# rTMS treatment of visual hallucinations using a connectivity-based targeting method - A case study

Invernizzi, Azzurra; Halbertsma, Hinke N; van Ackooij, Martijn; Bais, Leonie; Boertien, Jeffrey; Renken, Remco J; Cornelissen, Frans W; van Laar, Teus

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# rTMS treatment of visual hallucinations using a connectivity-based targeting method - A case study

*Dear editor:*

Visual hallucinations (VH) are conscious visual perceptions that occur in the absence of an external stimulus. VHs are neuro-ophthalmological dysfunctions that are very disabling and are based on various pathologies, including eye diseases and neurodegenerative disorders [1,2]. VHs are difficult to treat, because pharmacological interventions are only partially effective and related to many adverse effects. One of the alternative non-pharmacological treatments for VHs is repetitive transcranial magnetic stimulation (rTMS). However, the challenge rTMS faces is the identification of the optimal stimulation sites [3]. Usually, the same cortical stimulation site is used for all patients with a particular diagnosis. However, this does not account for possible inter-subject variability, both in functional neuroarchitecture and clinical symptoms. If we could determine individually optimized target sites for rTMS, this would improve its efficacy as treatment.

Here, we present a connectivity-based targeting approach, based on resting state (rs) fMRI data, to identify regions of high connectivity ("hubs") within functional networks. We used these regions as target sites for rTMS treatment of a 67-year-old female patient who was diagnosed with Parkinson's disease (PD) at the age of 62. Her hallucinations started two years after she had been diagnosed with PD, at the time of her first L-dopa treatment. In addition, she was diagnosed with retinitis pigmentosa (RP) 30 years previously, which was gradually progressive and resulted in Charles Bonnet syndrome. She had severely reduced vision in her right eye and only light perception in her left eye. The VHs were mostly present during daytime, with her eyes open. All conventional pharmacological treatments, including clozapine, rivastigmine, quetiapine and olanzapine, failed to reduce her VH, and were discontinued.

Firstly, a baseline fMRI scan served to gain an impression of potential functional neural networks involved in the VH of our subject. Subsequent fMRI data acquisition, rTMS treatment and clinical assessment were organised as follows: pre-treatment fMRI data were acquired in both eyes-open and eyes-closed conditions. Next, the patient was stimulated with 1 Hz rTMS during 5 days, followed by 30 Hz theta-burst stimulation for another 5 days. On the day of the last rTMS stimulation, post-treatment fMRI data were collected using identical experimental conditions. Clinical assessments consisted of brief daily interviews, to obtain qualitative data on the content and intensity of her VHs, both during rTMS treatment and follow-up for 6 months.

All (f)MRI data acquisition was performed on a Siemens Prisma 3T MRI-scanner with a standard 64-channel head coil. Image preprocessing, functional network identification and statistical analyses were performed using FSL, SPM12 [4], the fastECM toolbox [5] and customized scripts, implemented in MatLab 2014b. Rs-fMRI data were preprocessed and fastECM were performed on 111 ROIs total (48 left and 48 right cortical areas; 7 left and 7 right subcortical areas and 1 brainstem) based on the Harvard-Oxford Atlas. This atlas was chosen as it facilitated the localization of the areas of interest during the rTMS intervention and communication with clinicians. The eigenvector centrality (EC) method builds on the concept of node centrality, which characterizes functional networks active over time and attributes a centrality value to each ROI. In particular, EC quantifies the centrality of a given brain area based on the strength of the connections with its neighbors and the quality and number of their connections with the entire functional networks, without any *a priori* assumptions about the subject's brain state. Such EC centrality value is strictly dependent on the sum of centrality properties of the directly connected nodes within a network. Different EC values can be attributed to a given node, but only the EC with the highest eigenvalue will be assigned to it. Based on these values influential hubs can be identified, and if an intervention is applied to such a hub, network wide effects can be anticipated. ROIs with the 10% highest EC coefficients were considered as potential treatment areas.

In order to facilitate statistical inference, the autocorrelation structure was removed in a two-step GLM procedure [6]. To obtain a proxy distribution for the null hypothesis, surrogate BOLD time series were generated 1000 times using the iterative amplitude adjusted Fourier transform method (iAAFT) [7]. To define confidence intervals (CI) for the estimated EC value of each ROI, a bootstrap technique (across time points) was applied 3000 times to the fMRI data. We considered a result significant when the median of the bootstrapped results fell outside the 95% CI of the null distribution. Furthermore, when comparing conditions, we considered a shift in centrality to be meaningful when the interquartile ranges (obtained using bootstrap) did not overlap. Based on the results, we identified viable target areas (Fig. 1, panel A). Specifically, the bilateral SMAs and the precuneus (PCN) were consistently among the most influential hubs in all pre-treatment scans. Subsequently, we chose the bilateral SMAs as rTMS target areas as they are near the cortical surface, which makes them easily accessible. As mentioned, to compare the different experimental conditions, bootstrap and surrogate methods were applied to the EC values of each node (Fig. 1, panel B). Median eigenvector values of the

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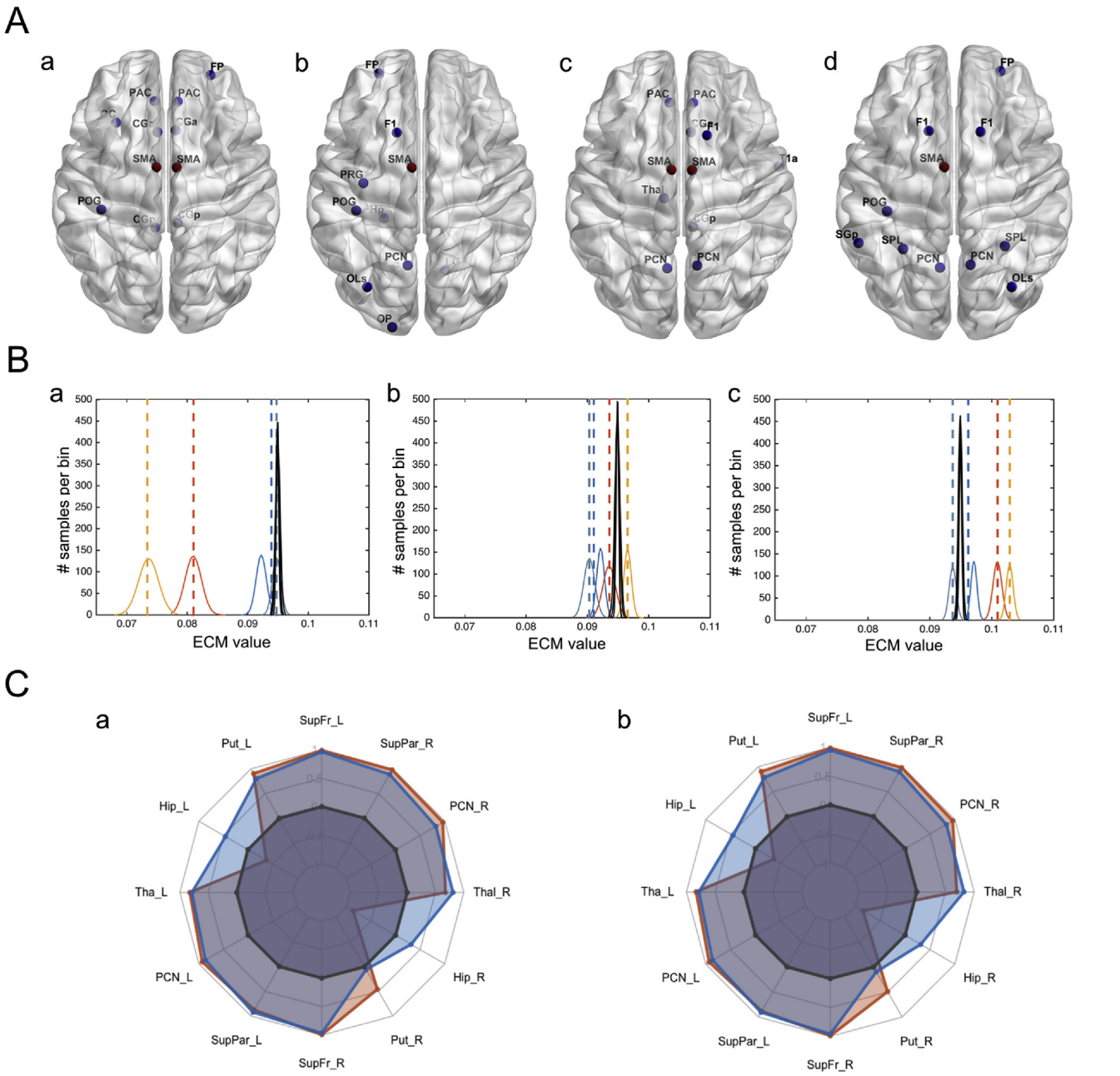


**Fig. 1. A - Functional connectivity network hubs.** The 10% highest centrality values have been plotted for the baseline scans. During different conditions, bright screen and eyes open (**a**), dark screen and eyes closed (**b** and **c**), SMA was associated with increased EC values and visual experiences of the subject. **B - EC values across conditions and areas**. Eigenvector values for open and closed eyes pre-rTMS (light orange and orange dashed line) and post-rTMS (light blue and blue dashed line), bootstrapped distributions (solid line) and surrogates distributions (black lines) are reported for bilateral SMA (**a**), PCN (**b**) and hippocampus (**c**). To support visualization, a Gaussian (if needed, two) distribution was fitted to each distribution. **C - Fingerprints connectivity of SMA versus the rich club areas.** During rs-fMRI, left and right SMA (**a** and **b**) show an increased functional coupling in the hippocampal areas post-rTMS (blue) compared to pre-rTMS (orange) session. Surrogate data is reported (black lines). Note that the two lines overlap (97% Confidence Intervals [-0.0015, 0.0032]). P-values are computed using permutation statistics FWE corrected (pre: $p < 0.0008$; post: $p < 0.0003$).

SMAs and the hippocampus showed a consistent shift between experimental conditions, for the pre- and post-rTMS scans. In contrast, such a change was absent in the PCN.

To further monitor the effect of rTMS treatment, we calculated the functional connectivity (FC) between the SMA and a set of well-connected cortical ROIs (the "rich club" [8]; Fig. 1, panel C). A selective increase in FC between SMAs and the hippocampal formation was noticed in the post-rTMS scan compared to the pre-rTMS scan. In contrast, this effect was absent for most of the other rich-club areas. In parallel to the EC changes, a 44% decrease in the overall VH intensity was observed. This decrease lasted up to 6 months after intervention.

Therefore, our findings imply that even in the absence of a direct anatomical connection, in our specific case between the SMA and the hippocampus, rTMS can propagate and induce changes beyond the targeted area [3]. That we identified the SMA as an influential hub in VH, is consistent with it being strongly connected to regions known to be involved in auditory [9] and visual mental imagery [10]. Moreover, our results show that the effect of rTMS is specific, rather than brain-wide.

A clear limitation of the current study is the lack of a sham/placebo condition in the same patient. Such a trial was attempted but failed. The patient had a severe off period just before the post-sham fMRI scanning which made it necessary for her to take extra Ldopa resulting in hyperkinesia. Therefore, fMRI data from this session was not eligible for further analysis.

In summary, we presented a connectivity-based targeting approach that can be used to identify a target area for individually optimized rTMS treatment. Overall, our results support the use of individually customized rTMS as an alternative or complementary treatment in case of disabling VH. Future studies may benefit from applying this method to guide non-invasive brain stimulation.

## Conflicts of interest

None.

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Azzurra Invernizzi*
*Laboratory for Experimental Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

Hinke N. Halbertsma
*Laboratory for Experimental Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

Martijn van Ackooij
*Laboratory for Experimental Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

Leonie Bais
*Lentis, Center for Mental Health Care, Groningen, the Netherlands*

Jeffrey Boertien
*Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

Remco J. Renken[1]
*Laboratory for Experimental Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

*Cognitive Neuroscience Center, Department of Biomedical Sciences of Cells & Systems, University Medical Center Groningen, Groningen, the Netherlands*

Frans W. Cornelissen[1]
*Laboratory for Experimental Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

Teus van Laar[1]
*Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

* Corresponding author. Laboratory for Experimental Ophthalmology, University Medical Center Groningen, P.O.Box 30.001, 9700, RB, Groningen, Netherlands.
*E-mail address:* a.invernizzi@umcg.nl (A. Invernizzi).

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[1] These authors contributed equally to this work.