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Reducing auditory verbal hallucinations by means of fNIRS neurofeedback – A case study with a paranoid schizophrenic patient

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Auditory verbal hallucinations (AVHs) are a core symptom of schizophrenias and are associated with increased activation in speech-relevant regions (e.g. Allen et al., 2012). As AVHs can be resistant to antipsychotic medications (25–30% of patients) (Shergill et al., 1998), alternative intervention methods are needed. Neurofeedback (NF) constitutes an alternative approach, as it can modulate excitation levels and altered brain activity in the long-term (Butnik, 2005; Sterman, 1996). In a curative trial aimed at symptom reduction, we conducted a functional near-infrared spectroscopy (fNIRS)-based NF training of posterior superior temporal gyrus (STG) regulation. We developed a training protocol, which adapted to the current state of patients' AVHs.

The patient (25, female, right-handed) had a 6-year history of paranoid schizophrenia (F20.0; ICD10) with persistent, distressing AVHs, hearing different voices several times per hour. The AVHs were resistant to different antipsychotics and complimentary psychotherapy. Before and throughout the study, she was medicated with constant dosage (Quetiapine 300 mg and 100 mg/day, Haloperidol 2 mg, Clozapine 100 mg, Citalopram 30 mg). Her IQ was rated with a score of 69 (HAWIE; 2011, age 22), but as she exhibited pronounced impairments in working memory, the result should be regarded with caution. An EEG measurement (2011) revealed no pathological patterns. Before this NF trial, the patient participated in an NF pilot study (Ehlis et al., 2018) (15 sessions of fNIRS NF training), but failed to learn neural activity regulation.

Training sessions were conducted using a continuous wave NIRS system (ETG-4000 Optical Topography System; Hitachi Medical Co., Japan), with two probe-sets covering fronto-temporo-parietal areas (Supplementary material). In total, 47 sessions were conducted, comprising each two feedback (FB) (simplified feedback of neural activity) and two transfer (TR) (no contingent feedback of regulation performance) blocks with 8 trials each (FB, TR, FB, TR design) (Supplementary material). The feedback signal was the average amplitude of O_2Hb of the bilateral posterior STG relative to a pre-recorded baseline. The patient had to down-regulate (decrease O_2Hb) neural activity in the target region when she was experiencing AVHs during the trial (hallucination trials) and during trials when she was not experiencing AVHs (non-hallucination trials). Whenever she felt that AVHs were about to begin ("soon" trials), she had to up-regulate neural activity (increase O_2Hb). The "soon" condition is based on the results of Diederen et al. (2010), revealing deactivations preceding AVH-onset in speech-relevant regions, including the STG. After each trial, she reported the state of AVHs. Furthermore, a pre-test before the first NF session and a post-test after all sessions were completed, comprising a clinical assessment, including the Positive and Negative Syndrome Scale (PANSS) and the *Psychotic Symptom Rating Scale* (PSYRATS), and a 7-minute fNIRS resting-state measurement.

fNIRS raw data was pre-processed (compare Hudak et al., 2017) and separated into six conditions: AVHs FB/TR, no AVHs FB/TR, AVHs soon FB/TR. Regions of interest (ROIs) were calculated as the averaged O_2Hb data of feedback channels. Amplitudes were averaged over the trials (last 20 s of each trial with 5 s baseline correction) for each session and condition to evaluate regulation performance. Furthermore, we calculated the number of successful trials, operationalized as the signal >50% above/under (up- or down-regulation trial) the baseline during the last 15 s of a trial. We analysed this "behavioral" data calculating the percentage of successful trials for each condition.

To calculate regulation ability, amplitudes of left and right ROIs for each condition were compared against zero, utilizing *t*-tests. Regression analyses, with amplitudes of the ROIs and ascending session number, assessed learning performance. The number of hallucination trials (i.e., hallucination events per session) was correlated (Spearman correlation) with ascending session number (1–47) to assess symptom reduction.

The patient was able to regulate posterior STG in the "soon" condition, showing a significant increase of O_2Hb amplitudes in nearly all sessions in left ROI for FB ($t(42) = 3.41$, $p = .001$) and TR ($t(42) = 5.44$, $p < .001$) and in right ROI for FB ($t(42) = 2.58$, $p = .014$), but not for TR (t

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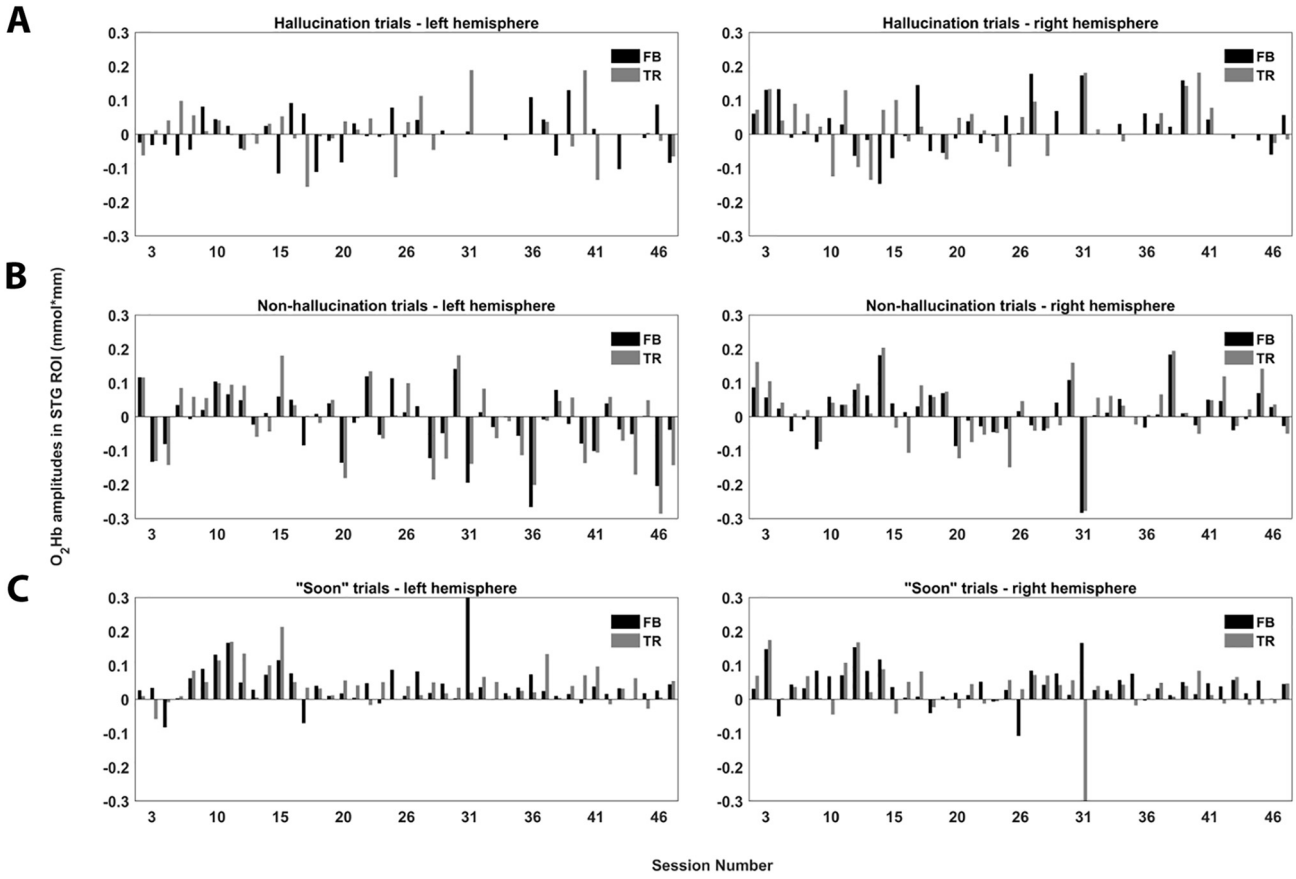

Fig. 1. O_2Hb amplitudes in the left and right feedback channels (STG ROIs) for feedback (FB) and transfer (TR) trials in hallucination trials (A), non-hallucination trials (B) and "soon" trials (C).

(42) = 1.18, $p = .245$) (Fig. 1). In hallucination trials, the patient did not exhibit significant down-regulation of neural activity in the left ROI ($p > .05$ for FB/TR) and only on a trend level in the right ROI (FB: $t(42) = 1.965$, $p = .056$; TR: $t(42) = 1.987$, $p = .053$). In non-hallucination trials, amplitudes over sessions did not differ significantly from zero ($p > .05$ for FB/TR, left/right ROIs). However, a learning effect was present: a systematic increase of deactivations in non-hallucination trials was registered in the left ROI (regression analysis with quadratic model fit: $F(1,41) = 6.731$, $p < .05$; $\beta = -0.376$, $t(41) = -2.594$, $p < .05$, $R^2 = 0.141$ for TR trials; for FB trials at a trend level: $R^2 = 0.087$, $F(1,41) = 3.904$, $p = .055$; $\beta = -0.295$, $t(41) = 1.987$, $p = .055$). No learning effect was detected in other conditions.

The patient's hallucinations decreased sharply after the 27th session. The analysis of behavioral data showed significant reduction of AVHs (FB: $r = -0.509$, $p < .001$; TR: $r = -0.508$, $p = .001$ for TR). A significant negative correlation between successful "soon" trials and total "hallucination" trials (FB: $r = -0.507$, $p = .001$; TR: $r = -0.629$, $p < .001$) indicated that overall successful regulation in the "soon" condition may have accounted for symptom reduction (Supplementary material). We assume that the constant successful increase of the O_2H amplitude in the target region immediately preceding AVHs led to a compensation of neural activity and prevented the emergence of hallucinations. Additionally, a subjective reduction of symptoms over the course of the training was detected ($r = -0.591$, $p < .001$).

We further investigated changes in functional connectivity (FC) from pre to postresting-state measurements (compare Rosenbaum et al., 2016). The analysis revealed increased FC following training between the left ROI and inferior temporal gyrus (IFG), STG and medial temporal gyrus (MTG) in both hemispheres, and additionally the motor cortex in the right hemisphere (Supplementary material).

The evaluation of questionnaires indicated a decrease of symptoms after training (Supplementary material). Interestingly, the patient changed her conceptualization of her voices after the training. Before the NF, she believed that the hallucinations were externally generated; after the NF, she assumed that she was the one who evoked them. This modification of cognition could have a more profound and longer-term impact on the symptoms. The results indicate that adaptive fNIRS-NF is a promising intervention method in reducing AVHs and altering functional connectivity, but controlled studies with schizophrenic patients are needed to generalize the effects.

The results indicate that adaptive fNIRS-NF is a promising intervention method in reducing AVHs and altering functional connectivity, but controlled studies with schizophrenic patients are needed to generalize the effects.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.09.018.

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Contributors

HS designed the study, collected the data, undertook the analysis and drafted the manuscript. JH wrote the protocol, was involved in analysis and contributed significantly to final version. FH and DR were involved in analysis. DR was involved in analysis. AF was involved in interpretation of analysis and contributed significantly to final version. A-CE was involved in study design, interpretation of analysis and contributed significantly to final version. All authors have approved of the final version of this manuscript.

Conflict of interest

HS, JH, FH, DR, AF and A-CE declare no commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Allen, P., Modinos, G., Hubl, D., Shields, G., Cachia, A., Jardri, R., Thomas, P., Woodward, T., Shotbolt, P., Plaze, M., Hoffman, R., 2012. Neuroimaging auditory hallucinations in schizophrenia: from neuroanatomy to neurochemistry and beyond. Schizophr. Bull. 38, 695–703. https://doi.org/10.1093/schbul/sbs066.

Butnik, S.M., 2005. Neurofeedback in adolescents and adults with attention deficit hyperactivity disorder. J. Clin. Psychol. 61, 621–625. https://doi.org/10.1002/jclp.20124.

Diederen, K.M.J., Neggers, S.F.W., Daalman, K., Blom, J.D., Goekoop, R., Kahn, R.S., Sommer, I.E.C., 2010. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. Am. J. Psychiatry 167, 427–435. https://doi.org/10.1176/appi.ajp.2009.09040456.

Ehlis, A.-C., Barth, B., Hudak, J., Storchak, H., Weber, L., Kimmig, A.-C.S., Kreifelts, B., Dresler, T., Fallgatter, A.J., 2018. Near-infrared spectroscopy as a new tool for neurofeedback training: applications in psychiatry and methodological considerations. Jpn. Psychol. Res. https://doi.org/10.1111/jpr.12225

Hudak, J., Blume, F., Dresler, T., Haeussinger, F.B., Renner, T.J., Fallgatter, A.J., Gawrilow, C., Ehlis, A.-C., 2017. Near-infrared spectroscopy-based frontal lobe neurofeedback integrated in virtual reality modulates brain and behavior in highly impulsive adults. Front. Hum. Neurosci. 11, 1–13. https://doi.org/10.3389/fnhum.2017.00425.

Rosenbaum, D., Hagen, K., Deppermann, S., Kroczek, A.M., Haeussinger, F.B., Heinzel, S., Berg, D., Fallgatter, A.J., Metzger, F.G., Ehlis, A.C., 2016. State-dependent altered connectivity in late-life depression: a functional near-infrared spectroscopy study. Neurobiol. Aging 39, 57–68. https://doi.org/10.1016/j.neurobiolaging.2015.11.022.

Shergill, S.S., Murray, R.M., McGuire, P.K., 1998. Auditory hallucinations: a review of psychological treatments. Schizophr. Res. 32, 137–150.

Sterman, M.B., 1996. Physiological origins and functional correlates of EEG rhythmic activities: implications for self-regulation I. Biofeedback Self Regul. 21, 3–33.