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Letter to the Editor

Left prefrontal high-frequency rTMS may improve movement disorder in schizophrenia patients with predominant negative symptoms – A secondary analysis of a sham-controlled, randomized multicenter trial

Dear Editor,

Recent research suggests that different first- and second-generation antipsychotics bear risk for extrapyramidal side effects (EPS) including akathisia, acute dystonic reactions, parkinsonism and neuroleptic malignant syndrome, occurring within days or weeks after initiation of an antipsychotic medication or after dosage escalation (Hasan et al., 2013; Leucht et al., 2013). High-frequency rTMS of the primary motor cortex has the potential to improve motor function in patients with Parkinson's disease (Lefaucheur, 2005). In more detail, frontal rTMS (repetitive transcranial magnetic stimulation) has been shown to rebalance disturbed cerebral networks, to normalize cortical activity and to increase dopamine release (Chou et al., 2015). Little is known about the impact of rTMS on motor symptoms in schizophrenia. On the one hand, one might speculate that rTMS may cause a worsening of motor functions as a side-effect comparable to antipsychotic-induced motor symptoms. On the other hand, there might be an improvement in motor function bearing the dopaminergic effect of frontal rTMS in the ipsilateral caudate in mind demonstrated in an experimental neuroimaging study (Strafella et al., 2001).

In the present secondary analysis of the RESIS trial (Wobrock et al., 2015), we analyzed changes in the St. Hans Rating Scale (SHRS) (Gerlach et al., 1993), which was used as a safety parameter controlling for EPS possibly caused by the treatment in a sample of schizophrenia patients with predominant negative symptoms using 10 Hz rTMS over the left DLPFC (15 sessions with 1000 stimuli/session with 5 sessions per week across 3 weeks) in a sham-controlled randomized design (for details of methodology and inclusion criteria see (Cordes et al., 2009; Wobrock et al., 2015)). 197 in- and outpatients from 3 German university hospital centers (Düsseldorf, Göttingen, and Regensburg) were included in the multicenter study. 126 patients received at least 10 rTMS sessions and were therefore used for further analyses. After the intervention, patients entered a 12-week follow-up phase without any further intervention. Study visits and assessments were performed at screening, day 0 (start of rTMS sessions), day 21 (end of rTMS sessions), and for follow-up at day 28, 45 and 105. To test for relative group differences in the SHRS variables during time we calculated for each variable the relative difference between T0 and the other visits (for example $(EPS_{treat0} - EPS_{treat21})/(EPS_{treat0} + 1)$, $(EPS_{treat0} - EPS_{FU28})/(EPS_{treat0} + 1)$ etc.) and then conducted Mann-Whitney-*U* tests with the relative differences as dependent variables and group (active/sham) as the independent variable. Using the relative instead of the absolute difference takes into account the T0 values of the SHRS variables. The effect size of the Mann-Whitney-*U* test was calculated using the formula $\eta^2 = z^2 / (n - 1)$. Correlations between SHRS variables and PANSS negative subscale relative differences of T0 with the other assessment days were assessed by using Spearman correlation. We used Bonferroni significance level correction for multiple testing (five variables [Dyskinesia total passive, Akathisia subjective, Dystonia severity, parkinsonism total, EPS sum score]: $\alpha = 0.05/5 = 0.01$). The values for demographic and clinical data did not differ between active and sham group at the beginning of the study (see Table A.1). Two-sided Mann-Whitney-*U* test shows that the parkinsonism total score was reduced significantly between T0 and FU28 ($U = 286.5$, $z = -2.967$, $p = 0.003$, $\eta^2 = 0.142$) in the active group ($n = 40$, Mdn = 2.00, Q25 = 0.00, Q75 = 5.00 vs. $n = 29$, Mdn = 0.00, Q25 = 0.00, Q75 = 4.00) compared to the sham group ($n = 41$, Mdn = 1.00, Q25 = 0.00, Q 75 = 5.00 vs. $n = 34$, Mdn = 2.50, Q25 = 0.00, Q75 = 6.00), with a medium effect size according to Cohen (1992). Moreover, Mann-Whitney-*U* test could show a trend for a relative difference between the groups (active: $n = 32$, Mdn = 0.00, Q25 = 0.00, Q75 = 2.50 vs. $n = 22$, Mdn = 0.00, Q25 = 0.00, Q75 = 1.50; sham: $n = 33$, Mdn = 0.00, Q25 = 0.00, Q75 = 2.75 vs. $n = 15$, Mdn = 1.00, Q25 = 0.00, Q75 = 2.00) regarding the EPS sum score at T0 and FU105 ($U = 94.0$, $z = -2.264$, $p = 0.024$, $\eta^2 = 0.142$), which was not significant after Bonferroni correction. However, this calculation reached medium effect size (Cohen, 1992). All other calculations failed to reach significance ($p > 0.061$). In addition we calculated correlations between changes in depressive and negative symptoms, and EPS scores and found only one significant positive correlation between the differences of the parkinsonism total score and the PANSS negative subscore between T0 and FU28 (rho = 0.464, $p < 0.001$). Therefore, it cannot be totally ruled out that the improvement in parkinsonism is at least partly influenced by an improvement in negative symptomatology.

However, our results show that there was no evidence suggesting that rTMS over the left DLPFC was associated with worsening of motor function in this sample of patients with schizophrenia. We showed that parkinsonism even seems to be partly improved. Moreover, a trend towards an improvement in EPS sum score between T0 and the last follow-up visit was demonstrated.

The parkinsonism total score significantly improved from day 0 to day 28 in the active group compared with that in the sham group. The treatment groups differed significantly at day 28; 7 days after the last stimulation session in the parkinsonism total score. Thus, one might speculate that stimulation induces changes within the neuronal plasticity, which leads to a change in clinical features after a period of time (May et al., 2006). The present analysis provides additional justifications for the assumption, that rTMS is related to an increased dopamine release in the ipsilateral Ncl. caudatus, which could be the explanation for the improvement of EPS (Strafella et al., 2001).

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Possible limitations include the explorative design of the study, the decreasing number of patients during the follow-up visits and the uncertain appropriateness of the SHRS to examine improvements in movement disorders (as a safety measurement). Moreover, we did not measure interrater reliability for the St. Hans scale, which can be considered as a further limitation.

Altogether, we found, that active 10 Hz rTMS applied to the left DLPFC may have the potential to improve antipsychotic-induced EPS, especially parkinsonism.

Conflicts of interest

This work was supported by the Deutsche Forschungsgemeinschaft Grant No. FA–210/1. The trial protocol has been published (Wobrock et al., 2015).

DK, CE, WW, GW, CSK, BL, ML, PE, EF, CO, PEV, AR, BM, TSA, and PF report no biomedical financial interests or potential conflicts of interest.

TW received speakers' honoraria from Alpine Biomed, Astra Zeneca, Bristol-Myers Squibb, Eli Lilly and Company, I3G, Janssen-Cilag, Novartis, Lundbeck, Roche, Sanofi-Aventis, Otsuka, and Pfizer; was a member of the Advisory Board of Janssen-Cilag and Otsuka/Lundbeck; and has received restricted research grants from AstraZeneca, Cerbomed, I3G, and AOK (health insurance company).

WG has received symposia support from Janssen-Cilag GmbH, Neuss, Lilly Deutschland GmbH, Bad Homburg, and Servier, Munich and is a member of the Faculty of the Lundbeck International Neuroscience Foundation, Denmark.

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GH has received payments as speaker, consultant, or author or for research funding from Actelion Pharmaceuticals, Affectis, AstraZeneca, Bayerische Motorenwerke, Bayer Vital, Boehringer Ingelheim, BmBf, Bundesministerium für Strahlenschutz, BrainLab, Bristol-Meyers Squibb, Cephalon, Daimler Benz, Deutsche Forschungsgesellschaft, Elsevier, EuMeCom, Essex, Georg Thieme, Gerson Lerman Group Council of Healthcarev Advisors, GlaxoSmithKline, Janssen-Cilag, Lilly, Lundbeck, Medice, McKinsey, Meda, Merck, Merz, Network of Advisors, Neuraxpharm, Neurim, Neurocrine, Novartis, Organon, Orphan, Pfizer, Proctor & Gamble, Purdue, Sanofi-Aventis, Schering-Plough, Sepracor, Servier, Springer, Takeda, Transcept, Urban & Fischer, Volkswagen and Wyeth.

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WGH reports other from In Silico, personal fees from Eli Lilly, personal frees from Roche, personal fees from Lundbeck, personal fees from Otsuka outside the submitted work.

AH has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received a paid speakership from Desitin, Otsuka and Lundbeck. He was a member of an advisory board of Roche.

From 2015 until now JC was involved in studies which were sponsored by Boehringer Ingelheim Pharma GmbH, Otsuka Pharmaceutical Europe Ltd., EnVivo Pharmaceuticals, Bundesministerium für Gesundheit, BMBF and Deutsche Forschungsgemeinschaft (DFG).

Role of the funding source

This work was supported by the Deutsche Forschungsgemeinschaft Grant No. FA–210/1. The trial protocol has been published (Wobrock et al., 2015).

Authors' contributions

The Authors Daniel Kamp, Thomas Wobrock, Wolfgang Wölwer, Georg Winterer, Wolfgang Gaebel, Berthold Langguth, Michael Landgrebe, Peter Eichhammer, Elmar Frank, Göran Hajak, Christian Ohmann, Pablo E. Verde, Marcella Rietschel, Raees Ahmed, William G. Honer, Berend Malchow, Thomas Schneider-Axmann, Peter Falkai, Alkomiet Hasan, Joachim Cordes worked on the conception and design of the study.

Moreover the Authors Daniel Kamp, Thomas Wobrock, Wolfgang Wölwer, Georg Winterer, Wolfgang Gaebel, Berthold Langguth, Michael Landgrebe, Peter Eichhammer, Elmar Frank, Göran Hajak, Christian Ohmann, Pablo E. Verde, Marcella Rietschel, Raees Ahmed, William G. Honer, Berend Malchow, Thomas Schneider-Axmann, Peter Falkai, Alkomiet Hasan, Joachim Cordes worked on the acquisition of the data.

Authors Daniel Kamp, Christina Engelke, Christian Schmidt-Kraepelin, Joachim Cordes, Thomas Wobrock, Alkomiet Hasan and Thomas Schneider-Axmann worked on the analysis and interpretation of the data. All authors worked on drafting the article or revising it critically for important intellectual content. Moreover all authors worked on the final approval of the version to be submitted.

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Appendix A

Table A.1
Descriptive details and test values.

	Time		Active	Sham	Stat. analysis
N			62	64	
Gender	Screening	(Female/male)	12/50	18/46	$\chi^2(1) = 1.335$, $p = 0.248$
Employment	Screening	(Yes/no)	12/50	9/55	$\chi^2(1) = 0.635$, $p = 0.425$
Center	Screening	(Duesseldorf/Goettingen/Regensburg)	16/19/27	18/19/27	$\chi^2(2) = 0.086$, $p = 0.958$
Hand preference	Screening	(Right/left)	53/7	55/5	$\chi^2(1) = 0.370$, $p = 0.543$
Age (years)	Screening	(Mdn (Q25, Q75))	33.5 (27.0, 48.0)	36.0 (30.0, 44.0)	U = 1917, $p = 0.744$
Education (years)	Screening	(Mdn (Q25, Q75))	14.0 (12.0, 17.0)	14.0 (12.0, 17.3)	U = 1788, $p = 0.831$
Duration of schizophrenia (years)	Screening	(Mdn (Q25, Q75))	8.00 (4.00, 17.5)	10.5 (4.00, 19.0)	U = 156, $p = 0.669$
Chlorpromazine equivalent dose (woods; mg) Day 0	T0	(Mdn (Q25, Q75))	450.0 (304.45, 744.84)	422.22 (200.0, 1000.0)	U = 1766.5, $p = 0.879$
PANSS negative	Screening	(Mdn (Q25, Q75))	25.0 (23.0, 30.0)	25.0 (23.0, 27.0)	U = 1746.5, $p = 0.244$
PANSS positive	Screening	(Mdn (Q25, Q75))	14.0 (12.0, 17.0)	12.0 (10.0, 14.0)	U = 1336.5, $\mathbf{p = 0.007}$*
PANSS general	Screening	(Mdn (Q25, Q75))	43.0 (34.0, 49.75)	38.0 (31.75, 44.0)	U = 1485.5, $p = 0.055$
SHRS EPS sum score	T0	(Mdn (Q25, Q75))	0.00 (0.00, 2.50)	0.00 (0.00, 2.75)	U = 1069.5, $p = 0.896$
SHRS parkinsonism total score	T0	(Mdn (Q25, Q75))	2.00 (0.00, 5.00)	1.00 (0.00, 5.00)	U = 1156.5, $p = 0.400$
SHRS dyskinesia total passive score	T0	(Mdn (Q25, Q75))	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	U = 1092.5, $p = 0.716$
SHRS akathisia subjective score	T0	(Mdn (Q25, Q75))	0.00 (0.00, 2.00)	0.00 (0.00, 1.00)	U = 1145.5, $p = 0.276$
SHRS dystonia severity score	T0	(Mdn (Q25, Q75))	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	U = 1202.0, $p = 0.482$

Comparison of demographic and clinical data between the active and sham groups at screening and day 0. Values missing from the total sample size are due to missing data. Mdn: median, Q25: 25% quartile, Q75: 75% quartile.

* Alpha = 0.05.

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