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# Combining high and low frequencies in rTMS antidepressive treatment: preliminary results

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The antidepressive potency of repetitive transcranial magnetic stimulation (rTMS) seems to depend on variables such as the stimulation placements, different frequencies, stimulus intensities, coil shape and interstimulus intervals. The aim of this pilot study was to investigate the augmentation properties of rTMS combining low and high frequencies. Thirty six depressed medicated in-patients were recruited and assigned to three different rTMS treatment modalities as an add-on strategy (each $n = 12$). In group 1 a stimulus intensity of 110% of the motor threshold (MT) was used with a frequency of 10 Hz over the left dorsolatero prefrontal cortex (DLPC). The right DLPC was stimulated in the same session with 110% MT at 1 Hz. In group 2 the patients were stimulated only over the left DLPC with alternating trains of 110% MT at 10 Hz and trains of 110% MT at 1 Hz in the same session. In group 3 the high frequency stimulation over the left DLPC was performed as an internal control group. None of the treatment modalities was superior but different side effects were observed. These preliminary findings suggest that rTMS, at varying frequencies and stimulation placements, evokes different psychoactive effects of clinical relevance. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — repetitive transcranial magnetic stimulation; stimulation placement; high and low frequency; side effect

## INTRODUCTION

The antidepressive potency of repetitive transcranial magnetic stimulation (rTMS) seems to depend on variables such as the stimulation placement(s), different frequencies, stimulus intensity, coil shape, interstimulus intervals etc (George *et al.*, 1999; Sackeim, 2000). The importance of frequency is thus unclear, despite knowledge that neuronal stimulation at different frequencies can have widely divergent and even antagonistic psychotropic effects (Conca *et al.*, 1996; Post *et al.*, 1997; George *et al.*, 1999; Klein *et al.*, 1999). Furthermore, TMS/rTMS can affect neuronal and/or glial activities in cortical and subcortical areas, ipsi- and contralaterally, also distant from the stimulation site (Cracco *et al.*, 1993; Kimbrell *et al.*, 1997; Conca *et al.*, 2001). However, stimulation at $\leq$1 Hz over the right prefrontal cortex inhibits ipsilateral neuronal activity and seemingly activates the contralateral area (Fox *et al.*, 1997; Post *et al.*, 1997). An opposite mechanism may be assumed by stimulating at $\geq$10 Hz over the left prefrontal cortex (Kimbrell *et al.*, 1997; Post *et al.*, 1997; Stallings *et al.*, 1997). Both stimulation conditions were reported to exhibit antidepressive activities (George *et al.*, 1999; Sackeim, 2000). Thus, the first aim of our study was to investigate the possible augmentation of the antidepressive potency of rTMS by combining low frequency over the right dorsolatero prefrontal cortex (DLPC) and high over the left during the same session. Furthermore, it is known from the ECT research that the synchronization of spikes (reflecting excitatory phenomena) and slow waves (reflecting inhibitory phenomena) recorded by EEG during the ECT treatment supports the therapeutic quality of the seizure (Swartz, 1993; Sackeim, 1999). Based on this knowledge and raising the hypothesis that ipsilateral magnetic stimulation at alternating low and high

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frequencies over the same placement might also synchronize neuronal excitation and inhibition, the second aim of this study was to analyse possible antidepressive properties of rTMS alternating low and high frequencies over the left DLPC, during the same session.

## PATIENTS AND METHODS

### *Patients*

After approval of the study by the Local Ethics Committee and after written informed consent, we recruited 36 severely depressed medicated in-patients diagnosed according to ICD 10 criteria; 21 were suffering from unipolar depression, six from bipolar depression both with psychotic feature, seven from dysthymia and two from atypical depression; 21 patients were diagnosed also suffering from the dependent personality disorder. The medication conditions were defined using the classification of Thase and Rush (1995); all patients had to be classified at stage four of treatment resistance, indicating the failure to respond to two different adequate monotherapy trials of medications with different pharmacological profiles and the failure to response to a second augmentation strategy. Two senior psychiatrists blinded for treatment modalities completed the 21-item Hamilton Rating Scale for Depression (HAM-D) 1 day before the first treatment and 1 day after completion of the rTMS course. For inclusion a minimum score of $\geq$24 had to be achieved (Hamilton, 1967). The Clinical Global Improvement (CGI) scale was completed 1 day after rTMS (Beneke and Rasmus, 1992). Patients remained on the last prescribed pharmacotherapy. Patients were randomly assigned to three different rTMS treatment modalities whilst on stable medication conditions for 5 consecutive days.

### *rTMS protocol*

The motor threshold (MT) was defined as the minimum stimulator output able to evoke a discernible potential with an amplitude of at least 50 μV in the muscle abductor digiti minimi (ADM) in five of ten trials. rTMS was delivered with a Cadwell stimulator on 5 consecutive days at one session/day with a figure of 8 shaped water-cooled coil. For group 1 ($n = 12$) a the stimulus intensity of 110% of the motor threshold of ADM was used at a frequency of 10 Hz, 10 trains, train duration 10 s, each with a train interval of 60 s over the left DLPC. Over the right DLPC a stimulus intensity of 110% of MT at 1 Hz, 1 train at 300 s for a total dose of 6500 stimuli was applied. In group 2 ($n = 12$) only the left DLPC was stimulated at 110% of MT, 10 Hz, 10 s train duration (110 stimuli) alternating with 110% MT, 1 Hz, 30 s train, with an interval of 6 s for 10 times/session, resulting in a total dose of 6500 stimuli in 5 days. In group 3 ($n = 12$) standard stimulation over the left DLPC was performed using 110% of MT, 10 Hz, 13 train and 10 s train duration, also applying in total 6500 stimuli. The study period was scheduled for 5 days.

### *Therapeutic outcome measurement*

Dichotomous outcome rating was based on CGI scores. Patient response was defined as achieving at least moderate improvement (CGI improvement score $> 4$) and being no more than mildly ill (CGI severity score $<4$).

### *Statistical analysis*

Because the different previous and present drug treatment, illness and patient characteristics, as related to the responder group and the non responder group, were examined, the non parametric Mann Whitney U test and the $\chi^2$ test for categorical variables, respectively were used. $p$ values $\leq 0.05$ were accepted as significant (Sachs, 1992).

## RESULTS

Table 1 summarizes the patient characteristics and illness-related data. In group 1 six of twelve patients presented a good clinical outcome (50%), four showed no change (33.3%) and two patients deteriorated (16.7%). In group 2 eight patients had a good clinical outcome (66.7%) and four had no change (33.3%). In group 3 ten patients showed a good clinical outcome (83.3%). In two cases (16.7%) a psychotic reaction was observed causing the discontinuation of rTMS.

No statistical differences in clinical outcome between these groups could be calculated $\chi^2 = 5.1$; $p =$ n.s.). Furthermore, none of the demographic, illness, diagnosis or co-diagnosis related data revealed any influence on the response rate except for handedness; right-handed patients showed a weak statistical tendency to greater therapeutic response (non responders vs responders: $\chi^2 = 8.1$; $p < 0.08$). No seizure as well as no after discharge phenomena recording MEP could be observed. Seven (19.1%) patients of 36 experienced a mild headache during the first session, which remitted spontaneously.

 

Table 1. Patients, illness and outcome related data

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Number of patients | 12 | 12 | 12 |
| Age ( ± SD) | 48.2 ± 16.1 | 44.8 ± 14.8 | 46.8 ± 10.3 |
| Sex (F/M) | 9/3 | 8/4 | 8/4 |
| Handedness (R/L/Bi) | 9/3 | 12 | 9/1/2 |
| Illness duration in years ( ± SD) | 10.3 ± 10.7 | 7.9 ± 8.7 | 15.6 ± 8.8 |
| Episode duration in months ( ± SD) | 5.3 ± 2.9 | 4.9 ± 4.0 | 7.6 ± 5.9 |
| Episode number ( ± SD) | 6.1 ± 3.7 | 5.7 ± 4.9 | 6.9 ± 4.7 |
| HRDS ( ± SD) | | | |
| Before rTMS | 29.4 ± 4.3 | 31.4 ± 6.3 | 30.2 ± 5.7 |
| After rTMS | 22.5 ± 3.9 | 21.8 ± 7.7 | 21.4 ± 6.7 |
| Patients with CGI > 4 (%) | 6 (50%) | 8 (66.7%) | 10 (83.3%) |
| Patients with adverse events (%) | | | |
| Drowsiness | 0 | 5 (41.7%) | 0 |
| Cephalea | 8 (67%) | 0 | 8 (67%) |
| Psychotic deterioration | 0 | 0 | 2 (16.7%) |

In group 1 five patients of the subgroup suffering from personality disorder were defined as non-responders (83.3%). In group 2 six of nine patients affected by personality disorder were responders (86.7%). Six (50%) patients of group 3 suffered from a personality disorder, all of them showed a good clinical outcome.

## DISCUSSION

Pascual Leone *et al.* (1998) presented data indicating that responders to high frequency rTMS do not respond to low frequency and vice versa; nonetheless rTMS seems to evoke an antidepressive efficacy in our patients treated with the combination of low frequency over the right DLPC and of high frequency over the left during identical sessions. Additionally, the results support the hypothesis that ipsilateral magnetic stimulation at alternating low and high frequencies over the left DLPC might also exhibit antidepressive efficacy. Although the number of responders (10 of 12 patient) to the left DLPC high frequency rTMS could suggest a better outcome our preliminary findings did not indicate a supremacy in terms of efficiency of one of the selected parameters. It is noteworthy that none of the expected variables such as the illness and episode duration, the episode numbers, pre-existent drug therapies, the age and the gender modulated the clinical outcome. Especially, the role of co-morbidity seems of interest. Despite reports suggesting that the presence of the co-morbidity of personality disorders generally predicts a poorer outcome (Shea *et al.*, 1993), in our pilot study the incidence of personality disorders varied within the responders and revealed no influence on the outcome. These different impacts of diagnosed personality disorders support the hypothesis described by Svarkic and Cloninger (1994) that the relationship between personality and affective disorders is still an open question.

However, the reported side effects, differing between the groups, are of interest. Five (41.7%) patients in group 2, where the frequencies were alternated over the left DLPC, described a pleasant drowsiness during the all stimulation sessions, whereas high frequent stimulation alone in groups 1 and 3 was accompanied by a localized painful feeling over the high stimulation site in 70% of all patients during the first session yet dissolving in almost all patients at the second session. These observations support the different acute psychoactive properties of rTMS depending on the stimulation site and on the frequencies (George *et al.*, 1996).

Two patients (16.7%), left handed women in group 3, showed a psychotic deterioration complaining of aggravated suspiciousness and on nihilism as well as on delusions of guilt during the second rTMS session. Patients refused to undergo further rTMS treatments, and since the delusions dissolved within 2 days after the discontinuation of rTMS a psychotomimetic potency of rTMS at high frequency over the left DLPC should at least be assumed. In this context the significance of handedness should be considered since this adverse event has a high impact and all responders were right-handed; although the statistical significance for handedness was indeed weak regarding the outcome, further research on adopting low and high frequencies over both hemispheres should be informed of this lateralization phenomenon.

## CONCLUSION

These preliminary findings suggest that repetitve transcranial magnetic stimulation (rTMS), at varying

 

frequencies and stimulation placements evokes different psychoactive effects of clinical relevance especially with regard to possible side effects.

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