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Accelerated iTBS treatment applied to the left DLPFC in depressed patients results in a rapid volume increase in the left hippocampal dentate gyrus, not driven by brain perfusion

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ABSTRACT

Background: Accelerated intermittent Theta Burst Stimulation (aiTBS) has been shown to be an effective antidepressant treatment. Although neurobiological changes shortly after this intervention have been reported, whether aiTBS results in structural brain changes must still be determined. Furthermore, it possible that rapid volumetric changes are driven by factors other than neurotrophic processes.
Objectives: We examined whether possible grey matter volumetric (GMV) increases after aiTBS treatment could be driven by increased brain perfusion, measured by Arterial Spin Labeling (ASL).
Methods: 46 treatment-resistant depressed patients were randomized to receive 20 sessions of active or sham iTBS applied to the left dorsolateral prefrontal cortex. All sessions were delivered over 4 days at 5 sessions per day (trial registration: http://clinicaltrials.gov/show/NCT01832805). Patients were scanned the day before starting stimulation and three days after aiTBS.
Results: There was a significant cluster of increased left hippocampal GMV in the dentate gyrus related to HRSD changes after active aiTBS, but not after sham stimulation. These GMV increases became more pronounced when accounting for changes in cerebral perfusion.
Conclusions: Active, but not sham, aiTBS, resulted in acute volumetric changes in parts of the left dentate gyrus, suggesting a connection with adult neurogenesis. Furthermore, taking cerebral perfusion measurements into account impacts on detection of the GMV changes. Whether these hippocampal volumetric changes produced by active aiTBS are necessary for long-term clinical improvement remains to be determined.

Introduction

Major depression is a common, often treatment resistant, psychiatric disorder affecting hundreds of millions worldwide. Besides its psychological sequalae, major depression results in several functional and structural brain abnormalities. Structural changes, such as grey matter decreases, have been consistently reported and are mostly found in the frontal cortices and the hippocampal regions [1,2].

New treatment applications have been introduced and repetitive transcranial magnetic stimulation (rTMS) is now recognized to be a safe and effective treatment strategy in treatment-resistant depression (TRD) [3]. Furthermore, when applied to the left dorsolateral prefrontal cortex (DLPFC), several studies found that the clinical effects were accompanied by grey matter volume (GMV) increases in the temperomedial brain areas, including the hippocampus [4–7]. Similar volumetric changes in hippocampal areas have been observed following electroconvulsive therapy (ECT), another noninvasive neurostimulation intervention. Of note, there does not appear to be an association between the extent of

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these volumetric changes following ECT and clinical outcome [8,9]. Compared to the 20–30% remission rate found with the classical daily applied rTMS protocols [10], remission rates with ECT are often in the range of 48–70% in TRD [11–13].

A main objective in developing accelerated (a)rTMS has been to enhance the speed of clinical improvement to be more comparable to that obtained with ECT [14]. With arTMS, the number of pulses per session or the number of daily sessions is markedly increased, so that a given patient receives a similar number of total pulses spread over a significantly shorter time period [15]. Encouragingly, arTMS and classical daily rTMS appear to be quite similar in clinical outcomes [16], indicating that the major advantage of accelerated stimulation protocols is a shorter treatment duration. Given that the clinical outcomes of high frequency (HF) rTMS and intermittent theta burst stimulation (iTBS) in TRD seem to be quite similar [17], here we have combined the accelerated protocol with iTBS, producing aiTBS, delivering a similar amount of pulses over a shorter time period.

In this sham-controlled brain imaging study, in line with the findings using classical daily rTMS protocols, we evaluated whether 20 sessions of aiTBS influence GMV in TRD patients. Given that all stimulation was delivered within only 4 days (5 sessions per day) - a relatively short time to induce neuroplastic changes [18] - we also evaluated whether potential GMV changes could be driven by changes in brain perfusion. A topic receiving growing interest, also in ECT literature [19]. Moreover, regional variations in both venous and arterial density may correlate with cortical thickness [20].

Arterial spin labelling (ASL) is a non-invasive fMRI technique that uses arterial water as an endogenous tracer, providing reliable absolute quantification of regional cerebral blood flow (rCBF) [21]. ASL-fMRI is particularly well suited for multi-session longitudinal studies and has successfully been used to examine the neurobiological mechanisms of antidepressant response to ECT [22]. The effects of GMV on rCBF - or the reverse - has been examined in a variety of neuropsychiatric disorders [23–26]. However, when comparing structural and functional measures from disparate imaging modalities (e.g., MRI and PET), one must rely on simple region-of-interest type analyses, which do not allow the voxel-by-voxel comparisons necessary to answer more sophisticated neuroscience questions [27]. To overcome these limitations, and to examine GMV and perfusion within the same brain voxels we used robust Biological Parametric Mapping (BPM) software, widely used for integrative analysis of different neuroimaging (functional or structural) modalities [28]. This approach has already been successfully applied in psychiatric research (e.g. Refs. [29,30]).

We hypothesized that active and not sham aiTBS would result in GMV increases particularly in hippocampal subregions. Given the short time period between the scans, i.e., one week, we determined whether cerebral perfusion increments might have driven GMV increases in the specific subregions.

Methods and materials

This study (http://clinicaltrials.gov/show/NCT01832805) was approved by the local ethics committee of the Ghent University, and all participants provided written informed consent. This study was part of a larger project investigating the effects of aiTBS on various neurocognitive markers.

Subjects

Right-handed TRD patients (33 females, 13 males; age = 41.48 years, SD = 11.81) with a complete set of the baseline structural and perfusion scans were included. The full behavioral data were reported by Duprat et al. [31]. In brief, patients were selected using the Mini-International Neuropsychiatric Interview (MINI [32]), and, as described by Rush et al. [33], all were at least Stage I TRD (i.e., they had insufficient benefit from at least one adequate antidepressant trial). Exclusion criteria included a history of epilepsy or neurosurgical intervention, pacemaker, metallic or magnetic objects in brain, and alcohol dependence, ECT, or any suicide attempt within the past 6 months. Patients with bipolar or psychotic major depressive episodes were also excluded. After a washout period, except for long-standing benzodiazepines, patients were free of psychotropic medications for a minimum of two weeks before the first MRI scan and the first aiTBS session. Depression symptom severity was assessed with the 17-item Hamilton Rating Scale for Depression (HRSD [34]) by a certified psychiatrist not related to the study and masked to the randomized treatment assignment.

In this sham-controlled, brain imaging study, we focused primarily on the first part of the stimulation protocol (see Fig. 1). This allowed us to examine the acute effects of aiTBS on imaging measures using a purely between-subjects design, uncontaminated by the issues intrinsic to use of a crossover. Restricting the analyses to the first phase limited the extent of patient unmasking to treatment condition, given the intrinsic differences in sensations produced by the active and the sham stimulation protocols. However, to explore whether aiTBS administered after the crossover would result in similar or other GMV changes, we also analyzed the MRI data between T_2 and T_3 as secondary outcomes (see Supplemental Fig. 1).

iTBS procedure

Accelerated intermittent TBS stimulation was applied using a Magstim Rapid2 Plus1 magnetic stimulator (Magstim Company Limited, Minneapolis, USA) with an active and sham, figure-of-eight, cooled coil. The Magstim 70 mm Double Air Film sham coil is identical in all aspects to its active variant, but without stimulation output. The Air Film sham coil produces similar sensory experiences, but it does not deliver active stimulation of cortical neurons. Not including brain anatomical information of each participant when identifying the target zone may result in stimulation outside the intended area. In this study the left DLPFC was targeted based on the individual structural MRI [35], using the Brainsight neuronavigation system (Brainsight™, Rogue Resolutions, Inc.). The left DLPFC was visually located on the 3D surface rendering of the brain based on the known gyral morphology, with the center part of the mid-prefrontal gyrus serving as the left DLPFC target (Brodmann 9/46). The treatment protocol consisted of 20 iTBS sessions spread over 4 days (five sessions per day), administering a total of 32,400 pulses (see Fig. 1). Stimulation intensity was fixed at 110% of resting motor threshold, and patients received 1620 pulses per session in 54 triplet bursts with a train duration of 2 s and cycling period of 8 s. There was a pause of approximately 15 min between consecutive sessions. Patients were blindfolded, fitted with earplugs, and they were kept blind to of the active or sham stimulation condition.

Brain imaging procedures

Scanning was performed on a Siemens 3T TrioTim MRI scanner (Siemens, Erlangen, Germany) with a 32 channel SENSE head coil. Patients were instructed not to drink coffee or smoke the day of the imaging procedures. Scanning was performed on Monday morning between 9 and 12 a.m. For the anatomical localization of the left DLPFC participants underwent a T1-weighted MRI brain scan (3D-TFE, TR/TE = 2530/2.58; flip angle = 7°; FOV = 220 × 220mm2; resolution = 0.9 × 0.9 × 0.9 mm^3; number of slices = 176). Multi-delay pulsed arterial spin labeled (pASL) images with a 3D GRASE readout were obtained with the following parameters: TR = 3.4s,

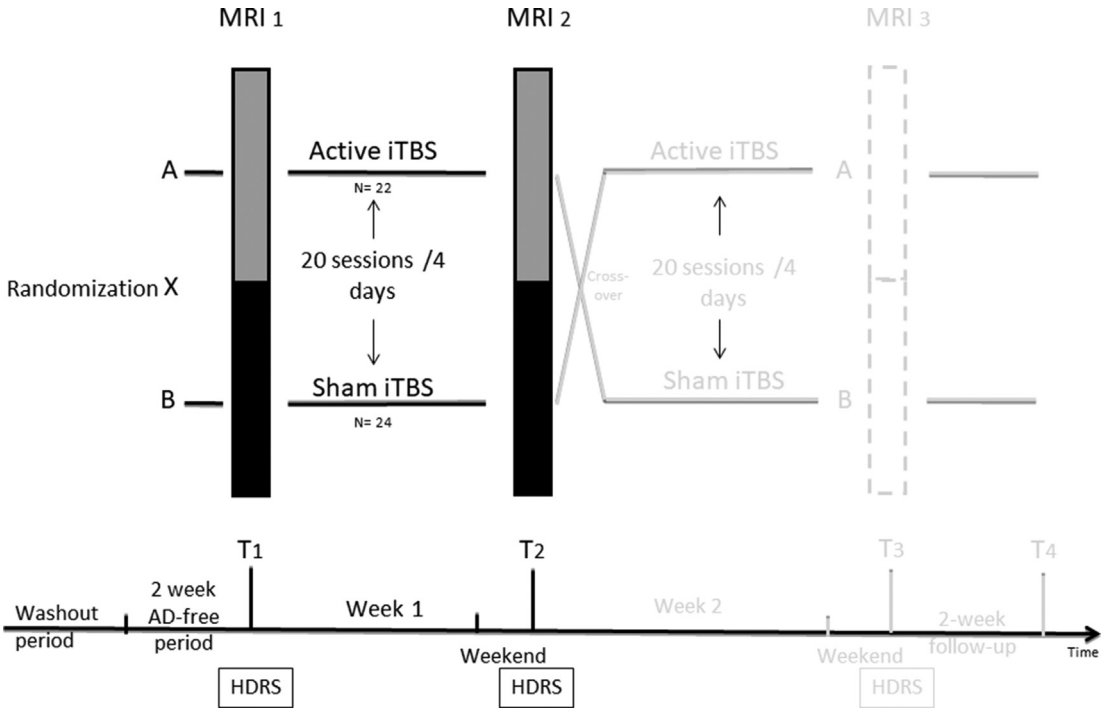

Fig. 1. Flow chart of the accelerated iTBS experimental procedure.
After a washout period, all MDD patients were at least two weeks antidepressant (AD) free before they underwent a first MRI scan at time T_1 (baseline). Hereafter, patients were randomly divided into two groups to receive 20 sessions of real or sham accelerated iTBS treatment respectively. aiTBS treatment was spread over four succeeding afternoons (5 daily sessions). A second MRI was performed exactly 1 week after the first week (time T_2) and a third one exactly after 2 weeks (time T_3). At each of these time points all patients were clinically assessed. However, for the current study hypothesis, although in the second week, strictly the same treatment schedule was followed but with a change of stimulation: line AB = a TRD patient who first received active aiTBS now received sham; line BA = a patient who first received sham treatment now received the active session, these data were not included in the analyses.

TE = 14.46 ms, labeling duration = 1400 ms, post-labeling delay changing from 250 to 3000 ms in steps of 250 ms, resulting in twelve pairs of slice-selective (SS) and non-selective (NS) images. All MR images were aligned to the AC-PC before scanning. During the ASL measurements, participants were asked to stay awake with their eyes closed.

The longitudinal voxel-based morphometry analysis was performed using the Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat/). After intra-subject realignment, the mean map of the realigned images was created for each subject. Bias correction and spatial segmentation were then performed on all time points and mean maps. The spatial normalization parameters estimated from the mean image were applied to the images of all time points. Finally, the normalized grey matter images (voxel size: $1.5 \times 1.5 \times 1.5$ mm^3) were modulated and smoothed using 8-mm full-width half-maximum Gaussian filter.

The pASL images were pre-processed and analyzed using SPM12 and FSL. The pASL images were realigned to correct for motion and registered to the anatomical image using SPM. Then 12 perfusion-weighted images were generated by surround subtraction. The perfusion-weighted images were submitted for CBF estimation using 'oxford_asl' in FSL. The partial volume correction was applied in the generated CBF maps [36]. Global mean normalization was applied to the CBF data. Finally, the CBF maps were spatially normalized into MNI space and smoothed with an 8 mm full-width half-maximum Gaussian kernel.

Statistical analysis

First, to investigate the relations between morphometric changes and change in depression severity, we conducted a voxel-wise multiple regression analysis. Age, gender, total intracranial volume (TIV), and change in HRSD scores ($HRSD_{t1}-HRSD_{t2}$) were the covariates, while the change in GMV ($GMV_{t2}-GMV_{t1}$) was the dependent variable. Second, to answer our main research question, and to exclude the possibility that morphometric changes in GMV induced by aiTBS were a result of concomitant perfusion change, the above analysis was performed again, adding voxel-wise delta ASL ($ASL_{t2}-ASL_{t1}$) maps as covariates, using the Robust Biological Parametric Mapping (BPM) toolbox ([28]; https://www.nitrc.org/projects/rbpm/). Casanova and co-workers [27] developed this BPM toolbox for multimodal image analysis. This software has been used widely for integrative analysis of different neuroimaging (functional or structural) modalities, further expanded to robust BPM, including robust regression and robust inference reducing sensitivity to outliers without substantial degradation in power [28].

Results were considered statistically significant using a whole-brain FWE cluster corrected threshold of $p < 0.05$, and uncorrected voxel-wise p-values < 0.001 by the cluster-forming threshold of 30 voxels.

Results

Behavioral results

After randomization, twenty-two TRD patients received active aiTBS and twenty-four TRD patients received sham aiTBS. Four additional patients (2 active, 1 sham, 1 spontaneous remission before starting the stimulation protocol) were included in the study reporting therapeutic outcomes (total n = 50) but were excluded here due to incomplete imaging data (n = 1), retrospective primary

neurological illness (n = 1), spontaneous remission (n = 1), suicide attempt in the first week of sham stimulation (n = 1). The active and sham aiTBS groups did not differ in age, gender, the duration of the current depressive episode, benzodiazepine intake, depression severity, and motor threshold (all p's > 0.05) (see Table 1). A repeated measures ANOVA was performed with HRSD depression severity scores at T_1 and T_2 with randomized treatment condition as the between-subjects factor and time as the repeated measure. There was a main effect of time, $F(1, 44) = 12.26$, $p < 0.01$, but not of treatment group $F(1, 44) = 0.95$, $p = 0.34$, and the interaction was not significant, $F(1, 44) = 1.08$, $p = 0.30$. Both the active aiTBS group [T_1: 21.05 (4.69), T_2: 16.82 (7.29), $t(21) = 2.80$, $p = 0.01$] and the sham aiTBS group [T_1: 21.50 (6.25), T_2: 19.21 (4.87), $t(21) = 2.04$, $p = 0.05$] had modest, but significant, decreases in HRSD scores over the one-week interval.

Brain imaging results

Before controlling for perfusion values and using a strict threshold for statistical significance ($p < 0.001$), we did not find a significant difference between the randomized treatment conditions in change in GMV across the two time points. Changes in GMV over this time period were also not associated with change in depression severity. Of note, we found GMV increases in the left hippocampal areas related to changes in depression severity without considering brain perfusion as a covariate, but at a lower significance threshold $p < 0.005$ (see Supplemental Fig. 2).

When accounting for change in ASL perfusion values, there was a significant cluster of increased left hippocampal GMV related to HRSD changes after active aiTBS, but not after sham stimulation. The exact anatomical localization of this significant cluster ($p < 0.05$, FWE-corrected) was obtained with the SPM Anatomy toolbox [38,39]. We found that the 77% of the major volumetric increases were in the left dentate gyrus, 13.3% of GMV increases were found in the left cornu ammonis (CA) subfields CA1, and 1.8% in the left CA2 (see also Fig. 2). To ensure that these GMV increases within this significant cluster in the left dentate gyrus were not related to perfusion changes, we extracted the individual perfusion values at T_1 and T_2. A paired t-test confirmed that perfusion within this left dentate gyral cluster was not significantly different before (0.13 (0.06)) and after (0.11 (0.03)) active aiTBS $t(21) = 1.58$, $p = 0.13$, nor before (0.11 (0.07)) and after (0.09 (0.05)) sham aiTBS $t(23) = 1.38$, $p = 0.18$. Thus, while the perfusion changes were not themselves statistically significant, controlling for their variability improved sensitivity in detecting between-group GMV changes. Of note, when change in HRSD scores served as the dependent variable and the other biological measures (age, gender, TIV, delta GMV, and delta ASL) as independent variables, we also found that the left hippocampal area/dentate gyrus is the common region related to changes in depression severity scores (see also Supplemental Fig. 3).

To verify that hippocampal GMV changed in a similar way in patients who first received sham treatment (T_1-T_2) and in the second week now active aiTBS (T_2-T_3), we examined GMV values after crossing over to active aiTBS. Although only with a lower significance threshold ($p < 0.005$), we found similar GMV increases in the dentate gyrus whether or not we included ASL perfusion values as covariates (see Supplemental Fig. 4). Change in GMV in the left hippocampal subregions were independent of change in symptom scores.

Discussion

In a well-defined sample of TRD patients, we determined whether 20 sessions of iTBS — delivered to the left DLPFC in an accelerated fashion — produces GMV change. Importantly, to ensure that such volumetric change was not simply driven by change in rCBF, ASL scans were collected at the same time as the volumetric measurements. Four days of active, but not sham, aiTBS resulted in a significant volumetric increase in the left dentate gyrus, a subregion of the left hippocampus. This volumetric

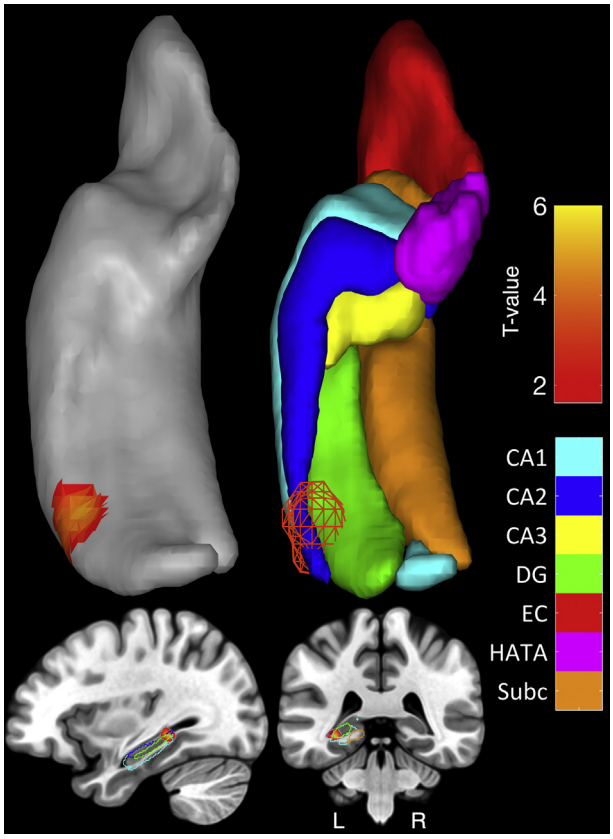

Fig. 2. Left hippocampus.
Upper left) Significant increases in left hippocampal grey matter volumes after active aiTBS (T_1-T_2). Upper right) Detailed overview of the different left hippocampal subregions including the significant increased left hippocampal volumetric increases after active aiTBS. Lower left and right) Detailed sagittal and coronal view of the significant left dentate gyral cluster using the SPM Anatomy Toolbox. L = left, R = Right. CA Cornu Ammunis, DG: dentate gyrus, EC: entorhinal cortex, HATA: hippocampal amygdala transition area, Subc: Subiculum.

Table 1
Baseline differences between the active and the sham aiTBS group.

	Active aiTBS (n = 22)	Sham aiTBS (n = 24)	*T or X^2 tests*
Age	40.09 (11.45)	42.75 (12.24)	0.45
Gender (Male: Female)	6:16	7:17	0.89
Duration depressive episode (years)	4.37 (6.69)	3.70 (5.83)	0.72
rMT (%)	60.88 (8.01)	57.27 (8.32)	0.14
Baseline depression severity	21.50 (6.25)	21.05 (4.69)	0.78

increase in the left dentate gyrus, related to clinical improvement, could not be attributed to change in local perfusion. Furthermore, those patients who received sham aiTBS in the first week and active aiTBS after the crossover in the second week displayed a similar GMV increase in the left hippocampus, although at a lower significance threshold ($p < 0.005$). This volumetric effect, related to clinical improvement, also could not be attributed to changes in perfusion (see Supplemental Fig. 4).

Somewhat unexpectedly, when not controlling for change in ASL values, we did not observe significant GMV change after the first week of active or sham aiTBS. This was likely due to the stringent statistical threshold we used with whole brain correction. Indeed, when using a lower significance threshold, a left hippocampal GMV increase predominantly in the dentate gyrus was observed after active aiTBS only (see Supplemental Fig. 1) without controlling for perfusion effects. Adding ASL values to the analysis as covariate produced clearer results regarding GMV change. This suggests that the assessment of cerebral perfusion can reduce noise in GMV measures when examining between-group differences in longitudinal volumetric effects. From a neuroanatomical point of view when voxel-wise examining GMV and perfusion this is not a contradictory observation. Arterioles penetrate the grey matter carrying blood and oxygen traversing all cortical layers into the capillary bed [40], leaving no portion of tissue without perfusion, with every neuron lying within 15 μm of a brain capillary [41]. It is estimated that a cortical volume of 1 cm^3 contains approximately ten million vessels [42]. Increased rCBF (via vessel vasodilation) may induce an overestimation of cortical thickness and grey matter volume [43]. By controlling for individual differences in change in perfusion can lead to more accurate estimation of cortical thickness or GMV change.

Our observations are consistent with the recent open-label findings of Hayasaka et al. [5] and Noda et al. [7], who observed left lateralized hippocampal GMV increases following classical daily HF-rTMS applied to the left DLPFC. Furthermore, our findings are also consistent with repeated observations that ECT results in hippocampal GMV increases [19,44,45]. Our findings indicate that left hippocampal GMV increases occur after active aiTBS stimulation and not sham aiTBS and are detectable after only 4 days of aiTBS. It has been proposed that the (bilateral) hippocampal volume increases found after ECT may be an epiphenomenon, and that hippocampal enlargement may be a consequence seizure induction that is independent of its therapeutic effects [45]. Given that (r)TMS applications do not require seizures, our current aiTBS findings are of interest in demonstrating in a sham-controlled manner that iTBS produces a similar GMV increase. Since the sample showed only modest symptom change over the one-week measurement period, and the degree of symptom reduction did not covary with the volumetric change, it is also possible that these volumetric effects of iTBS are epiphenomena with respect to therapeutic mechanisms. Alternatively, these volumetric effects may mark necessary components of the therapeutic process. At this stage, we can only state that the GMV changes we observed should not be viewed as an artifact of changes in cerebral perfusion.

It is of interest that the left hippocampal volumetric increases after 4 days of active aiTBS were principally located in the dentate gyrus (Fig. 2). This subregion is an integral portion of the larger functional brain system referred to as the hippocampal formation [46]. Dentate granule cells are the only neurons thought to be continuously generated into adulthood [47]. It is noteworthy that ECT in animals induces neurogenesis specifically in granule cells of the dentate gyrus [48,49] and human studies have noted volumetric increases in the same subregion following ECT in the human [50–52].

Largely based on studies blocking antidepressant effects in animal models, it has been hypothesized that hippocampal neurogenesis is an important and perhaps necessary component of antidepressant therapeutic processes [53–56]. Given that decreased neurogenesis in the dentate gyrus and glutamatergic neurotransmission dysfunction appear to contribute to the development of depression [57], ketamine, a non-competitive NMDA glutamate receptor channel blocker, produces a rapid onset of antidepressant responses, resulting in fast changes in synaptic function and plasticity [58]. Indeed, because the DLPFC and the hippocampus are synaptically connected via (glutaminergic) pyramidal neurons [59], from an electrophysiological point of view, aiTBS applied to the left DLPFC may also directly influence neuronal activity in hippocampal regions. Of note, prefrontal and hippocampal postsynaptic serotonin 5-HT_{2A} receptor density changes have been linked to clinical response with classic daily rTMS and such changes are thought to be related to neuroplastic processes [60].

Our study had important limitations. The single-masked, randomized control trial did not produce the hypothesized differences in clinical outcomes for the groups randomized to active or sham aiTBS, although overall rates of response and remission were not insubstantial (see Duprat et al. [31] for a complete overview of the clinical results). While this was an unexpected behavioral result, it helped to further dissociate the volumetric and therapeutic effects. The randomized groups differed in volumetric changes, but not in clinical outcome. Neuropsychological assessment was not conducted to evaluate potential (positive or negative) effects of aiTBS on cognitive processes putatively related to changes in neuroplasticity in the hippocampal formation. Additional scanning protocols were not conducted to examine the molecular basis of the left dentate gyrus neuroplastic process, and specifically whether the volumetric effects were mediated by impact on the serotonergic/glutamatergic transmission. Our aiTBS protocol was designed to produce rapid clinical and volumetric effects, with the time frame too brief (1 week) for neurogenesis to result in mature, functional neurons. Thus, any link between “neurogenesis” and clinical improvement must be mediated by earlier elements in the cascade that produces neuroplasticity, such as increased release of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors. Unfortunately, tissue samples were not collected at the relevant time points, leaving it an open question whether the left hippocampal GMV increases observed 3 days after the active aiTBS protocol were driven by early components of neuroplastic processes. Furthermore, no follow-up scans or other assessments were performed beyond the stimulation protocol reported here. In addition, cerebral perfusion change was not found to be associated with GMV change. However, we did not examine potential molecular or microstructural factors that could impact on either measure [22]. For instance, inflammatory processes are associated with increased blood flow [22] and decreased volumetric changes [61] in the depressed state. Finally, the time intervals between sessions using accelerated rTMS paradigms may impact on outcomes [62], and our 15-min intersession interval may have been too brief to optimally alter synaptic plasticity, as 60-90-min intersession iTBS intervals may induce stronger synaptic plasticity effects [63]. Nevertheless, our study clearly shows volumetric increases in specific hippocampal areas after 4 days of active stimulation delivered on 5 daily sessions with an intersession interval of 15 min.

In summary, active, but not sham, aiTBS results in significant GMV increases in the left dentate gyrus, part of the hippocampal formation. These volumetric increases could not be attributed to changes in cerebral perfusion. On the other hand, including ASL measurements in our analysis made detection of the volumetric

changes more sensitive, suggesting that it is useful when investigating GMV in depressed patient samples to take cerebral perfusion into account. Indeed, multimodal brain imaging may not only help to increase our insights into the neurobiology of TRD but also into the working mechanisms of non-invasive brain stimulation methods, such as rTMS [64]. For instance, it would be interesting to investigate whether there were any changes in white matter isotropy in the pathways related to DLPFC-hippocampal connectivity. Although our observations suggest that, like psychopharmacotherapy and ECT, active aiTBS induces neuroplasticity and changes brain structure however, the exact mechanisms subserving this neuroplastic effects, its relation to neurotransmitter systems, and its functional significance remain to be determined. Nevertheless, it is striking that only four days of active aiTBS induces GMV increases in areas of the brain well documented to be involved in the pathophysiology of TRD.

Declarations of competing interest

Dr. Baeken and Dr. Wu declare that they have no conflict of interest. Dr. Sackeim is a consultant to LivaNova LPC, MECTA corporation, and Neuronetics, Inc. He is the originator of Magnetic Seizure therapy and is the inventor on US patents for Focal Electrically-Administered Seizure Therapy (FEAST), titration in the Current Domain in ECT, and ECT devices that adjust current.

CRediT authorship contribution statement

Chris Baeken: Conceptualization, Funding acquisition, Methodology, Formal analysis, Project administration, Supervision, Writing - original draft, Writing - review & editing. **GuoRong Wu:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Harold A. Sackeim:** Conceptualization, Methodology, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.05.015.

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