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Impact of rTMS on functional connectivity within the language network in schizophrenia patients with auditory hallucinations

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ABSTRACT

This exploratory study investigated the functional connectivity (FC) in the language network in schizophrenia patients (SZ) with auditory verbal hallucinations (AVHs), and the therapeutic efficacy of rTMS on it. Eleven SZ with AVHs and 10 healthy controls (HC) underwent two fMRI sessions using a speech listening paradigm. SZ received 20 Hz rTMS following the first fMRI session. Compared to HC, SZ showed a reduced FC in the language network. While AVHs improved after 12 days, no changes in FC were observed. This suggests the efficacy of high-frequency rTMS on AVH without any impact for rTMS on FC within the language network.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) provokes both local and remote effects due to interconnected cortical regions (Gerrits et al., 2015; Gromann et al., 2012; Tracy et al., 2010), leading to the suggestion that its therapeutic effects might extend to normalizing abnormal functional connectivity (FC) (Gromann et al., 2012). Many studies have supported the hypothesis that schizophrenia is a disconnection syndrome since the seminal hypothesis of Wernicke (1906) (for review: (Stephan et al., 2009)). This abnormality is especially evident in the language network (Price, 2010), and could underlie auditory verbal hallucinations (AVHs) (Gavrilescu et al., 2010; Oertel-Knöchel et al., 2014; Shinn et al., 2013). The aim of the present exploratory study was to evaluate the impact of rTMS on FC within the intra- and inter-hemispheric language networks in patients with schizophrenia (SZ) and with AVHs.

2. Material and methods

2.1. Participants

Eleven SZ, including nine patients from a previous study (Montagne-Larmurier et al., 2009), with diagnoses based on the 2000 text-revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) with AVHs (evaluated with AHRS; Hoffman et al., 2003) were recruited and matched by age, handedness, level of education, and gender, to ten healthy controls (HC). Patient characteristics included an average age of 35.47 ± 9.96 years, 11.81 ± 1.60 years of education, 10 were right-handed, and 5 were male. All participants provided written informed consent. The local ethics committee approved the protocol.

2.2. Stimulation

Only schizophrenia patients underwent rTMS which was applied at 20 Hertz (Hz) at 80% of the intensity of the resting motor threshold, twice a day for two days, and for a total of 10,400 pulses. The stimulation site was guided by functional MRI (fMRI) to the region with the highest activation cluster along the posterior part of the left superior temporal sulcus according to a method previously described (Montagne-Larmurier et al., 2009).

2.3. Functional MRI

All participants underwent two fMRI sessions (sessions 1 and 2), at an interval of 15.2 ± 3.38 and 14.8 ± 2.39 days for SZ and HC respectively. Only patients received rTMS after the first fMRI. Participants listened to a factual story in French (4 blocks) alternating with periods of silence (5 blocks), for a duration of 5 min. This task is known to elicit

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activation in phonology and acoustical processing areas involved in AVHs and to induce good reproducible activations (Maïza et al., 2011).

2.4. Data analyses

MRI was acquired on a Philips 3 Tesla scanner with T_1-weighted and T_2-weighted images. Functional images were acquired using a T_2^*-weighted echo-planar sequence. Data were preprocessed using SPM12 (Statistical Parametrical Mapping, Wellcome Department of Cognitive Neurology, London, UK), allowing us to obtain anatomical and functional images in MNI space (Montreal Neurological Institute, Canada).

Post-processing of functional data consisted of generating, for each participant, a map of the Blood Oxygen Level-Dependent (BOLD) signal contrast between French language *versus* silence. A mean functional map was then generated for the whole population (SPM12, one-sample *t*-test, threshold at $P < 0.001$ and corrected by family wise-error, FWE), which allowed us to determine four seed regions: the left and right Heschl gyri (LHG and RHG) defined according to the AAL atlas (Tzourio-Mazoyer et al., 2002), and the left and right temporal (LT and RT), corresponding to the activated temporal cluster minus LHG or RHG (Fig. 1).

2.5. Paired-seed regions for functional connectivity

FC was evaluated between these four seed regions of interest (paired-seed regions). The average time series were extracted for each participant in each region and a Pearson correlation coefficient calculated for mean time courses between paired-seed regions. These coefficients were then converted to Z values according to Fisher's r-to-z transformation to obtain a normal distribution (Fisher, 1915).

2.6. Statistical analyses

To assess FC for each paired-seed region, data were subject to 2-way mixed effects ANOVA with the subject as a random effect, and the group (SZ *versus* HC) and session (session 1 *versus* session 2) as fixed effects. *Post-hoc* pairwise comparisons with Bonferroni correction were conducted when a significant effect was observed. A paired *t*-test was performed on AHRS scores to examine differences in severity of

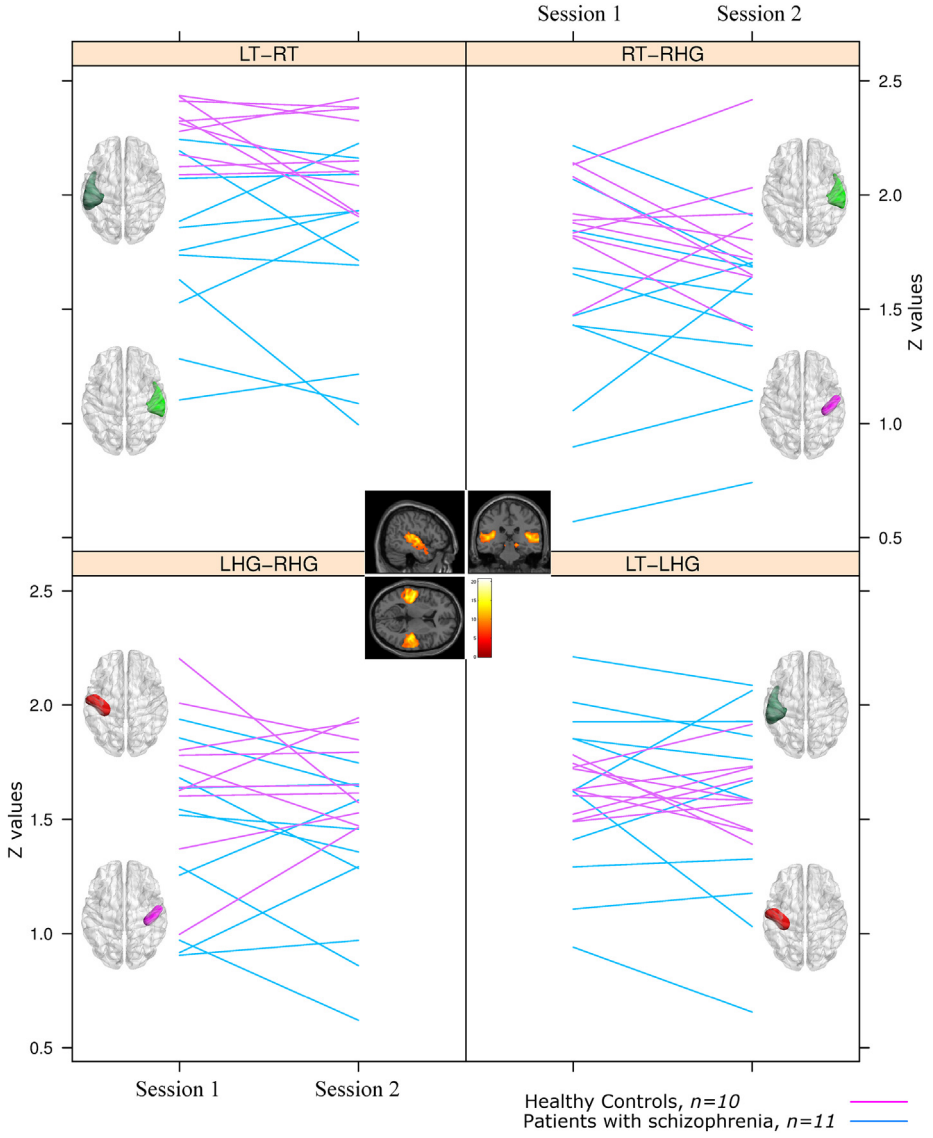

Fig. 1. Functional connectivity (FC) within the language network in fMRI session 1 and in fMRI session 2 (after rTMS for SZ). Each line represents one participant (healthy controls are designated pink; patients with schizophrenia are blue). The left and right temporal (LT-RT; dark and light green respectively), and left and right Heschl gyrus (LHG-RHG; colored red and pink respectively), were derived from the functional mean map ($p < 0.001$ corrected by FWE) represented at the center. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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