Changes in Mood and Hormone Levels After Rapid-Rate Transcranial Magnetic Stimulation (rTMS) of the Prefrontal Cortex

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Rapid-rate transcranial magnetic stimulation (rTMS) was administered to 10 healthy volunteers on different days over the right or left prefrontal cortex, midfrontal cortex, occipital cortex, or cerebellum. Mood (self-rated), reaction time, and hormone levels were serially measured. Consistent with a previous study, comparison of hemispheres revealed significant associations with decreased happiness after left prefrontal rTMS and decreased sadness after right prefrontal rTMS. Stimulation of all three prefrontal regions, but not the occipital or cerebellar regions, was associated with increases in serum thyroid-stimulating hormone. There was no effect on serum prolactin. rTMS applied to prefrontal cortex is safe and well tolerated and produces regionally and laterally specific changes in mood and neuroendocrine measures in healthy adults. rTMS is a promising tool for investigating prefrontal cortex functions.

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Since the early days of trephining, investigators have sought to research brain function by bypassing the skull. In modern times, Sherrington and Ferrier first attempted to understand regional brain function by directly stimulating specific regions in animals to produce behaviors.[1–3] Work in humans lagged behind, although considerable information has been gleaned from direct brain electrical stimulation during surgery.[4–6]

Recently a host of new static (CT and MRI) and functional (SPECT, PET, fMRI) imaging technologies have emerged that can noninvasively bypass the skull. The information from these new technologies has substantially advanced understanding of the brain in health and disease. Functional imaging studies are necessarily limited, however, in their ability to map brain function. Changes in regional brain activity (flow or metabolism) in association with a disease or behavior may be either causal or epiphenomenal to the behavior in question. That is, increases or decreases in regional brain activity occurring at the same time as a behavior do not indicate the nature of the relation between regional activity and

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the behavior. Altered regional activity may be causing the behavior, or it could be transiently associated with it (for example, via a mirror focus in the contralateral hemisphere), or it could indicate an attempt to brake or regulate the behavior.[7]

Rapid-rate transcranial magnetic stimulation (rTMS) is a new technology that extends the ability to noninvasively investigate regional brain function.[8,9] rTMS involves placing an electromagnet on the scalp and turning it rapidly on and off, thereby producing a time-varying magnetic field that passes unimpeded through the skull and soft tissue. This altering magnetic field induces a changing electric field, which causes current flow in cortical tissue, resulting in neuronal depolarization. TMS has been used for a decade to investigate cortical function relating to movement[10] and cognition[11] both in health and in disease states such as Parkinson's disease[12] and epilepsy.[13–16] To date, rTMS has been largely limited to studying the motor and visual cortex. Relatively few studies have examined effects on prefrontal cortex function.

Theoretically, rTMS could prove helpful in unraveling the function of the prefrontal cortex, which has been implicated in learning and memory,[13] personality,[17] emotion recognition,[18] and mood regulation.[19] The prefrontal cortex has also been implicated as dysfunctional in several neuropsychiatric illnesses, especially depression[19] and schizophrenia.[20]

A recent pilot study of rTMS in healthy volunteers found that left prefrontal rTMS was associated with transient sadness and right prefrontal stimulation was associated with transient happiness.[21] In that study, different brain regions were randomly stimulated in the same session on the same day, which did not allow an examination of the longer time course of the changes or neuroendocrine measures. Studies to date have suggested that subconvulsive rTMS does not cause significant changes in neuroendocrine measures such as prolactin, which has been used as a marker of seizure activity.[22] Therefore, as a pilot study of rTMS and its potential effects on emotion, we sought to explore the effects of rTMS stimulation of left, right, and midline prefrontal cortex and other areas on mood, reaction time, and hormone levels in healthy adult volunteers.

METHODS

Subjects

We studied 10 healthy volunteers (6 men and 4 women) ages 24 to 51 years (mean ± SD = 35 ± 8.1 years). Subjects were recruited with local announcements and were paid. All had normal MRI scans, neurological exams, and physical exams and had no past history or family history of mood disorders as determined by prescreening with the Schedule for Affective Disorders and Schizophrenia–LA.[23] All subjects specifically met the safety criteria outlined for rTMS in normal volunteers[22] and were right-handed.[24] Subjects were naive to rTMS and were instructed that the study was designed to explore the effects of magnetic stimulation on hormones, reaction time, and mood. Subjects were asked before the study if they had ideas about which brain regions might change mood. No one had such prestudy ideas, and the investigators were careful in the consent process and during the study not to prejudice the volunteers about regional brain function. All gave written informed consent prior to entering the study. Subjects were medication-free except for aspirin and acetaminophen throughout the study and for at least 2 weeks before entering the study.

Experimental Design

Subjects were studied on 5 separate days, each at least 2 days after the previous session (typically Monday, Wednesday, Friday, and the following Monday and Wednesday) between June and September of 1994. Each morning between 7:00 and 9:00 A.M., subjects reported to the 3-West Research Ward and had vital signs checked, performed self-ratings, and had an intravenous catheter inserted and blood sent for thyroid-stimulating hormone (TSH), T_3, T_4, prolactin, and cortisol testing. Subjects then underwent rTMS in the Human Motor Control Section TMS lab at the National Institutes of Health (NIH), one region per visit, in a semirandomized design. Subjects completed self-ratings and had blood drawn 30, 60, 90, and 180 minutes after the stimulation. Subjects completed self-ratings at 5:00 P.M. and the following morning. Reaction time was measured in each subject between 30 and 60 minutes after the stimulation.[25] At each rating point, subjects completed a modified version of the National Institute of Mental Health (NIMH) mood scale with explicit questions about sadness and happiness as well as a forced-choice visual analog mood scale and the Positive Affect–Negative Affect Schedules (PANAS).[26]

On different visits, stimulation was applied either to the left prefrontal cortex, right prefrontal cortex, midline prefrontal cortex, occipital cortex, or cerebellum (Figure 1). All sites were randomized except the cerebellum, which was always done last. This deviation from a purely random design was made because of concern before the study that cerebellar stimulation might induce a high dropout rate due to head movement from paraspinal muscle excitation. As described below under Results, this concern was ill founded; cerebellar stimu-

lation was, in fact, considered less painful and unpleasant than stimulation of the lateral prefrontal regions.

For each individual, the prefrontal stimulation site was determined from the location of the motor cortex. This is the best position for induction of motor evoked potentials in the abductor pollicis brevis (APB) muscle in the contralateral hand (see Figure 1). Wassermann et al.[27] have demonstrated that the APB site used as a reference point in this study corresponds to activation of the hand area representation of the anterior bank of the central sulcus, the primary motor cortex. The stimulation positions in the present study were based on Talairach atlas coordinates and are estimates of the best region to stimulate in order to influence the right and left dorsolateral prefrontal cortex, midline prefrontal cortex, visual cortex, and midline cerebellum (for midfrontal stimulation: coil centered 5 cm anterior in the midline of the APB site; for right or left prefrontal cortex stimulation: 5 cm anterior and in a parasagittal plane from the APB site; for occipital stimulation: 10 cm posterior and in the midline from the APB site; for cerebellar stimulation: 3 cm below the inion and in the midline between the mastoids).

Repetitive Transcranial Magnetic Stimulation

We used a Cadwell High Speed Magnetic Stimulator equipped with a specially designed figure-eight coil that allows continuous water cooling to prevent overheating during long stimulation trains. Each wing in the coil is approximately 7 cm in diameter. Technical characteristics of this stimulator and coil have been previously described.[8,13,22] At the initial visit, prior to rTMS, motor threshold was determined for each subject by the method of limits and was defined as the lowest stimulation intensity capable of inducing five motor evoked potentials in the right APB muscle of at least 50 μV in a series of 10 single magnetic stimuli with the coil centered over the optimal scalp position. On each visit, stimulation was applied at 120% of motor threshold at 5 Hz for 10 seconds. Subjects received 10 trains, each separated by 2 minutes of rest. Thus, each stimulation session lasted about 20 minutes. Subjects received 500 stimuli per session and 2,500 stimuli over the course of the study, not counting those stimuli associated with determining the motor threshold (first visit) and finding the primary motor site for landmarking (each visit except for cerebellar stimulation).

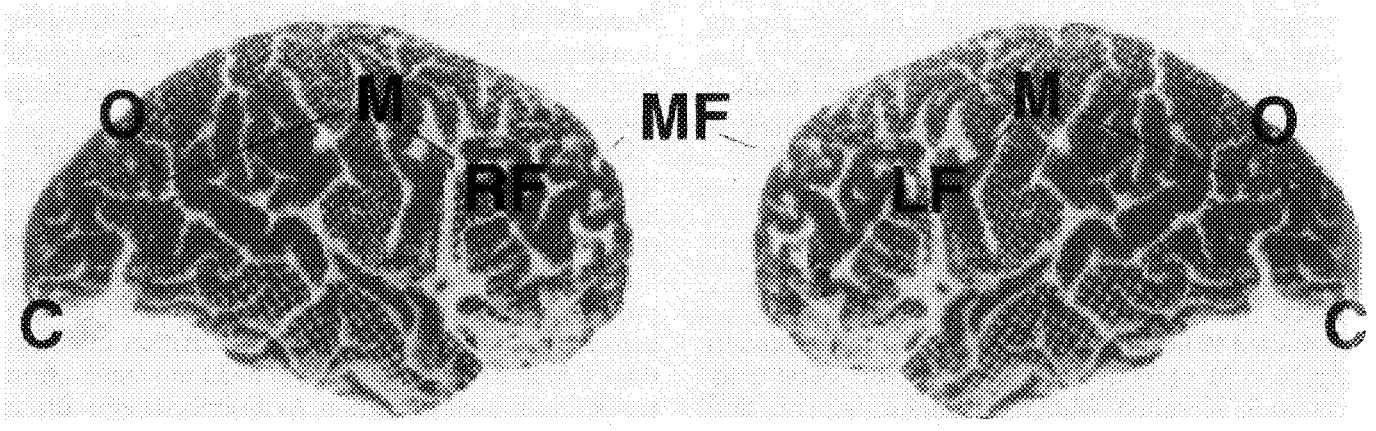
Safety of these stimulation parameters is supported by the available safety studies on rTMS and is discussed elsewhere.[22,28] Potential risks of the stimulation were discussed in detail with all subjects during the informed consent process. Magnetic stimulation was performed by trained neurologists (M.S.G., E.W., W.W.) in a room equipped with the necessary instruments and medication for the prompt treatment of a possible seizure.

RESULTS

Mood

The baseline ratings showed little variability across subjects or across sites. Mood ratings were therefore considered not in their absolute value but in their relative value, expressed as a difference from the morning baseline ratings.

FIGURE 1. **Lateral views of the two hemispheres illustrating the approximate regions stimulated in this study. In each individual, the region for optimal activation of the contralateral thumb was found ("M"), and then other brain regions were defined with respect to this. Because of variations in head size, the brain regions reported are only approximate. LF = left prefrontal; RF = right prefrontal; MF = midfrontal; M = motor; O = occipital; C = cerebellum.**



The overall effects of rTMS on the different mood ratings according to stimulation position were analyzed separately for each rating, using one-way analysis of variance (ANOVA) for repeated measurements.

On the "feel happy" rating, when one considers all regions and all time points, no significant differences appear. To determine whether the current study confirmed the previous report of Pascual-Leone et al.,[21] we confined the analysis to only the right and left prefrontal sites. There were significant differences in this rating by hemisphere. On the "feel happy" question, a repeated-measures ANOVA (right and left hemispheres by time) showed significant differences by hemisphere ($F = 7.1$, $P < 0.01$) with the largest difference between the two hemispheres occurring at 5:00 P.M. (Scheffé post hoc *t*-test, df = 1, $F = 4.7$, $P < 0.05$; Figure 2).

On the "feel sad" rating, again, there are no significant differences by regions or by time when all regions are combined. To directly test the findings of Pascual-Leone et al.[21] the right and left hemispheres were directly compared. Significant differences emerged by hemisphere (repeated-measures ANOVA, $F = 5$, $P = 0.03$).

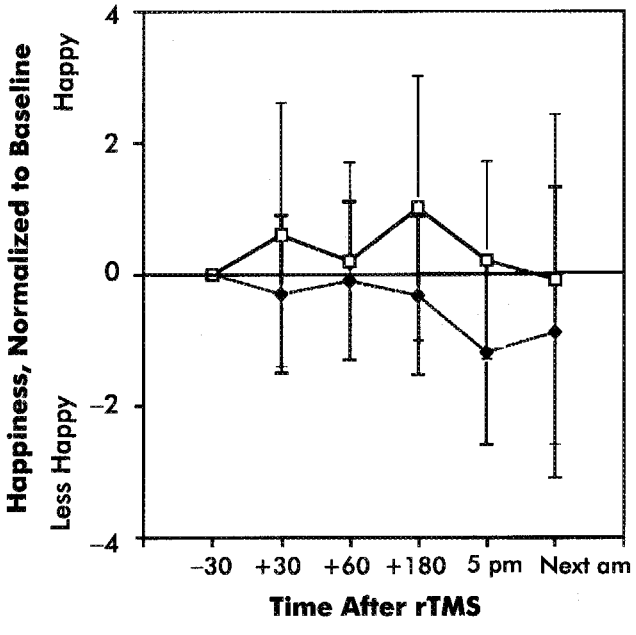
The forced-choice visual analog rating was less sensitive to changes than the specific questions above. Several individuals marked themselves as neutral on the visual analog scale while simultaneously reporting symptoms on the "feel happy" or "feel sad" scales. ANOVA by region and time for all regions revealed that there were no significant differences in visual analog ratings by region, although the graphs of the nonsignificant changes supported our findings above of increased sadness following left and increased happiness following right prefrontal stimulation.

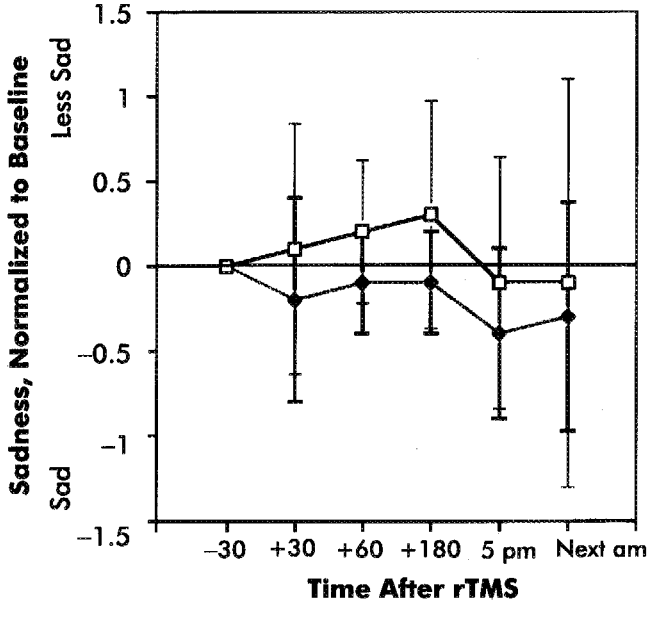
Spontaneous Subjective Reports

All subjects completed the study without complications. At the end of the study, subjects were asked to rank the sites in order of pain. The right and left prefrontal regions were ranked equally as the most painful, the midfrontal and cerebellum were intermediate, and the occipital site was the least painful. Overall, the absolute degree of pain was not troubling and did not interfere with the study.

One subject experienced profound dysphoria after the midfrontal stimulation. After the first train he spontaneously reported that it "made me want to smile." When asked whether he meant that it stimulated the smiling muscles or that it made him feel better, he replied, "both." After the fifth train he reported that he was no longer feeling "up." After the tenth train he spontaneously reported that he felt like he did at his grandmother's funeral, one month earlier. He was psychomotorically slowed, with a flat, saddened affect. This

FIGURE 2. **Different responses to the "feel happy" (top) and "feel sad" (bottom) questions following morning rTMS (10-point scale). All points are expressed relative to the morning baseline (with standard deviation error bars). After left prefrontal stimulation, subjects self-report as more sad and less happy (black diamonds). After right prefrontal stimulation, subjects are less sad and more happy (white squares). The differences by hemisphere are significant for both of these measures and confirm a previous study with higher frequency stimulation that looked at mood immediately after rTMS[21] and did not rate subjects throughout the day.**





lasted about an hour and then resolved. Interestingly, his prolactin levels increased mildly from baseline. Two other subjects also reported feeling slowed down or more apathetic the entire day following midline prefrontal stimulation.

Several subjects reported feeling more alert after left (1 subject), right (1 subject), or midline (2 subjects) prefrontal stimulation compared with how they felt immediately before the stimulation. Some subjects reported unusual sensations in their chest (2 reports: "coldness," "warmth") or stomach (1 report: "upset," "crawling," "nausea") during lateral prefrontal stimulation.

None of the subjects complained of a headache lasting more than several hours or required any treatment of complications.

Hormone Levels

The effects of rTMS on the different hormone levels according to stimulation position were analyzed separately for each hormone within regions and then across regions with one-way repeated-measures ANOVAs.

Serum TSH mean levels increased at +30 min and +60 min for both right and left prefrontal regions before returning to baseline at +180 min. Following midfrontal stimulation, serum TSH did not change at +30 or +60 but increased at +180 min. Serum TSH declined at all time points following occipital and cerebellar stimulation (Figure 3). Within regions over time, TSH changes were significant following left frontal stimulation ($F = 10$, df = 3, $P < 0.001$) as well as occipital stimulation ($F = 4.3$, df = 3, $P < 0.02$). Across regions, TSH varied significantly by region at +60 min ($F = 3.4$, df = 4, $P = 0.02$), with increased TSH following lateral prefrontal stimulation and decreased TSH following stimulation of other brain regions.

After a normal diurnal decline, serum prolactin mean levels declined following rTMS in all regions, with no significant differences across regions in levels at any time point. Interestingly, with the exception of the midfrontal site, within each region prolactin significantly declined throughout the morning (df = 3; right frontal $F = 5.3$, $P < 0.01$; left frontal $F = 5.5$, $P < 0.01$; occipital $F = 9.0$, $P < 0.001$; cerebellum $F = 4.5$, $P < 0.01$; midfrontal $F = 2.8$, $P = 0.07$). Only for the midfrontal region were there individuals in whom serum prolactin did not decline. One of these subjects also suffered transient dysphoria. Midfrontal stimulation also showed the least decline at +30 min, although the baseline was significantly lower than for the other regions.

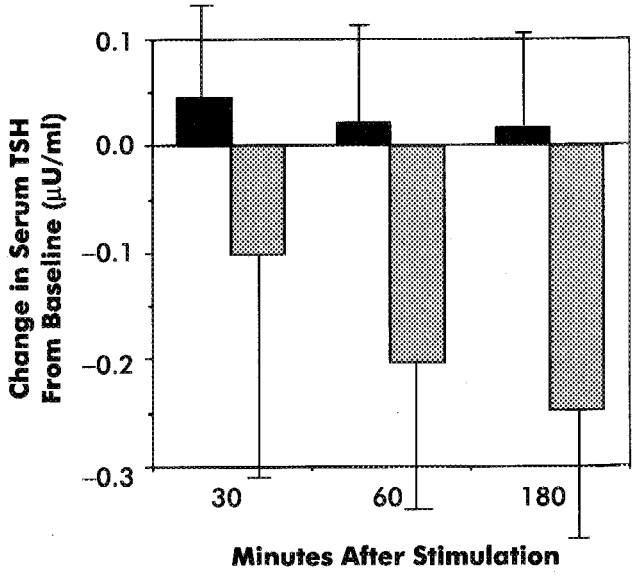
Serum cortisol mean levels increased slightly at +30 min after right and left prefrontal stimulation, then declined. Serum cortisol declined slightly after midfrontal and cerebellar stimulation and declined sharply after occipital stimulation. The changes in cortisol roughly corresponded to the subjective rankings of the amount of pain of the stimulus. Within regions, serum cortisol significantly varied by time in the right frontal ($F = 8.5$, df = 3, $P < 0.001$), left frontal ($F = 3.2$, df = 3, $P < 0.05$), and occipital sites ($F = 4.0$, df = 3, $P < 0.05$). Across regions, serum cortisol significantly differed at +30 min ($F = 6.3$, df = 4, $P < 0.01$).

We did not find any consistent relationships between subjective changes in mood and hormone levels in any of the prefrontal regions.

Reaction Time

Reaction time was measured on a Macintosh computer using a program described elsewhere.[25] Reaction times were analyzed by one-way ANOVA as absolute values according to stimulation position. There was no difference in reaction time by region ($n = 6$, $F = 1.07$, df = 4, $P = 0.38$). The reaction time test used in this study also indirectly measures implicit learning.[14,25] That is, in each block of stimuli, a pattern of 20 different responses is used. Subjects are not told that there is a repeating pattern. This pattern is repeated over 3 trials of 120 stimuli. If there is improvement in performance from

FIGURE 3. Serum thyroid-stimulating hormone (TSH) in the 3 hours following morning rTMS, by prefrontal (left, mid, right) or posterior (occipital, cerebellar) region and all normalized to the morning baseline. Serum TSH, which normally declines throughout the day, increases after all prefrontal and not after occipital or cerebellar stimulation. TSH values 60 minutes after stimulation varied significantly by region. Black bars: prefrontal. Gray bars: posterior.



Run 1 to Run 3, then some form of implicit pattern recognition or practice effect has occurred. We measured this difference in reaction time from Run 1 to Run 3 both within and between regions. Reaction time improved across the different blocks in all regions. There was no significant difference in this ability by region ($n = 6$, $F = 0.48$, df = 4, $P = 0.75$).

DISCUSSION

This study of the effects of a fixed dose of rTMS on prefrontal regions in healthy volunteers extends a previous study by Pascual-Leone and colleagues.[21] We found that right prefrontal stimulation was associated with transient happiness and left prefrontal stimulation was associated with subtle changes in sadness. These mood changes returned to normal the following day. Additionally, this study is the first to imply that rTMS might be associated with regionally specific changes in hormone levels (TSH and cortisol, but not prolactin) in rTMS doses that are relatively well tolerated and safe. Finally, the hormonal responses and subjective reports in this study raise the interesting possibility that rTMS, which directly excites superficial cortex in the prefrontal areas, may secondarily influence deeper brain regions and produce changes in the hypothalamal-hypophyseal-pituitary axis.

This study should be interpreted with some caution, however. It suffers from several of the current limitations in the evolving field of rTMS as a neuroinvestigative probe.

First, it is unclear to what extent the findings in this study might be specific to any of the numerous variables associated with rTMS. These variables include not only the brain region stimulated, but also the type of stimulator and stimulating coil (which determine the distribution and intensity of the stimulation, both absolute and relative to each person's motor threshold [MT]); the frequency and duration of the stimuli; the length of stimulated time relative to rest time; and the total number of trains within a day or over a day. It is conceivable that different dosing regimens may have varying effects on the underlying prefrontal cortical tissue. In motor cortex studies, some dosing regimens may be stimulative and additive and others may be inhibitory with respect to motor firing.[10] Reasoning from motor studies, we think that the dosing frequency used in this study is an additive, stimulative dose.[10] The previous study by Pascual-Leone et al.[21] used 10 trains of 110% MT at 10 Hz for 5 seconds separated by 25-second pauses, with a 30-minute rest between different sites. Preliminary data generated in these and other studies possibly indicate that more profound changes in mood occur with higher frequency stimulation and shorter pauses.

The regions chosen for stimulation were only approximate and were not MRI-defined. For better accuracy of regional localization, future studies might find the exact brain region on the basis of structural imaging (MRI scans and digitized scalp positions). It is also unclear how deep the stimuli reached in this study, either directly or secondarily. Work in our own lab (Wassermann, personal communication), as well as theory, indicates that direct stimulation is a function of coil geometry and field strength and, with the parameters used in this study, reaches up to 4 cm below the coil or into superficial layers of cortex.[9,29,30] Ongoing studies with functional neuroimaging (SPECT, fluorodeoxyglucose PET, and fMRI) will help to better address this issue as well as possibly map important areas that are indirectly stimulated.

This study, like many attempting to assess changes in mood or pain, inherently suffers from the problem of rating a subjective variable. However, the rating instruments used have been validated in several studies.[26]

Finally, there was no nonstimulated or placebo rTMS. Because of the difficulty of designing a true sham rTMS session, especially after someone has already experienced rTMS, we chose instead to stimulate a region of the brain with little predicted effect on mood (occipital cortex). This lack of a nonstimulated group allows for the possibility that our lateralized findings may have resulted not from direct brain but rather indirect sensory stimulation over the different hemispheres. Future studies with different placebo controls are necessary to exclude this possibility.

Despite these limitations, this pilot study has found 1) that prefrontal stimulation is safe and well tolerated, 2) that there are lateralized effects on mood, and 3) that prefrontal stimulation may affect some neuroendocrine measures.

Safety and Tolerance

The stimulation parameters used in this study were well within published guidelines, and no ill effects were found. Interestingly, subjects rated lateral prefrontal stimulation as much more painful than midfrontal, occipital, or cerebellar stimulation. The pain induced by lateral prefrontal stimulation is likely due to magnetic stimulation of the underlying temporalis muscle and nearby facial nerve. Several subjects had mild tension-type headaches afterward, which responded to treatment with non-narcotic agents such as aspirin or acetaminophen. Further, there was no effect on reaction time either by region or as a general effect of rTMS, thus

confirming that this is likely a safe procedure in an outpatient setting.

Mood

We found that left prefrontal stimulation was associated with an increase in self-rated sadness, whereas right stimulation was associated with increases in happiness. This study thus confirms and extends the study of Pascual-Leone et al., who stimulated different brain regions within the same day.[21]

Several different lines of investigation have linked the left prefrontal cortex to changes in mood. PET or SPECT scans have shown that clinically depressed subjects have abnormal prefrontal function, more commonly on the left than the right.[31–37] Several studies of poststroke subjects have found that damage to the left prefrontal cortex greatly increases the likelihood of a poststroke depression.[38–40] In addition, depressed subjects with multiple sclerosis (MS) have more white matter lesions on the left side compared with nondepressed MS control subjects.[41] Two PET studies in healthy volunteers have now demonstrated that there is increased left orbitofrontal and left prefrontal activity during states of transient sadness.[42,43] These findings are also consistent with sad, crying reactions to left-sided Wada or speech-arrest testing in epileptic patients.[13,44] Also in line with the findings in this study, damage to the right hemisphere, especially the right prefrontal or temporal cortex, has been linked to primary or secondary mania.[45–48]

It is unclear whether we have transiently augmented or diminished the primary function in this area. It is more likely that we have transiently caused hypofunction in these prefrontal regions, similar to a Todd's postictal paralysis; behaviorally, these data are more consistent with lesions of these regions than with excitation. Another possibility is that we transiently increased activity during stimulation and then later caused a hypoactivity. This better fits the temporal course of the mood changes. The studies to date imply that higher stimulation frequencies and intensities are associated with faster and more significant changes in mood than lower frequencies and intensities.

We and others have been interested in whether rTMS may be used to better understand the physiological basis of emotion regulation and to treat clinical depression.[49–54] The lateralized effects on mood in this study as well as the Pascual-Leone study[21] need to be integrated with recent data showing lateralized effects of rTMS as a treatment mode for clinical depression. Earlier we conducted a pilot open study of chronic daily rTMS in medication-resistant depression. In the first week we applied rTMS over the right or left prefrontal cortex and found that left prefrontal stimulation was superior in improving mood. In the later treatment mode of this study, chronic daily rTMS over the left prefrontal cortex (20 Hz, 80% MT, 2 s × 20 over 20 min) had a significant antidepressant effect on the group as a whole as well as producing remissions in 2 subjects who had been ill for years.[54] More recently, Pascual-Leone and colleagues have reported a crossover study in 3 medication-resistant depressed subjects (Pascual-Leone, personal communication). Daily treatment with left, but not right, prefrontal stimulation was an effective antidepressant (10 Hz, 120% MT, 5 s × 20 over 10 min). The challenge for the future is to resolve the paradox that in healthy control subjects left prefrontal stimulation subtly and subclinically produces sadness, whereas repeated daily administration in clinically depressed patients normalizes mood. We are currently investigating this with blinded clinical trials, animal studies looking at second messengers and gene expression, and the combination of rTMS with functional imaging (SPECT, PET, and fMRI).

Hormone Levels

Previous human studies of rTMS, largely over the motor strip, have failed to demonstrate significant changes in neuroendocrine measures. From a neuropsychiatric perspective, the ability to indirectly influence hormones with rTMS is quite important. Interestingly, in a recent study Belmaker and colleagues found that rTMS acted in the same way as ECT in a rat model of depression by potentiating apomorphine-induced stereotypy.[55] This potentiation is thought to be mediated through dopaminergic mechanisms. Because of the difference in stimulator coil to brain size ratio, rTMS in rats stimulates a much larger relative region than in humans. The lack of significant increases in serum prolactin in this study could be interpreted as indirect evidence that the rTMS stimulation was in fact subconvulsive, since most temporal and some frontal lobe seizures are associated with increases in prolactin.[56]

We found region-specific changes in TSH as well as serum cortisol. Increases in serum cortisol, and to a lesser extent TSH, can be a nonspecific response to an acute stress. The significant changes in serum cortisol by region 30 minutes after stimulation appear to roughly correspond to the subjective reports of the pain and distress of each region. That is, the regions where sensations were most unpleasant (right and left prefrontal) produced the greatest relative elevations of serum cortisol. Further work is necessary to delineate whether the changes in serum cortisol are specific or nonspecific in nature.

Serum TSH was elevated by all prefrontal regions, including the relatively painless stimulation of the mid-

frontal region. Between regions, serum TSH varied significantly 60 minutes after stimulation, with lateral prefrontal sites causing increases and other regions causing decreases. The time course of TSH rises differed, although nonsignificantly, between lateral and midline prefrontal stimulation; lateral caused immediate increases in TSH, whereas midfrontal had a peak TSH change at 180 minutes. TSH did not increase after stimulations of the occipital or cerebellar regions, which were rated as being equally as painful as the midprefrontal site.

Thus, the increase in serum TSH following stimulation of all prefrontal regions is likely more than a simple nonspecific stress response and may be due to a more direct mechanism. Thyroid abnormalities have been linked with abnormalities in mood[57–59] as well as regional blood flow.[60] However, we did not find a significant relationship between changes in mood and changes in serum TSH, although the small numbers in this study limited a formal investigation of this area. It is conceivable that direct prefrontal cortical stimulation has indirectly influenced regions dense in thyrotropin-releasing hormone (TRH)—limbic system, hypothalamus, pineal gland—thereby altering brain TRH and then serum TSH. We have recently found that intrathecal administration of TRH causes an improvement in mood in acutely depressed patients and also causes increases in serum TSH, which peaks at 180 minutes after administration.[59]

CONCLUSION

This study highlights the safety as well as the potential of rTMS to explore the prefrontal cortex and other brain regions. rTMS appears to be a promising new tool for advancing understanding of the brain basis of behavior in both health and neuropsychiatric diseases.

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