Predicting response to rTMS for auditory hallucinations

Koops, Sanne; Slotema, Christina W.; Kos, Claire; Bais, Leonie; Aleman, Andre; Blom, Jan Dirk; Sommer, Iris E. C.

Published in:
Schizophrenia Research

DOI:
10.1016/j.schres.2017.08.060

Publication date:
2018

Schizophrenia Research 195 (2018) 583–584

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Predicting response to rTMS for auditory hallucinations: Younger patients and females do better

Keywords:
Age
Gender
Psychosis
Schizophrenia
Non-invasive brain stimulation
Predictors of response

Dear editor

The past 15 years, many studies investigated the effectiveness of repetitive transcranial magnetic stimulation (rTMS) for auditory hallucinations (AH). Meta-analyses show effect sizes of 0.3–0.8, with individual treatment effects ranging from zero to full recovery. In rTMS for depression, similar results prompted researchers to investigate predictors for response. Some of these predictors are younger age, treatment refractoriness (Fregni et al., 2006) and female gender (Kedzior et al., 2014). We explored whether similar predictors exist in the field of AH.

We analyzed data from 123 patients who received rTMS, from five previously published randomized controlled trials (RCTs) of which patient-level data was available (Bais et al., 2014; De Weijer et al., 2014; Koops et al., 2016; Slotema et al., 2011; Van Lutterveld et al., 2012). See Table 1 for patient demographics and study-specific rTMS parameters.

We selected age, gender, and lifetime duration of AH as variables for analysis, based on previous findings in depression studies. We modeled their relationship with the change scores on the Auditory Hallucination Rating Scale (AHRS), using a forced-entry linear regression method. Three participants were excluded because of incomplete data.

The overall model was significant ($F(3116) = 3.43$, $p = 0.02$, $R^2 = 0.08$) and explained 8% of the variance in treatment responses of AH as measured with the AHRS. The model yielded two significant predictors for response to rTMS treatment, namely age and gender. A younger age predicted lower AHRS scores after rTMS ($\beta = 0.21$, $t(116) = 2.01$, $p = 0.05$), as did female gender ($\beta = -0.25$, $t(116) = -2.66$, $p < 0.01$). In this model, the lifetime duration of AH was not a significant predictor ($p = 0.76$).

The predictors gender and age are similar to those in depression studies (Fregni et al., 2006; Kedzior et al., 2014). Higher efficacy in female patients might be related to increased brain plasticity due to the protecting influence of estrogens on the brain (Crawford and DeLisi, 2016). The finding that younger age is associated with a better response on AH may partly be explained by the relative absence of cortical atrophy, which in those cases increases the distance between the coil and targeted brain areas (Nahas et al., 2004). Consistent with this, rTMS treatment with adjusted stimulation intensity for cortical atrophy yielded increased responses in depression (Nahas et al., 2004). The finding that younger age is associated with a better treatment response to rTMS may also reflect higher brain plasticity in young people (Ridding and Ziemann, 2010), which facilitates the induction of long-term depression (LTD) by rTMS in targeted (language-related) brain areas.

Currently, rTMS for AH is almost exclusively offered to patients with treatment-refractory AH, mostly after lengthy treatment with multiple antipsychotic agents and cognitive behavioral therapy (CBT). This place at the end of the treatment protocol is similar to that of ECT for depression: only to be used when everything else fails. As a consequence, many patients are relatively old when they first receive rTMS, with decreased chances of success. However, unlike ECT, the side effects of rTMS are mild (comparable to placebo). rTMS can therefore be offered much earlier when patients are still young. Although the effects of rTMS are not likely to be permanent, and maintenance treatment may be necessary, early rTMS treatment does have important advantages. Our results imply that starting rTMS at an early age increases the chances of success. It cannot replace antipsychotic medication, as it has little impact on delusions, but in patients without delusions, rTMS treatment may well postpone or prevent the need to start with antipsychotic medication. To our knowledge, no studies investigating the effects of rTMS for hallucinations at an early stage (i.e., ultra-high risk stage or first psychotic episode) have been published yet, but our analysis indicates that such studies are warranted because treatment responses might be higher.

It should be kept in mind that the model explains a relatively small proportion of the outcome variance. However, the included patients were all relatively old, and the age range of participants was limited (most were 40–50 years). Therefore, effects might prove stronger in studies that also include younger patients. Furthermore, our dataset includes heterogeneous studies concerning rTMS stimulation protocols, which may influence predictive factors of treatment response. Lastly, the included studies had a relatively low response rate. Results may improve when studies with higher response rates are included, of such studies we did not have patient-level data available to include in our analysis. In light of these remarks we emphasize that our findings are preliminary and require replication.

Because efficacy may be higher in younger patients, we urge researchers to investigate rTMS as an early therapeutic tool in young people with AH in the relative absence of other psychotic symptoms. Such trials may shed more light on the place of rTMS in the treatment of AH.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Iris Sommer designed and supervised the research. Sanne Koops gathered data, conducted the analyses and wrote the first draft of the manuscript. Jan Dirk Blom, Christina Slotema, Claire Kos, Leonie Bais and Andre Aleman gathered and contributed data. All authors contributed to and approved the final manuscript.

http://dx.doi.org/10.1016/j.schres.2017.08.060

Table 1
Study parameters and patient demographics.

Study	N	TMS target	TMS frequency	% MT	Coil positioning	TMS sessions
Slotema et al., 2011	34	LTPJ, fMRI-guided[a]	1 Hz	90	10–20[b]/Neural navigator[c]	15
Van Lutterveld et al., 2012	16	LTPJ, RTPJ	1 Hz	80	10–20	3
De Weijer et al., 2014	12	fMRI-guided	1 Hz/20 Hz	90/80	Neural navigator	8
Bais et al., 2014	31	LTPJ, BTPJ	1 Hz	90	10–20	12
Koops et al., 2016	30	LTPJ	Theta burst (50 Hz)	80[d]	10–20	10
Total N			123			
			Male/female			73/50
			Age (M, SD)			37.3 (13.0)
			Baseline AHRS score (M, SD)			27.8 (6.7)
Diagnosis						
			Schizophrenia			94
			Psychosis NOS			19
			Schizoaffective disorder			10
Type of antipsychotic medication						
			Typical			12
			Atypical			97
			Both			7
			None			7

Abbreviations: M = mean, SD = standard deviation, AHRS = Auditory Hallucination Rating Scale, LTPJ = left temporoparietal junction, RTPJ = right temporoparietal junction, BTPJ = bilateral temporoparietal junction, MT = motor threshold.
[a] Target based on individual peak activity during hallucinations as measured with functional magnetic resonance imaging.
[b] Placement according to 10–20 International System for EEG Electrode Placement.
[c] www.neuralnavigator.com, Brain Science Tools B.V. (Neggers et al., 2004).
[d] Up to a maximum of 51% of stimulator output.

Acknowledgements
We would like to thank Rachel Brouwer for her statistical support and Antoin de Weijer and Remko van Lutterveld for their contributions to the data.

References

Bais, L., Vercammen, A., Stewart, R., van Es, F., Visser, B., Aleman, A., Knegtering, H., 2014. Short and long term effects of left and bilateral repetitive transcranial magnetic stimulation in schizophrenia patients with auditory verbal hallucinations: a randomized controlled trial. PLoS One 9 (10), e108828.
Crawford, M.B., DeLisi, L.E., 2016. Issues related to sex differences in antipsychotic treatment. Curr. Opin. Psychiatry 29 (3), 211–217.
De Weijer, A.D., Sommer, I.E.C., Lotte Meijering, A., Bloemendaal, M., Neggers, S.F.W., Daalman, K., Boezeman, E.H.J.F., 2014. High frequency rTMS; a more effective treatment for auditory verbal hallucinations? Psychiatry Res. 224 (3), 204–210.
Fregni, F., Marcolin, M.A., Myczkowski, M., Amiaz, R., Hasey, G., Rumi, D.O., Rosa, M., Rigonatti, S.P., Camprodon, J., Walpoth, M., Heaslip, J., Grunhaus, L., Hausmann, A., Pascual-Leone, A., 2006. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int. J. Neuropsychopharmacol. 9 (6), 641–654.
Kedzior, K.K., Azorina, V., Reitz, S.K., 2014. More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): a meta-analysis of 54 sham-controlled studies published between 1997–2013. Neuropsychiatr. Dis. Treat. 10, 727–756.
Koops, S., van Dellen, E., Schutte, M.J.L., Nieuwdorp, W., Neggers, S.F.W., Sommer, I.E.C., 2016. Theta burst transcranial magnetic stimulation for auditory verbal hallucinations: negative findings from a double-blind-randomized trial. Schizophr. Bull. 42 (1), 250–257.
Nahas, Z., Li, X., Kozel, F.A., Mirzki, D., Memon, M., Miller, K., Yamanaka, K., Anderson, B., Chae, J.-H., Bohning, D.E., Mintzer, J., George, M.S., 2004. Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55–75 years of age: a pilot study. Depress. Anxiety 19 (4), 249–256.
Neggers, S.F., Langerak, T.R., Schutter, D.J., Mandl, R.C., Ramsey, N.F., Lemmens, P.J., Postma, A., 2004. A stereotactic method for image-guided transcranial magnetic stimulation validated with fMRI and motor-evoked potentials. Neuroimage 21 (4), 1805–1817.
Ridding, M.C., Ziemann, U., 2010. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J. Physiol. 588 (Pt 13), 2291–2304.
Slotema, C.W., Blom, J.D., de Weijer, A.D., Diederen, K.M., Goekoop, R., Looijestijn, J., Daalman, K., Rijkaart, A.-M., Kahn, R.S., Hoek, H.W., Sommer, I.E.C., 2011. Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. Biol. Psychiatry 69 (5), 450–456.
Van Lutterveld, R., Koops, S., Schutter, D.J.L.G., Geertsema, E., Stam, C.J., Kahn, R.S., Sommer, I.E.C., 2012. The effect of rTMS on auditory hallucinations: clues from an EEG-rTMS study. Schizophr. Res. 137 (1–3), 174–179.

Sanne Koops
Psychiatry Department, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands,
Brain Center Rudolf Magnus, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
Corresponding author at: University Medical Center Utrecht, Postbus 85500, 3508 GA Utrecht, The Netherlands.
E-mail address: s.koops@umcutrecht.nl.

Christina W. Slotema
Parnassia Psychiatric Institute, Kiwistraat 43, 2552 DH The Hague, The Netherlands
E-mail address: c.slotema@psyq.nl.

Claire Kos
University of Groningen, University Medical Center Groningen, Department of Neuroscience, Antonius Deusinglaan 1, 9700 AD Groningen, The Netherlands
E-mail address: c.kos@umcg.nl.

Leonie Bais
University of Groningen, University Medical Center Groningen, Department of Neuroscience, Antonius Deusinglaan 1, 9700 AD Groningen, The Netherlands
Lentis, Psychiatric Institute, Groningen, The Netherlands
E-mail address: l.bais@umcg.nl.

André Aleman
University of Groningen, University Medical Center Groningen, Department of Neuroscience, Antonius Deusinglaan 1, 9700 AD Groningen, The Netherlands
Department of Psychology, University of Groningen, Grote Kruisstraat 2/1, 9712 TS Groningen, The Netherlands
E-mail address: a.aleman@umcg.nl.

Jan Dirk Blom
Parnassia Psychiatric Institute, Kiwistraat 43, 2552 DH The Hague, The Netherlands
Faculty of Social and Behavioural Sciences, Leiden University, P.O. Box 9555, 2300 RB Leiden, The Netherlands
University of Groningen, University Medical Center Groningen, Department of Psychiatry, P.O. Box 30.001, 9700 RB Groningen, The Netherlands
E-mail address: jd.blom@parnassia.nl.

Iris E.C. Sommer
Psychiatry Department, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands,
Brain Center Rudolf Magnus, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
E-mail address: i.sommer@umcutrecht.nl.

13 June 2017