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## Treatment of auditory verbal hallucinations with transcranial magnetic stimulation in a patient with psychotic major depression: 1-year follow-up

Catarina Freitas<sup>1</sup>, Chester Pearlman<sup>1</sup>, and Alvaro Pascual-Leone<sup>1,2,\*</sup>

<sup>1</sup> Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

<sup>2</sup> Institut Universitari de Neurorehabilitació Guttmann, Universidad Autónoma de Barcelona, Badalona, Spain.

### Abstract

Auditory verbal hallucinations (AVH) in patients with schizophrenia can respond to repetitive transcranial magnetic stimulation (TMS). We report the therapeutic utility of rTMS in a 48 year-old patient with a 20-year history of severe depression (five suicidal gestures and previous failure of ECT) and internal AVH. First, 20Hz rTMS to left prefrontal cortex for three weeks significantly improved depression (BDI-II: 89% change, lasting 14 months along with weekly/biweekly maintenance treatments), but AVH remained unchanged. The patient also underwent a further course of left temporo-parietal 1Hz rTMS and amelioration of AVH severity was achieved (PSYRATS-AH: 53% change) and maintained at 1-year follow-up. AVH respond to rTMS in disorders other than schizophrenia. Furthermore, targeted rTMS to different brain regions can address diverse symptoms in neuropsychiatric conditions.

### Keywords

Transcranial magnetic stimulation; auditory verbal hallucinations; psychotic depressive disorder; treatment; 1-year follow-up

### Introduction

Auditory hallucinations are cardinal symptoms of schizophrenia, characterized by complex forms of auditory phantom perceptions of verbal (speech) or non-verbal (e.g., musical) content in the absence of auditory stimuli. Auditory verbal hallucinations (AVH) can be observed in patients with various neuropsychiatric disorders other than schizophrenia, such as Parkinson's disease (Fénelon et al., 2000), and even occasionally in otherwise healthy individuals (Tien, 1991; Johns et al., 2002; Sommer et al., 2010).

Major depression (MD) with psychotic features is relatively frequent in the general population (Ohayon and Schatzberg, 2002), is a most difficult form of depression to treat

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\* Correspondence to: Alvaro Pascual-Leone, M.D., Ph.D., Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (USA). T.: (617) 667-0203; Fax: (617) 975-5322. ap Leone@bidmc.harvard.edu.

Conflicts of interest

The authors disclose having no conflicts of interest.

(Rothschild, 2003), and is easily misdiagnosed (Rothschild et al., 2008). In addition to delusions and hallucinations, patients with psychotic major depression (PMD) show higher levels of overall depression severity and of illness chronicity, relapse, and psychiatric hospitalization; they also respond less to standard treatments for depression, often requiring adjunctive antipsychotic medication or electroconvulsive therapy (Gaudiano et al., 2008).

The Neuronetics® Neurostar protocol for therapeutic application of repetitive transcranial magnetic stimulation (rTMS) in pharmaco-resistant MD has been approved in the United States by the Food and Drug Administration (FDA) based on a multisite, randomized, controlled clinical trial (O'Reardon et al., 2007). The efficacy of rTMS in MD was recently confirmed by a multicenter study supported by the National Institutes of Health (George et al., 2010). On the other hand, the treatment of AVH in pharmaco-resistant schizophrenia patients using rTMS was first introduced by Hoffman and colleagues (1999). Since then, various speech-related areas have been probed and the left temporo-parietal cortex (TPC) has been found to be the rTMS target leading to the greatest improvements (Hoffman et al., 2007; Vercammen et al., 2009). The theoretical background for applying rTMS to the TPC is based on functional neuroimaging demonstrating hyperactivity in this region while the patients are hallucinating (e.g., Silbersweig et al., 1995; Shergill et al., 2000). Given that AVH are regarded as a manifestation of pathological brain hyperexcitability (Hoffman and Cavus, 2002), low-frequency rTMS (1 Hz) has been delivered to suppress neuronal excitability (Pascual-Leone et al., 1998; 2002). The efficacy of low frequency rTMS to TPC in AVH is supported by a recent meta-analysis (Freitas et al., 2009).

However, to our knowledge, there are no reports of rTMS treatment of AVH in non-schizophrenia patients. Herein, we report a case with clinical diagnosis of severe, suicidal PMD referred to our Clinical Program for Depression. Because psychotic features consisted of isolated AVH, which persisted after successful antidepressant response to rTMS, the patient subsequently received rTMS for AVH. Reduction of AVH severity was clinically meaningful and significantly improved overall quality of life. Continued improvements were noticed at 3 months' follow-up, and maintained at 9 and 12 months after AVH treatment. This case illustrates that successful treatment of PMD with rTMS can be achieved by combining different stimulation protocols targeting different brain regions to address various symptoms.

## Case report

The patient is a 48 year-old, Caucasian, right-handed male fulfilling DSM-IV-R (APA, 2000) criteria for PMD and referred to our outpatient clinic for treatment of depression by his psychiatrist. Since age 28, he had a history of hopelessness and suicidality (five suicidal gestures), severe anxiety, and internal degrading, dysphoric voices diminishing his accomplishments and urging him to end his emotional suffering. Three distinct and malevolent voices were described (1 female, 2 male) and were highly disruptive of the patient's working, personal, and social life. Consequent symptoms of worthlessness and helplessness with severe difficulty in resisting the voices were prominent. Symptoms of post-traumatic stress disorder were also present, attributable to early experiences of bullying and physical abuse in school for his homosexuality, and rape as an adult. Additionally, the patient suffered from erratic sleep patterns, frequent crying, extreme loneliness, difficulty concentrating and reading, low energy, low libido, and difficulty in getting out of bed most days. He could only work part-time. He had trials of several antidepressants, mood stabilizers, and antipsychotics, with only moderate relief despite good compliance. Additionally, he had an ineffective course of 12 electroconvulsive therapy sessions (ECT), and several years of psychotherapy.

Prior to beginning rTMS, neurological examination was normal. Informed consent was obtained from the patient before each course of rTMS treatments, and medication was kept constant throughout (citalopram 80mg/d, bupropion 450mg/d, quetiapine 600mg/hs, and clonazepam 5mg/d). Figure 1 displays a schematic representation of the timings of rTMS procedures. All rTMS treatment sessions were performed using a Magstim SuperRapid Stimulator (UK) with a 70-mm figure-of-eight coil.

Prior to rTMS, the severity of depression was 30 on the 24-item Hamilton Rating Scale for Depression (HAM-D-24; Hamilton, 1967), considered ‘very severe depression’ (maximum severity score: 74), and 55 on the Global Assessment of Functioning (GAF; Endicott et al., 1976) scale (range: 0-100, with higher scores representing “Superior functioning in a wide range of activities. No symptoms”), each administered by a psychiatrist. The self-report 21-item Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was also administered before rTMS.

The patient had an initial course of 15 consecutive daily sessions (over 3 weeks) of high-frequency (20Hz) rTMS. Prior to each rTMS session, the resting motor threshold (RMT) for the stimulated hemisphere was determined according to the recommendations of the International Federation for Clinical Neurophysiology (Rossini et al., 1994). Each session consisted of 1600 pulses, with 2s-trains and an inter-train interval of 28s. Stimulation was administered at 110% RMT over the left dorsolateral prefrontal cortex (DLPFC), defined as the site 5 cm anterior—in the same parasagittal plane—to the optimal scalp location of the hand cortical representation identified in the single-pulse TMS studies.

Depressive symptoms were greatly improved after this induction phase, as indicated by clinical observations and a decrease in the patient's BDI-II score (44 to 5). Treatment effects were also assessed daily with Visual Analog Scales (VAS). Figure 2 exhibits three of the domains assessed (mood, anxiety, energy), revealing noticeable improvements. As sleep patterns continued to be erratic over the following months, we referred the patient for a sleep study, which detected moderate to severe sleep apnea, managed since with continuous positive airway pressure (CPAP). CPAP restores adequate oxygen flow throughout all stages of sleep, which may thus contribute to improve cognition as suggested by a recent report of improved language in a non-fluent post-stroke patient after treatment with CPAP and TMS (Naeser et al., 2010).

Despite a clear improvement in MD symptomatology, AVH persisted. Given the debilitating nature of the persistent AVH, two months later we completed a second rTMS course for the treatment of AVH. The patient received 10 consecutive daily sessions (over 2 weeks) of low-frequency (1Hz) rTMS over the left TPC, defined as halfway between T3 and P3 (Hoffman et al., 2003) using the EEG International 10/20 System. RMT was also determined daily, and 1200 stimuli per session were given at 90% RMT.

Severity of AVH and treatment effects were assessed with the 11-item Auditory Hallucinations (AH) subscale of the Psychotic Symptoms Rating Scales (PSYRATS; Haddock et al., 1999). Data were collected at baseline and at the end of week 2 of rTMS to the left TPC. Moreover, the progression of treatment effects was followed on a daily basis using VAS while the ‘number of voices’ was also daily recorded by the patient, according to the 7-item Auditory Hallucination Rating Scale (AHRs; Hoffman et al., 2003). The same VAS were administered at 12, 36, and 52 weeks post-AVH treatment.

Overall, significant reduction of the patient's hallucinatory experience was achieved, as assessed by clinician-rated scoring on PSYRATS-AH (Table 1). A similar improvement was noted by the patient on the VAS. At 3-month follow-up, no decrement of beneficial effects was noticed, and two AVH features (frequency and length/duration of voices) appeared to

have further improved. At 9-month follow-up, therapeutic benefits were sustained, although a slight worsening of frequency of voices and attentional salience was detected, without causing subjective distress. At 1-year follow-up, voices were still perceived as whispers, lasting for a few seconds, and occurring less than once a day. The number of voices remained unaltered at all follow-up time-points. Figure 3 displays the effects after rTMS. BDI-II scores at 3, 9, and 12 months after treatment of AVH were 8, 11, and 5, respectively.

Starting one week after rTMS for AVH, the patient continued weekly maintenance rTMS sessions for depression (20 Hz, left DLPFC), lasting approximately 6 months and once every two weeks thereafter. No complications or adverse effects of TMS were experienced at any time.

## Discussion

### Antidepressant response

The antidepressant efficacy of high-frequency rTMS over the left DLPFC is becoming increasingly recognized. A recent meta-analysis (Schutter, 2009) including 1164 patients with MD (30 sham-controlled studies) resulted in a pooled effect size of 0.39. Although moderate, this effect size is similar to those seen in placebo-controlled trials with medications (e.g., Moncrieff et al., 2004). Furthermore, another meta-analytic study (Gross et al., 2007) comparing recent *versus* earlier rTMS trials showed a substantial difference between the estimated effect sizes ( $d=0.76$  for more recent studies and  $d=0.35$  for older trials), indicating that recent refinements of rTMS protocols are leading to improved therapeutic efficacy. For our patient, the antidepressant response to rTMS was remarkable given the severity of his depression, its psychotic features, and the previous failure of ECT. The benefit of the initial rTMS phase has since been successfully sustained for 14 months by weekly and later biweekly rTMS maintenance sessions.

### Short-term response to AVH treatment

The hallucinatory experiences of our patient were not affected by the high-frequency rTMS to the left DLPFC or the resulting mood improvement, but responded strikingly after the course of low-frequency rTMS to the left TPC. The reason for the lack of improvement in our patient's psychotic features after significant amelioration of mood is unclear, but it suggests that different neural networks or different dysfunctions of overlapping networks sustain mood and psychotic features of PMD. The pathophysiological mechanisms underlying PMD may compromise not only the central dopaminergic system but also other neurotransmitter systems, e.g., serotonergic or cholinergic. Repetitive TMS to the DLPFC induces increased dopamine release in the head of the caudate and ipsilateral anterior cingulate and orbitofrontal cortices (Straffella et al., 2000; Cho and Strafella, 2009). This may help with the mood symptoms, but have little or no impact on AVH. Alternatively, modulation of the DLPFC may lead to transsynaptic modulation of activity in subgenual regions and limbic and frontal structures leading to mood effects, while minimally affecting hallucinations due to a relatively small impact on temporal regions and language neural networks implicated in AVH. Studies combining rTMS with brain imaging, for example tracer positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), might help further clarify some of these issues.

Voices changed from almost continuously occurring to a few short episodes a day. Voices became softer, perceived as a whisper. The amount of negative content of the voices was unchanged after treatment, although there was still a slight shift in the content of the personal insults, from personal self-evaluation to behavior. These changes resulted in a marked reduction in the distress, anxiety, and disruption of family/social activities induced

by the AVH, and an overall improvement in daily life. The self-administered VAS followed very closely the results measured by the PSYRATS-AH. The patient's subjective, verbal reports emphasized the impact noticed on work performance (memory and concentration substantially improved) as well as in personal (including family/social and libido) and overall quality of life.

### Long-term response to AVH treatment

Improvement of some AVH features were sustained for 1-year of follow-up, with rTMS maintenance sessions only targeting the DLPFC for depression. In schizophrenia patients, significant effects with 1Hz rTMS have been shown to persist for 13 weeks on average (Hoffman et al. 2005; Sommer et al., 2007), but complete remission has also been reported (Poulet et al., 2008). Importantly, some features, namely the frequency and length/duration of the voices, which showed only partial amelioration immediately after rTMS treatment, further improved during the subsequent months. This seems to be in agreement with the findings of Montagne-Larmurier et al. (2009) showing a significant reduction in the severity of AVH at day 12 after rTMS, and a variation of therapeutic effects between patients occurring from 1 day to 3 weeks after treatment. It is also plausible that further improvements happened earlier in our patient, but were only recognized at the time of first follow-up (3 months).

Despite the response to rTMS, our patient continued to perceive the hallucinated voices as real and distinguishable from his own inner voice, and their number remained unchanged. The patient was aware that the voices were hallucinations, but a component of the distorted sense of reality was unaffected by the rTMS. This is consistent with prior findings (e.g., Hoffman et al., 2005; Fitzgerald et al., 2005; Sommer et al., 2007). Recently, Raij and colleagues (2009) showed that the subjective reality of AVH is significantly and strongly related to activation of bilateral inferior frontal gyrus (IFG), rather than to any AVH-related activation in the temporal lobe (including the auditory cortices). Furthermore, negative content of the voices of our patient was only mildly ameliorated. In this regard, Sommer et al. (2008) demonstrated that lateralization of AVH-related activity to the right (particularly right IFG) is correlated with negative emotional valence. In addition, as elegantly demonstrated by Vercammen et al. (2010), perceived reality, contrary to loudness, does not relate to the inner speech network. Such findings suggest that targeting IFG, perhaps on the right, in addition to the left TPC, might be beneficial in regard to reality and negative valence of AVH. Moreover, we predict that targeting the posterior portion of the pars triangularis (PTr), instead of pars opercularis (POp) of the frontal operculum, may lead to a better outcome. It was recently shown that the horizontal portion of arcuate fasciculus fibers—traditionally thought to connect Broca's area to posterior language regions—tracks to POP and not to PTr in the right (and left) hemisphere (Kaplan et al., 2010). The connections from PTr to posterior language regions are primarily via the extreme capsule (Frey et al., 2008; Saur et al., 2008). Furthermore, if reality of AVH relates to an unintentional activation of episodic memories (Waters et al., 2006; but see Vercammen et al., 2010), it is also conceivable that areas superior to PTr, including the DLPFC, may also be involved. Studies by Schönfeldt-Lecuona et al. (2004) and Hoffman et al. (2007) found no consistent improvement in AVH severity after rTMS to Broca's area or to the right homologue of Broca's area, respectively. Nevertheless, poor improvement was based on overall scores, so that relevant items relating to these specific features were not analyzed separately from other features. In addition, it is unknown if the POP or the PTr within Broca's area, in the left or right hemisphere, was targeted, or if targeting either area alone would have made a difference.

## Conclusions and outlook

This case shows that AVH in conditions besides schizophrenia can respond to rTMS to the left TPC and the benefit can be long-lasting and sustained. This suggests that the pathophysiological mechanisms involved in AVH might be independent and distinct from the concurrent neuropsychiatric disorder with which they are associated. If so, rTMS treatment of AVH in different patient populations may be worth considering, for example in Parkinson's disease, where hallucinations are often overlooked (Papapetropoulos et al., 2008).

With regard to depression, this patient demonstrates that rTMS might be beneficial even in patients who have failed ECT, and that maintenance of the benefit with weekly sessions is possible for long-periods of time. Finally, our case illustrates the therapeutic potential of rTMS applied in several courses targeting different symptoms in a given patient. This approach offers the opportunity of truly individualized therapeutic planning.

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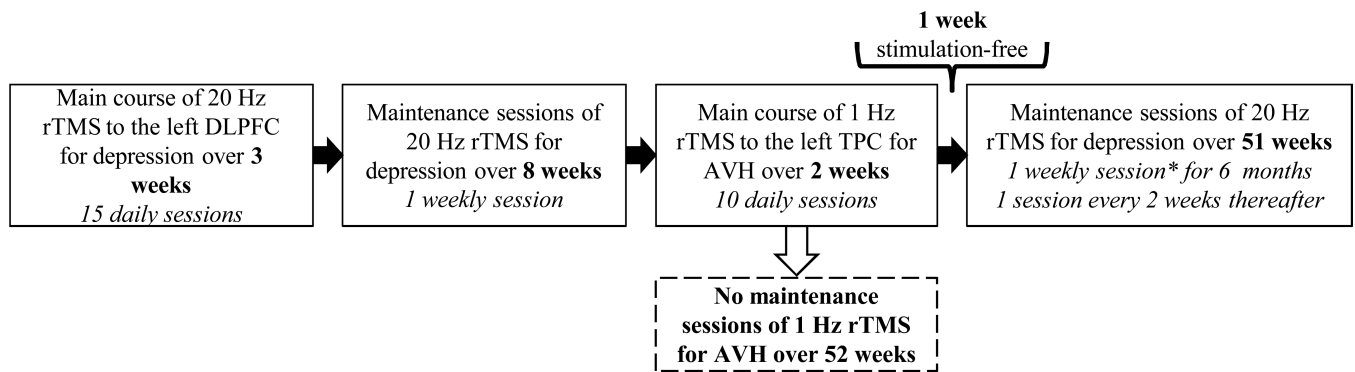
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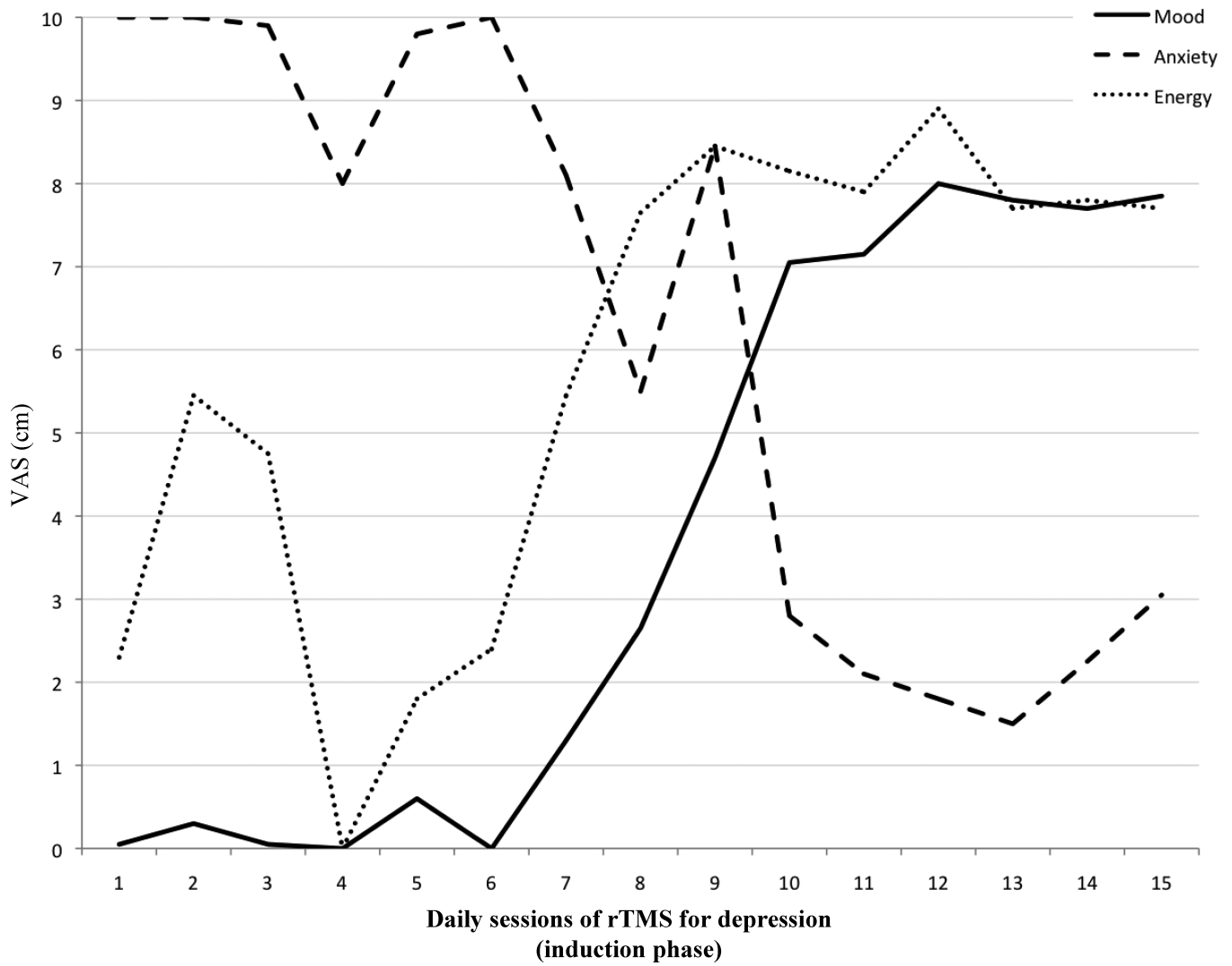




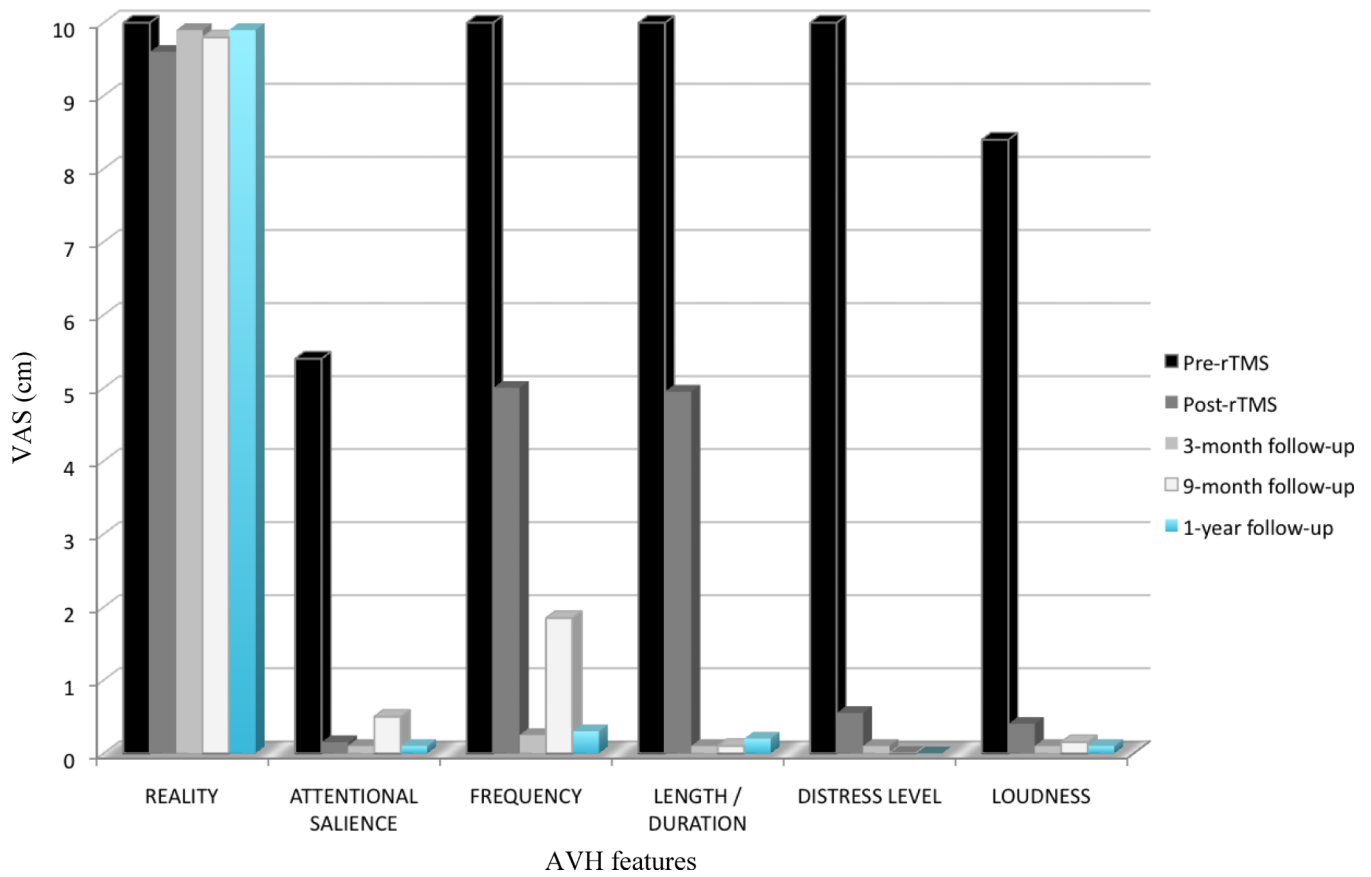
**Figure 1.**

Schematic representation of the progression of treatments for depression and auditory verbal hallucinations, including maintenance protocol for depression.

\*: 2 sessions exceptionally performed during week 2 of 2nd period of maintenance sessions, after rTMS for AVH.



**Figure 2.** Patient's ratings on visual analog scales (VAS; measured in centimeters) for 'mood', 'anxiety', and 'energy' levels during the initial 15 daily treatments.



**Figure 3.** Changes in features of auditory verbal hallucinations, as rated by the patient on VAS, after 10 daily sessions of 1 Hz rTMS to the left temporo-parietal area, and at follow-up of 3 and 9 months, and at 1 year.

**Table 1**

Clinician-rated AVH treatment outcome immediately after the 10-day rTMS course as assessed by the Auditory Hallucinations subscale of the Psychotic Symptoms Rating Scales (PSYRATS-AH).

PSYRATS-AH	Pre-rTMS	Post-rTMS	% Change
<b>Total scoring</b>	<b>30</b>	<b>14</b>	<b>53.33%</b>
Frequency of appearance	4	2	50%
Duration	4	3	25%
Location	1	1	0%
Intensity (volume)	2	1	50%
Degree of belief on the origin of the voices	1	1	0%
Amount of negative content of the voices	3	3	0%
Frequency of negative content of the voices	3	2	33.3%
Frequency with which they cause anxiety	4	0	100%
Intensity of anxiety	3	0	100%
Repercussion on daily life caused by the voices	2	0	100%
Control on the voices	3	1	66.7%