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LETTER TO THE EDITOR

Potential differential effects of 9 Hz rTMS and 10 Hz rTMS in the treatment of depression

To the Editor:

The majority of high-frequency repetitive transcranial magnetic stimulation (rTMS) studies in depressed patients use 10 Hz stimulation over the left dorsolateral prefrontal cortex (DLPFC). However, several placebo-controlled trials have used *different* stimulation frequencies such as 5, 10, 15, 17, 20, and 25 Hz[1] and all found antidepressant effects. The choice of high-stimulation frequencies to date has remained fairly random and has rarely been based on individual physiological characteristics of a patient. To the authors' knowledge, only two studies, neither in depressed patients, have used an electroencephalogram (EEG)-based approach to establish the rTMS frequency that was linked to the individual patients' alpha peak frequency (iAPF). Klimesch et al.[2] and Jin et al.[3] both demonstrated that subjects with a personalized iAPF, it was detemined that rTMS had a greater effect (better improvement at a mental rotation task[2] and a higher improvement in negative symptoms in a group of patients with schizophrenia[3]) in comparison to two groups that received treatment with 3 Hz and 20 Hz stimulation frequencies. Both these studies demonstrated frequency-specific effects titrated to the individual subject.

These two papers and the availability of full quantitative EEG (QEEG) data led us to investigate the relationship between the iAPF and the decrease in depressive symptoms in a group of depressed patients who were treated with a 10 Hz rTMS protocol (110% motor threshold [MT]; ITI=30 seconds, 30 trains; train length 5 seconds, based on 5-cm rule, for more details also see Spronk et al.[4]) treated in an open-label manner. The iAPF was quantified from location F3 during Eyes Closed EEG. Figure 1 shows the percentage decrease on the Beck Depression Inventory (BDI) against the frontal iAPF of the patients who received treatment with the standard stimulation frequency of 10 Hz (black). The black bars, representing treatment responses of 24 patients treated with 10 Hz rTMS, show a relation between iAPF in which a lower APF was related to a smaller decrease in depressive symptoms. The most striking finding was that patients with an iAPF of 9 Hz (1 Hz below the stimulation frequency of 10 Hz) seemed to benefit most from the treatment. Based on these initial findings and the study by Klimesch,[2] we adjusted our protocol to stimulate all patients at an individualized stimulation frequency of iAPF + 1 Hz (Figure 1, grey bars). We kept all other stimulation parameters identical such as total number of stimuli, interstimulus interval, and percentage MT.

On the basis that previous high-frequency studies have shown beneficial treatment effects for various stimulation frequencies (e.g., 5, 10, 15, 17, 20, and 25 Hz),[1] there was no reason to assume that treatment frequencies other than 10 Hz would result in nonbeneficial treatment effects. In contrast; by means of individualizing the stimulation frequency based to one's iAPF, larger and faster beneficial treatment effects were expected.

An interim analysis of the first 18 subjects treated with this iAPF + 1 Hz stimulation protocol, however, did not support our hypothesis. Overall, treatment efficacy for the group that was treated with the individualized stimulation frequency was generally lower as compared to the group who was treated with standard 10 Hz rTMS. This was mainly the result from the clients with an iAPF of 8 Hz (who were stimulated with 9 Hz). An independent sample *t* test showed that within the group of patients with an iAPF 8 Hz, the patients who were treated with an individualized stimulation frequency of 9 Hz, showed a trend toward worse treatment effects as compared with the group who received the standard protocol with a stimulation frequency of 10 Hz ($P=.078$). It has to be noted that this effect is not corrected for multiple tests. Hence, it indicates only a small trend. Differences in treatment effect for patients who fell in the groups with other iAPF were not significant. For the two subgroups with an iAPF of 8 Hz, there were no differences between the average age (43 versus 44 years; $P=.75$), Beck Depression Inventory (BDI) at intake (27 versus 34; $P=.19$), and percentage of female subjects (50% versus 43%). In the iAPF rTMS group, there seemed to be more unmedicated subjects (3/7) as compared with the 10 Hz rTMS group (1/8); however, when comparing the difference in BDI scores between unmedicated versus medicated patients the difference

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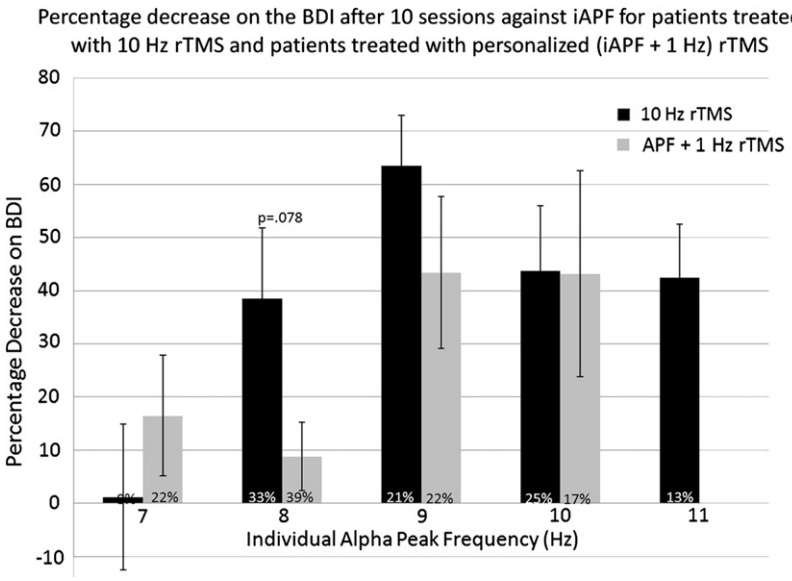

Figure 1 This figure shows the percentage decrease on the BDI after 10 sessions rTMS plotted against the frontal iAPF of clients. Error bars indicate standard error of the mean. The black group was the original group in which all subjects were stimulated with 10 Hz (n=24) and the grey group was treated with iAPF + 1 Hz rTMS (n=18). Note the near significant lower response for only the group with an iAPF of 8 Hz (rTMS frequency of 9 Hz).The percentages at the bottom indicate the percentage of clients with that specific iAPF in that group. BDI= Beck Depression Inventory; rTMS=repetitive transcranial magnetic stimulation; iAPF=individual alpha peak frequency;

was 5% versus 11%, respectively, making it unlikely that medication status could explain this finding. Data on previous medication failures were not available.

These results suggest that there are possibly differential effects of different rTMS stimulation frequencies, which in turn might be dependent on individual characteristics such as the iAPF. Furthermore, our results do not support the proposition that iAPF + 1 Hz stimulation in depression improves clinical efficacy as measured by the decrease in BDI score after 10 sessions. Note that for all these patients rTMS was combined with psychotherapy that was exactly the same for both groups. It is unlikely that the psychotherapy should cause such differential effects within the short treatment period.

Few other studies that used rTMS stimulation frequencies that are not harmonics of 10 Hz have been performed. For instance, Bretlau et al.[5] used 8 Hz (90% MT) and found a large effect size of 0.70, whereas Miniussi et al.[6] used 1 Hz and 17 Hz stimulation of the left DLPFC and found very modest effects. Interestingly, 17 Hz is almost a harmonic of 9 Hz, potentially connecting their findings to ours.

Finally, it can be concluded that, regardless of the chosen stimulation frequencies, the iAPF to some degree does predict treatment outcome to rTMS treatment in depression. In general, a lower iAPF of 7-8 Hz was associated with a lower efficacy; this was true for both stimulation approaches. Conca et al.[7] also found that nonresponders to rTMS showed a lower iAPF (8.0 Hz) as compared with responders (9.5 Hz).

Further controlled studies are needed to elucidate the differential effects of different stimulation frequencies and investigate the potential relation to EEG parameters such as iAPF to further improve the clinical efficacy of rTMS.

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