation 5 s, arrêt 5 s) au niveau de la partie médiane du cervelet ou du cortex occipital, ou une stimulation simulée, en séquences randomisées contrebalancées, 3 jours consécutifs. Un test masqué de décodage de l’émotion exprimée par des visages a permis de mesurer le traitement émotionnel implicite des expressions faciales heureuses, craintives et neutres. Nous avons utilisé des échelles d’évaluation des effets positifs et négatifs pour mesurer les changements de l’humeur liés à la SMTr. Résultats : La SMTr de haute fréquence appliquée au cervelet a été associée à des augmentations significatives des réponses émotionnelles masquées, mais uniquement des réponses aux expressions faciales heureuses. Nous n’avons observé aucun changement de l’humeur consciente. Limites : Même si la SMTr simulée nous a servi de mesure de départ, d’autres données pré-SMTr montrant que le temps de réaction augmente immédiatement après l’application de la SMTr au cervelet auraient donné plus de poids à nos résultats. Conclusion : Les résultats reproduisent et élargissent les conclusions antérieures en établissant un lien direct entre le cervelet et le traitement émotionnel de l’information. Le parallèle entre les effets actuels de l’application de la SMTr de haute fréquence au cervelet et le traitement antidépresseur à court terme, en ce qui a trait à une modification du traitement implicite des stimuli positifs en l’absence de labilité de l’humeur, est notable et justifie que l’on approfondisse la recherche.
Transcranial magnetic stimulation and the cerebellum

included a study of a patient who underwent electrical stimulation of the dentate nucleus and superior peduncle and experienced negative feelings.\(^7\) The link between the cerebellum and emotions was further strengthened by the seminal work of Heath and colleagues,\(^4,7\) demonstrating that chronic electrical stimulation of the superficial parts of vermis normalized behaviour in severely emotionally disturbed patients. A neuroanatomical basis for cerebellar involvement in emotive processes is grounded in the multiple direct and indirect connections of the cerebellum to limbic and cortical areas of the brain. Functional neuroimaging studies have also demonstrated consistent cerebellar activation during emotive processing and mood.\(^8\) One of the prevailing models proposes that the cerebellum functions as a “general-purpose modulator” in governing mental activities (for a review see Andreasen and colleagues\(^9\)).

Further evidence of a direct link between the human cerebellum and emotive processes has been provided by repetitive transcranial magnetic stimulation (rTMS) studies. In a previous study, it was shown that a single session of high-frequency rTMS over the cerebellum had positive effects on mood in healthy volunteers.\(^10\) Interestingly, mood elevations often go accompanied by increased attention for implicit positive stimuli that can even occur before actual changes in mood.\(^11\) One of these changes in implicit attention for positive stimuli can, for instance, be evaluated by measuring reaction times to the colour naming of a mask that is preceded by a short (nonconscious) presentation of a happy facial expression.\(^12\) Increased emotional responsiveness for implicit positive stimuli would then result in longer reaction times to the colour naming of the mask preceded by a happy facial expression and allow researchers to gather insights into information processes associated with mood.

Building on the previous high-frequency rTMS study, we recently showed that low-frequency rTMS to the medial part of the cerebellum in healthy volunteers impairs emotion regulation and augments negative mood.\(^13\) These findings are not only in accordance with the alleged opposite actions of high- and low-frequency stimulation parameters, but also demonstrate the modulatory effects of a single session of cerebellar rTMS on behaviour.

We conducted a sham and occipital cortex controlled, double-blind, crossover study to further explore the effects of high-frequency rTMS over the cerebellum on emotive information processing and mood. In keeping with our previous findings, we hypothesized that a single session of high-frequency cerebellar rTMS would increase self-reported positive mood and facilitate information-processing of positive emotional stimuli.

**Methods**

**Participants**

We enrolled healthy, nonsmoking young women in the study. We obtained written informed consent and paid the volunteers for their participation. The study was approved by the medical ethical committee of the Utrecht University in accordance with the declaration of Helsinki. All volunteers were unaware of the hypotheses being tested in the study.

**Transcranial magnetic stimulation**

We performed high-frequency rTMS using a biphasic magnetic brain stimulator (maximum output 2300 A peak / 1750 VAC peak) with an iron core coil (Neotonus). Maximum magnetic field strength was 2 Tesla. We performed sham rTMS using an identical coil with a built-in aluminum plate directly underneath the iron core (Neotonus). The coil mimics the sound click and sensation of real TMS, but the brain is shielded from actual stimulation.

**The masked emotional faces response task**

The masked emotional faces response task requires participants to name the colour of the ink in which the mask is printed. Performance in terms of slowing down or speeding up colour naming varies as a function of the participant’s motivational state and the rapid emotional face presentation (14 ms) prior to the mask.\(^12\) In this task, the motivational state of the individual is presumed to direct pre-attentive (automatic) reactions to the emotional facial expressions and influence the colour naming of the subsequent presentation of the mask.\(^14,15\) Thus, slower colour naming of the masking stimulus following happy facial expressions is indicative of increased appetitive motivation and reward sensitivity, whereas the opposite holds for relatively faster colour naming.\(^16\) Figure 1 depicts the outline of the masked emotional faces response task.

The general idea of the task is that presenting emotional facial expressions outside conscious awareness prevents cognitive elaborative strategies and subsequently gains access into the core aspects of the individual’s motivational stance.

We used stimuli from Ekman and Friesen’s *Pictures of facial affect*\(^17\) and Lundqvist and colleagues’ *Karolinska directed emotional faces set.*\(^18\) In the masked emotional faces response task, we displayed a fixation point for 750 ms, followed by a 14-ms presentation of a happy, fearful or neutral facial expression.
that we then replaced by a masking stimulus. Masking stimuli included randomly cut, reassembled and rephotographed pictures of faces.

We presented 30 happy, 30 fearful and 30 neutral faces in random order, and the inter-trial interval randomly varied between 1500 and 2500 ms. All stimuli (14 × 9 cm) were coloured either red, green or blue and projected in the centre of a 17-inch computer screen (70 Hz refresh rate) on a black background at a distance of 150 cm. We instructed participants to name the colour of the masking stimulus as fast as possible. For optimizing stress-related workload, we used a rapid externally paced version of the task with a termination of mask display after 300 ms.\(^{19}\) We used the reaction time as the dependent variable.

To check for the absence of conscious awareness, we used a 3-alternative, forced-choice happy–fear–neutral recognition check (3AFC). We showed a random set of 60 masked facial expressions to each participant. Prior to the check, we explicitly told participants that the set contained 20 happy, 20, fearful and 20 neutral faces, and we instructed them to indicate whether the presented stimulus was a happy, fearful or neutral emotional expression by pushing 1, 2 or 3, respectively, on the keypad. We set the critical level of perceptual threshold at 26 correct trials, as indicated by a nonparametric simple paired-sample \(t\) tests. We set the \(\alpha\) level of significance at \(\leq 0.05, 2\) tailed.

**Results**

**Participants**

All 15 participants were aged 18–22 (mean 20.4, standard deviation [SD] 1.9) years, right-handed (mean 45.9, SD 2.7, as per Edinburgh handedness inventory) and used oral contraceptives. The mean motor threshold of the left and right hemisphere was 57.7 (SD 10.0). None had a history of psychiatric or neurologic conditions, and all had normal or corrected-to-normal vision.

**Procedure**

TMS was well tolerated and, although some participants noticed differences in sensation between the sessions, blinding was effective because participants were not able to separate the experimental from the control conditions when interviewed. None of the volunteers passed the masked emotional faces awareness check criterion, and we entered data on all 15 participants in the statistical analyses. We observed a significant main effect of rTMS on reaction times to masked happy facial expressions (\(F_{14} = 4.23, p = 0.032, \varepsilon = 0.99\)); however, we observed no significant effect of the order of conditions (\(F_{4,60} = 1.16, p = 0.37, \varepsilon = 0.99\)). Post-hoc paired-samples \(t\) tests revealed that reaction times were significantly increased after cerebellar compared with sham (\(t_{14} = 2.5, p = 0.021\)) and occipital cortex rTMS (\(t_{14} = 2.3, p = 0.037\)). Reaction times between the sham and occipital rTMS condition did not statistically differ (\(t_{14} = 0.18, p = 0.86\)). We observed no main effects of rTMS on reaction times for the masked neutral (\(F_{14} = 1.36, p = 0.28, \varepsilon = 0.85\)) and fearful facial expressions (\(F_{14} = 1.67, p = 0.22, \varepsilon = 0.69\)). We found no order effects of TMS in the masked neutral and fearful facial expressions (\(p > 0.36\)). Figure 2 shows the mean and standard error of the threshold of the left and right hemisphere using the 5-step motor threshold estimation procedure described by Schutter and van Honk.\(^{26}\) On testing days, we instructed participants to refrain from taking psychotropic substances, including alcohol, coffee, tea and chocolate, for 2 hours before the experiment. We administered the positive and negative affect schedule questionnaire immediately after high-frequency rTMS. Next, participants performed the masked emotional faces response task. Finally, at the end of the final session participants performed the 3AFC, and we debriefed them and paid them for participation.

**Statistical analysis**

We used a general linear model for repeated-measurements with 3 levels using cerebellar, occipital and sham rTMS as within-subject factors and order of rTMS conditions as the between-subject factor. We applied Greenhouse–Geisser correction (degrees of freedom > 1) to the \(p\) values and reported the \(\varepsilon\). We performed post-hoc significance testing with simple paired-sample \(t\) tests. We set the \(\alpha\) level of significance at \(\leq 0.05, 2\) tailed.

**Self-reported mood questionnaire**

We assessed consciously experienced mood using the positive and negative affect schedule.\(^{20}\) The questionnaire consisted of 20 items and visual analogue scales (0 = not at all, 100 = extremely).

**Procedure**

Participants received 15 minutes of 20 Hz rTMS (5 s on, 5 s off, 9000 pulses per session) over the midline cerebellum. Sham rTMS over the midline cerebellum and real rTMS over the occipital cortex served as the inactive and active control conditions, respectively. The current in the coil was directed downward to maximize cerebellar stimulation.\(^{21}\)

We defined the midline cerebellum target site as the point located 1 cm below the inion.\(^{22,23}\) The occipital cortex target site was located 3 cm above the inion. Stimulation intensity was 80% of the individual motor threshold. We randomized the order of sessions and counterbalanced it among participants. Sessions were 24 hours apart and controlled for daytime. Volunteers underwent 1 condition per session. Stimulation parameters were in accordance with the safety guidelines formulated by the International Federation of Clinical Neurophysiology (www.ifcn.info).

On a separate day prior to the testing sessions, we used a safety-screening list to check for contraindications, and we assessed the health of all participants using a standard interview.\(^{24}\) In addition, we explained safety issues and the experimental procedures to each participant and obtained informed consent. We assessed handedness using the Edinburgh handedness inventory,\(^{27}\) and we determined the average motor
mean colour naming reaction times to masked facial expressions for the rTMS conditions.

Our repeated-measures multivariate analysis of variance did not yield significant differences between the rTMS conditions on positive ($F_{2,18} = 0.31, p = 0.68, \varepsilon = 0.75$) and negative mood scores ($F_{2,18} = 0.10, p = 0.90, \varepsilon = 0.98$), as seen in Figure 3.

Discussion

Our goal was to examine the effects of high-frequency rTMS over the cerebellum on responses to masked emotional facial expressions and consciously experienced mood. Results showed that cerebellar rTMS, compared with occipital cortex and sham rTMS, resulted in the enhanced implicit processing of happy facial expressions without changes in self-reported mood. Our findings concur with those of pharmacological studies that found selective increases in implicit processing of positive emotional material, but no changes in consciously experienced mood related to antidepressant therapy in healthy nondepressed volunteers.\textsuperscript{11,27,28} Furthermore, our results are in agreement with findings of increased attentional biases (i.e., slower reaction times) to happy facial expressions in nondepressed versus depressed individuals.\textsuperscript{29} In contrast, the absence of a significant increase in self-reported positive mood is not consistent with our previous work in which we did find a positive effect on mood. Notably, the fact that the current rTMS findings were confined to the implicit level of information-processing coincides with the general idea that the early effects of antidepressants are manifested at the level of implicit and automatic aspects of information-processing rather than the conscious experience of mood.\textsuperscript{28}

Our results further support the involvement of the cerebellum in affective information-processing. Admittedly, our study design does not permit us to draw strong inferences on the underlying biological mechanisms. There are at least...
3 lines of indirect evidence suggesting that the effects of high-frequency rTMS to the medial cerebellum involve the brain’s reward circuitry. First, the vermis part of the human cerebellum has projections to the ventral tegmental area of the mid-brain, showing that the vermis can modulate mesolimbic areas via dopaminergic fibre bundles. Second, a comparative study has demonstrated enhanced dopamine turnover in the nucleus accumbens to electric stimulation of the cerebellar vermis in rats. The finding is further supported by observations of increased dopamine metabolite homovanillic acid in the cerebrospinal fluid of 2 patients with movement disorders who received chronic electrical cerebellar stimulation. Third, high-frequency electrical stimulation of Purkinje cells in the cerebellar cortex selectively modulates dopaminergic activity in the prefrontal cortex.

Together, these findings suggest that the cerebellum plays a significant role in the modulation of brain regions associated with cognition and emotion. Finally, it is proposed that the cerebellum may be a suitable entry point for targeting dopaminergic pathways in the mesolimbic and mesocortical systems as an alternative way to treat depression, for instance, with high-frequency rTMS.

Limitations

Our study has some limitations. First, we used a Likert-type scale to assess consciously experienced mood. Previous research has demonstrated that slight but systematic changes in mood may remain unnoticed when using Likert-type scales. Second, the fewer number of pulses that we applied in the present study (i.e., 9000 v. 20,000 pulses in our earlier study) to prevent coil heating and minimize participants’ discomfort may explain the absence of a significant increase in self-reported positive mood among participants in the present study. Analogous to the therapeutic onset delays often observed in drug as well as in rTMS treatment studies, a greater number of magnetic pulses at higher intensities might be necessary to obtain changes in consciously experienced mood. Third, although the sham rTMS served as our baseline measurement, additional pre-rTMS data showing that reaction time increases immediately after cerebellar rTMS would have made the results more compelling. Finally, it should be noted that the conclusion of increased emotional responses is indirectly drawn from increased reaction times. Except for the fact that our results suggest a role for the cerebellum in the implicit processing of positive emotional stimuli, the brain mechanisms responsible for the change in emotional responsiveness remain speculative and additional research on this matter is needed.

In sum, the results of our high-frequency rTMS study replicate and extend previous findings by establishing a direct relation between the cerebellum and emotive information processing. The parallel between the present effects of high-frequency cerebellar rTMS and short-term antidepressant therapy regarding the change in implicit processing of positive stimuli in the absence of mood changes is notable and warrants further research.

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Contributors: Dr. Schutter designed the study. Dr. Schutter and Mr. Hoppenbrouwers analyzed the data and wrote the article. All authors acquired the data, reviewed the article and gave final approval for publication.

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