

## INTENSIVE rTMS APPLICATIONS IN DIFFICULT TO TREAT PSYCHIATRIC PATIENTS: SOME CASES

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### SUMMARY

Despite adherence to treatment guidelines, some patients are resistant to several psychopharmacological interventions. Guidelines to overcome treatment resistance are scarce and new treatment modalities are needed. When confronted with psychopharmacological failure, repetitive transcranial magnetic stimulation (rTMS) therapy can be considered. In these case series a combative high frequency (HF)-rTMS protocol with frequent stimulations at suprathreshold intensity was applied for treatment-resistant depression (TRD), schizoaffective- and bipolar I disorder, mixed episode. Besides effectiveness, tolerability was closely monitored. All three patients, suffering from different psychiatric conditions were experiencing limited to excellent clinical improvement without serious side effect or adverse events. These very preliminary results suggest, along with research using comparable intensive stimulation parameters for treatment-resistant depression, that 'aggressively' targeting the left DLPFC is well tolerated and safe. Our clinical results suggest a possible beneficial treatment strategy of HF-rTMS protocols following unsuccessful. Larger sham-controlled studies are needed to substantiate our results.

**Key words:** HF-rTMS - treatment-resistance - psychiatric disorders

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### Introduction

Over the past decades, repetitive transcranial magnetic stimulation (rTMS) applied to the left DLPFC has been proven safe and relatively efficient for patients with treatment-resistant depression (TRD)(George et al. 2010). However, it has been hypothesized that more intensive rTMS protocols could increase clinical outcome (Gershon et al. 2003). Currently, more intensive rTMS protocols spread over 2 weeks or more are investigated. Few studies used this rTMS application on a more intensive way by stimulating patients more than once a day. (Holtzmeier et al. 2010; Zeeuws et al., 2010). The following presentation will report on the use of a new intensive high frequency (HF)-rTMS protocol in three psychiatric patients with different psychopathologies who did not respond to current psychopharmacological treatment strategies.

### Subjects and method

Subjects were recruited through psychiatrist referral. The diagnosis was confirmed in our university hospital (UZBrussel) with the Mini (Sheehan et al., 1998).. A 66 year old female patient was diagnosed with TRD, a 24 year old male patient with schizoaffective disorder bipolar type and the female patient, 52 years old, with bipolar type I disorder, mixed episode. The case of this last patient is more extensively describe in Zeeuws et al. (2010). All patients had been unresponsive to adequate psychopharmacological treatments. None of them had been treated with rTMS in the past. No patient had increased risk of seizure and medication that lowers the seizure threshold was tapered off. In practice, only our schizoaffective patient was on his antipsychotic medication (clozapine 300 mg/day).

For the administration of HF-rTMS, we used a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK), connected to a figure-of-eight-shaped coil. Before each application we determined the motor threshold (MT) using EMG. A stimulation intensity of 120% of the subjects MT of the right abductor pollicis brevis muscle was used. To accurately target the left (DLPFC), the patient underwent a T1-weighted MRI (3DTFE, voxel size 1 x 1 x 1 mm) of the brain using a 1.5 T Intera MR scanner (Philips, Best, the Netherlands). Based on the patients' own known gyral morphology, we localized the left DLPFC visually on the 3D surface rendering of the brain and marked the middle part of the midfrontal gyrus as the centre of the left DLPFC (Brodmann area 9/46). The corresponding coil position was located by determining the perpendicular projection of this point on the scalp (Peleman et al. 2010). In each high-frequency (20 Hz) stimulation session, the patient received 40 trains of 1.9 seconds duration, separated by an intertrain interval of 12 seconds. The treatment protocol of in total 20 HF-rTMS sessions was spread over 4 days (5/day in the afternoon; from 14:00 to 18:00 hours), yielding a total of 31,200 stimuli. Patients were visually monitored for seizure during treatment and were asked about adverse effects following each treatment session and after 2 and 4 weeks.

The severity of depression was assessed with the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton 1967). As it has been reported that depressed mood might switch into mania during left sided HF-rTMS treatment (Sakkas et al. 2000) and concerning the known mood instability in 2 patients, manic symptoms were rated with the Young Mania Rating Scale (YMRS; Young et al. 1978).

Psychomotor symptoms were rated by a psychiatric nurse using the Depressive Retardation Rating Scale (DRRS). The DRRS was designed to measure the motor and mental features of depressive slowing and consists of an objective (motor and verbal items) and a subjective subscale (ideational items) (Widlöcher 1983).

## Results

The psychiatrists assigned to the patients during their hospitalisation, independent of the rTMS administrators, evaluated clinical outcome. Importantly, no seizure activity nor serious adverse event was observed. Side effects reported upon questioning included headache on the first two days and mild pain at the stimulation site in one case.

As described in Zeeuws et al. (2010), in the case of the bipolar patient with mixed episode, clinical response was even immediately observed following the first day of HF-rTMS treatment (defined as a 50% reduction of the baseline HDRS score).

The TRD patient could also be considered as a responder, but with slight delay. Her HAMD score went from 28 to 5 only after having completed the entire treatment protocol a couple of days later.

Although there was only a small change (minus 5) in the HAMD scores of the schizoaffective patient, his scores were already low initially (ranging from 9 to 11) prior to HF-rTMS. Moreover the primary focus for this patient wasn't as much treatment of depression but the improvement of negative symptoms. Thus for this subject the brief psychiatric rating scale BPRS was additionally taken and the subscales blunted affect and emotional withdrawal improved during treatment, however not significantly. No positive symptoms were present during or after HF-rTMS. None of the patients had a significant elevation of their YMRS scores; neither did the DRRS reveal an important change in psychomotor activity.

## Discussion

First of all, our current case observations indicate that the use of intensive HF-rTMS treatment applied to the left DLPFC is safe and well tolerated. Furthermore, based on these very preliminary case results in medication resistant psychiatric patients, our intensive HF-rTMS treatment protocol suggest a positive clinical efficacy comparable with common rTMS treatment paradigms delivered over several weeks. Our clinical observation in our TRD patient supports the results of Holtzmeier et al. (2010) open study in TRD patients, were also comparable combative stimulation parameters were used. However, this case series is limited by the

lack of placebo. All patients were experiencing improvement without serious side effect or adverse events.

## Conclusion

Along with research using comparable intensive stimulation parameters for treatment-resistance, 'aggressively' targeting the left DLPFC was tolerated and safe in our three patients. Our clinical results suggest a possible beneficial treatment strategy following unsuccessful psychopharmacological therapy. Larger sham-controlled studies are needed to substantiate these recent findings.

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