Low- vs high-frequency repetitive transcranial magnetic stimulation as an add-on treatment for refractory depression

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INTRODUCTION
Depression constitutes a major public health concern with a considerably high level of morbidity and mortality. Although antidepressant (AD) treatments have demonstrated their efficiency, a substantial number of depressed patients (50–60%) respond only partially or not at all to at least one trial of an antidepressant medication (Steffens et al., 1997) and close to 20% of these patients are refractory to any antidepressant medication (Fava, 2003). Moreover, the clinical utility of antidepressant drugs is impaired by the delay in onset of their therapeutic action.

Most of recent studies as well as meta-analysis support an antidepressant effect of high frequency (HF) repetitive transcranial magnetic stimulation (rTMS) applied to the left dorsolateral prefrontal cortex (LDLPC; George et al., 2010; for review: Brunelin et al., 2007). However there remains some confusion about the best beneficial stimulation site to target as well as the best parameters to apply. While the impact of starting a combination between rTMS and an AD at the same time is still poorly studied, some authors support the hypothesis that this association could shorten the AD treatment delay of action (Poulet et al., 2004; Rumi et al., 2005). On the other hand, there is growing evidence that HF LDLPC is as effective as low frequency (LF) rTMS applied to the right DLPFC (RDLPFC) in the treatment of depressive episode (Höppner et al., 2003; Isenberg et al., 2005; Stern et al., 2007; Fitzgerald et al., 2009; Pallanti et al., 2010; Rossini et al., 2010).

We report here results from a pilot single blind double arms controlled study investigating the antidepressant effect, in association with venlafaxine, of active HF (10 Hz) LDLPC rTMS compared to active LF (1 Hz) LDLPCF rTMS (150 mg) in patient with refractory depressive symptoms.

MATERIALS AND METHODS
Sixteen patients with unipolar major depression according to DSM IV were included through clinical and MINI evaluation (Mini version 4.4). All of them gave their written informed consent before entering the study which was approved by a regional ethical committee. They were aged between 18 and 65 and have not tried venlafaxine for the present depression episode. Patients were recruited at the “Le vinatier” Hospital. At inclusion, all of them present a Montgomery and Asberg (1979) Depression Rating Scale (MADRS) score >20 despite the prescription of an AD at efficient dose for at least 12 weeks. Patients respond to stage 1 of treatment-resistant depression as described in Fava (2003).

Prospective patients were screened for contraindications to rTMS, including a history of personal or family seizures, neurological or neuropsychiatric antecedent, inner ear prosthesis, pacemaker, and anticonvulsive medication. Electroencephalographic and clinical examination was made before the first rTMS sequence.

Participants were randomly allocated into two groups after 2 weeks of wash out period for all medications. Venlafaxine
A psychiatrist blind to group assignment conducted all assessments of patients’ symptoms. To assess antidepressant effects, we measured MADRS scores at baseline, after 5, 10, 15, and 20 rTMS sessions. Number of responders was compared between the groups using Fisher’s chi-square tests. Asberg Depression Rating Scale. Results are given as mean (SD).

Analysis
Comparisons between groups at baseline were assessed using student t-tests except for gender (Fischer’s chi-square). Statistical analysis was performed at a significant threshold of 0.05 using a repeated measures analysis of variance (ANOVA) on MADRS scores at each assessment times. Number of responders was compared between the groups using Fischer’s chi-square test. Statistics were done using the Statistica software.

Results
At baseline, the two groups did not significantly differ for age, sex ratio, and for MADRS scores (Table 1). No adverse event was observed in both groups.

Number of responders did not differ in each group at each assessment ($\chi^2 = 0.4; df = 1; p = 0.57$). First responders (MADRS < 15) were observed after 10 rTMS session in both groups (Table 1). More than 50% of patients were responders at the end of the study period (4 weeks).

Effect of treatment (time) was significant in both group $[F(4,44) = 15.42; p < 10^{-7}]$. No significant statistical difference was observed for MADRS scores between the two groups $[F(1,11) = 0.32; p = 0.58]$. We reported no interaction between group (HF or LF) and time $[F(4,44) = 0.61; p = 0.66]$, suggesting that decreases of MADRS scores were comparable in both groups (Figure 1).

Table 1 | Characteristics of patients throughout the study period.

|                      | 1 Hz (n = 8) | 10 Hz (n = 6) | p       |
|----------------------|-------------|--------------|---------|
| BASELINE CHARACTERISTICS |             |              |         |
| Age                  | 46.1 (16.3) | 50.8 (9.4)   | 0.54*   |
| Gender (male/female) | 2/6         | 4/2          | 0.27†   |
| Inpatient/outpatient | 2/6         | 2/4          | 0.9     |
| MADRS                | 32.0 (8.0)  | 29.8 (6.9)   | 0.59*   |
| AFTER 5 rTMS SESSION |             |              |         |
| MADRS decrease (%)   | −15.39 (12.02) | −19.78 (10.57) |         |
| Responders (%)       | 0           | 0            |         |
| AFTER 10 rTMS SESSION|             |              |         |
| MADRS decrease (%)   | −22.18 (22.65) | −34.95 (14.95) |         |
| Responders (%)       | 25          | 50           |         |
| AFTER 15 rTMS SESSION|             |              |         |
| MADRS decrease (%)   | −29.72 (34.79) | −47.11 (19.29) |         |
| Responders (%)       | 375         | 66.7         |         |
| AFTER 20 rTMS SESSION|             |              |         |
| MADRS decrease (%)   | −51.25 (35.35) | −52.96 (21.58) |         |
| Responders (%)       | 50          | 66.7         |         |

rTMS: repetitive transcranial magnetic stimulation/MADRS: Montgomery–Asberg Depression Rating Scale. Results are given as mean (SD).

*Student t-test; † Fischer Chi-square test.

Responders were defined as patients with a MADRS score < 15.
DISCUSSION

Our results replicate and extend previous findings showing that DLPFC LF-rTMS administered on the right side results in a similar effect compared to left-sided DLPFC HF-rTMS (Höppner et al., 2003; Isenberg et al., 2005; Stern et al., 2007; Fitzgerald et al., 2009; Pallanti et al., 2010; Rossini et al., 2010). Despite a failure in response to one previous AD, we reported that some patients could be considered as responders only 2 weeks after the start of treatment and after 4 weeks, more than a half of group could be qualified as responders as defined by a MADRS score <15.

In combination with venlafaxine (150 mg/day), 120 pulses/session of LF-rTMS over the RDLPFC (delivered during 4 min) could be as effective as 2000 pulses/session of HF-rTMS over the left DLPFC (delivered during 16 min). As the most serious potential side effect of rTMS is seizure, and that LF-rTMS may be protective against it (Theodore et al., 2002), thus, more than potential side effect of rTMS is seizure, and that LF-rTMS may be protective against it (Theodore et al., 2002), thus, more than a half of group could be qualified as responders as defined by a MADRS score <15.

We have observed no relapse during the study period (4 weeks) but a follow up period is required before any conclusion on this point. We reported no adverse events in the combination of medication.

The lack of an arm with placebo venlafaxine in association with active rTMS and of an arm with active venlafaxine and sham rTMS are some limitations of our study. However, it has been reported that 1 Hz rTMS is as effective as venlafaxine in the treatment of resistant depression (Bares et al., 2009). Moreover, it is important to note that in a large randomized controlled trial using venlafaxine alone (Rush et al., 2006), with a demographic comparable depressed group, among the patients who had a remission (24.8% of the sample), the mean time to remission was 5.5 ± 4.7 weeks (median, 4.2). We reported more than 50% decrease of MADRS score after 4 weeks of treatment while a 30% decrease of HDRS was reported in a large study investigating the impact of venlafaxine after previous AD failure (Baldomero et al., 2005). On the other hand, as it seems to be the case in our results, Rumi et al. (2005) have reported that in add-on therapy rTMS may be able to accelerate the delay efficacy of AD.

In conclusion, although limited by small sample size and lack of venlafaxine placebo arm, in a sample of patients who have not responded to one trial of antidepressant medication, in combination with venlafaxine 150 mg/day, right-sided LF-rTMS seems as effective as left-sided HF-rTMS. In order to investigate the real impact of LF-rTMS without any antidepressant treatment compared to rTMS in add-on therapy with venlafaxine and to venlafaxine alone, we have started a large multicentric study (clinicaltrials.gov; NCT00714090).

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