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Significant repetition probability effects in schizophrenia

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ABSTRACT

Background: A growing body of evidence suggests that the comparison of expected and incoming sensory stimuli (the prediction-error (ε) processing) is impaired in schizophrenia patients (SZ). For example, in studies of mismatch negativity, an ERP component that signals ε, SZ patients show deficits in the auditory and visual modalities. To test the role of impaired ε processing further in SZ, using neuroimaging methods, we applied a repetition-suppression (RS) paradigm.

Methods: Patients diagnosed with SZ (n = 17) as well as age- and sex- matched healthy control subjects (HC, n = 17) were presented with pairs of faces, which could either repeat or alternate. Additionally, the likelihood of repetition/alternation trials was modulated in individual blocks of fMRI recordings, testing the effects of repetition probability (P(rep)) on RS.

Results: We found a significant RS in the fusiform and occipital face areas as well as in the lateral occipital cortex that was similar in healthy controls and SZ patients SZ. More importantly, we observed similar P(rep) effects (larger RS in blocks with high frequency of repetitions than in blocks with low repetition likelihood) in both the control and the patient group.

Conclusion: Our findings suggest that repetition probability modulations affect the neural responses in schizophrenia patients and healthy participants similarly. This suggests that the neural mechanisms determining perceptual inferences based on stimulus probabilities remain unimpaired in schizophrenia.

Acronyms and abbreviations

AltB	Alternation Blocks
AltT	Alternation Trial
BPRS	Brief Psychiatric Rating Scale
ε	Prediction error
FFA	Fusifrom face area
fMRIa	fMRI adaptation
HC	Healthy control subjects
LO	Lateral Occipital cortex
MMN	Mismatch-negativity
OFA	Occipital face area
PC	Predictive coding models
P(rep)	Repetition probability
RepB	Repetition Blocks
RS	Repetition suppression
RepT	Repetition Trial
SANS	Negative Symptoms
SAPS	Scales for Assessment of Positive
SZ	Schizophrenia patients

1. Introduction

Bayesian views postulate that frequent stimuli are less informative and that the brain allocates fewer resources to their processing. Multistage Bayesian models were proposed to explain repetition suppression (RS; Friston, 2005b), a phenomenon where stimulus repetitions elicit reduced neuronal responses when compared to first presentations (Henson and Rugg, 2003). In Bayesian models, the top-down predicted and bottom-up observed information are compared, and their mismatch (prediction error, ε) is calculated; hereby, repetitions attenuate ε, reflected in RS. Conversely, for rare stimuli, the top-down ε is high,

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augmenting neural responses. Such predictive coding models (PC, Rao and Ballard, 1999) assume that RS depends on statistical factors that determine expectations. Indeed, recent functional magnetic resonance imaging (fMRI) studies, manipulating repetition probabilities (P(rep)) and therefore modulating expectations, found that P(rep) affects the degree of blood oxygen-level dependent (BOLD) signal reduction (fMRI adaptation; fMRIa): It was larger in blocks with high compared to low P(rep) (Grotheer et al. 2014; Kovacs et al. 2012; Larsson and Smith, 2012; Summerfield et al. 2008; but see Grotheer and Kovacs, 2014; Kovács et al. 2013). This suggests that the modulation of P(rep) enables the subjects to build expectations about whether repetitions are likely to occur, and these expectations reduce ε and the BOLD signal further.

PC models were also associated with schizophrenia (SZ), showing that numerous symptoms are related to PC deficits (Corlett et al., 2007; Voss et al., 2010; Yamashita and Tani, 2012). Furthermore, it has been proposed that—due to disconnectivity of prefrontal—posterior brain networks (Banyai et al. 2011; Friston, 2005a; Stephan et al. 2006, 2009)—the sensory and predicted information are not compared adequately in SZ (review in: Fletcher and Frith, 2009). This idea agrees with a large body of mismatch negativity (MMN; Naatanen et al., 1978) studies reporting attenuated MMN in SZ patients (Butler et al., 2012; Fisher et al. 2012; Kargel et al. 2014; Todd et al., 2014; Umbricht and Krljes, 2005), and it has been proposed that this attenuation is related to abnormal predictive processes (Baldeweg, 2006; Friston, 2005b; Garrido et al., 2008; Garrido et al. 2009; Stefanics and Czigler, 2012; Wacongne et al. 2012). It should be noted, however, that several different types of predictions in different paradigms my exist (summary in: Grotheer and Kovacs (2016)), and oddball paradigms of MMN studies are only one particular situation where surprising/infrequent stimuli are embedded in a continuous stream of standard (and therefore expected) stimuli. Thus, the testing of abnormal predictive processes in SZ requires evidence from different paradigms; thereby eliciting predictions in different ways.

The motivation behind our study was threefold. Firstly, we reasoned that - if P(rep) modulations of RS reflect fulfilled perceptual expectations and rely on predictive functions—SZ patients, showing deficient ε processing, should have impairments of these modulations. Secondly, most studies linking SZ to impaired perceptual expectancy and predictions commonly apply variations of the same oddball paradigm. In order to draw general conclusions about the neural mechanisms of SZ, it is essential, however, to show impairments in ε processing in paradigms that also reflect fulfilled perceptual expectations. Thirdly, we assessed the role of impaired ε processing in SZ patients by applying an fMRI P(rep) modulation paradigm that has previously been linked to fulfilled perceptual expectations.

2. Methods

2.1. Subjects

Seventeen patients with schizophrenia (meeting both DSM-IV and DSM-5 criteria) as well as a healthy, age- and sex-matched control group (13 male in each group) were tested. All subjects gave written informed consent, and the experiment had been approved by the Ethics Committee of the Friedrich Schiller University Jena Medical School and was in compliance with the Declaration of Helsinki. General exclusion criteria for all subjects were major neurological disorders, substance dependence, history of traumatic brain injury or learning disability. (Pre-morbid) IQ was estimated using the MWT-B (Mehrfachwahl–Wortschatz-Test / multiple choice vocabulary test; Lehrl et al. 1995). Handedness was assessed using the Edinburgh Handedness Inventory (EHI, Oldfield, 1971). Patients were recruited from the in- and out-patient services of the Department of Psychiatry and Psychotherapy of Jena University Hospital. Diagnosis was first performed according to DSM-IV criteria, but patients also met DSM-5 criteria. Current psychopathology was assessed using the Scales for Assessment of Positive (SAPS, Andreasen, 1984) and Negative Symptoms (SANS, (Andreasen, 1983), and the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962). Chlorpromazine dose-equivalents of antipsychotic medication were calculated (Gardner et al. 2010); q.v., Table 1.

Table 1
Overview of the demographical data and clinical characteristics of the participants.

EHI –Edinburgh Handedness Inventory, SAPS – Scale for Asssesment of Positive Symptoms, SANS – Scale for Assesment of Negative Symptoms, BPRS-Brief Psychiatric Rating Scale, CPZ- Chlorpromazine dose equivalent.

	Schizophrenia patients	Control
Sex (female / male)	3 /14	3 /14
Age years (± SE)	34.6 (9)	34.5 (8.6)
Education (years)	11.1 (0.4)	10.1 (0.5)
IQ (± SE)	107.4 (3.32)	103.29 (2.63)
EHI (± SE)	79 (6.1)	75.2 (7.6)
SAPS (± SE)	13.53 (2.28)	–
SANS (± SE)	36.65 (3.94)	–
BPRS (± SE)	34.7 (1.8)	–
Duration of illness (years)	9.5 (1.3)	–
Episodes	2.7 (0.36)	–
CPZ	318.73 (65.1)	–

2.2. Stimulation and procedure

The design was similar to previous work (Fig. 1A; (Grotheer and Kovacs, 2014; Kovacs et al., 2012; Summerfield et al., 2008): 240 gray-scale photos of full-frontal Caucasian faces, similar to stimuli used by Grotheer and Kovács (2015), were fit behind a circular mask (diameter = 5.5°) and presented in the centre of the screen in front of a uniform grey background. Each stimulus was presented once per run; with a 2.75° visual angle in non-target trials (back-projected via an LCD video projector [NEC GT 1150, NEC Deutschland GmbH, Ismaning, Germany] onto a translucent screen inside the scanner bore). To reduce local feature adaptation, the size of the first or second stimulus (S1 or S2; chosen randomly) was reduced by 18%. Target stimuli were reduced in size by 54%. Stimulus presentation was controlled using Matlab R2014a (The MathWorks, Natick, MA, USA) with Psychtoolbox (Version 3.0.9). Faces were presented for 250 ms each pairwise, separated by an inter-stimulus interval varied between 400–600 ms and followed randomly by a 1 or 2 s inter-trial interval. The first stimulus (S1), was either identical to (eepetition trial, RepT) or different from the second stimulus (S2) (tlternation Trial, AltT). Two block types were presented (Fig. 1B), separated by a 7 s pause during which the phrase "*Short Break*" was presented centrally. In the repetition blocks (RepB), 75% of the non-target trials were RepT while 25% were AltT. In the alternation blocks (AltB), 75% were AltT and 25% RepT. With the exception of the first four trials of each block, which always consisted of the more frequent trial type of that specific block, RepT and AltT were presented randomly. In addition, 20% of all trials were target trials, which could be AltT or RepT with the same probability. Overall, AltB contained 70% AltT and 30% RepT, and RepB had 70% RepT/30% AltT. Both AltB and RepB contained 20 trials and were repeated 4 times during each run. Two runs were administered to each subject. The participants' task was to maintain central fixation and signal the occurrence of target stimuli by pressing a button.

2.3. Imaging parameters and data analysis

The study was performed using a 3-Tesla MR scanner (Siemens Magnetom Trio, Erlangen, Germany). High-resolution sagittal T1-weighted images (magnetization prepared rapid gradient echo imaging sequence TR = 2300 ms; TE = 3.03 ms; 1 mm isotropic voxel size) and

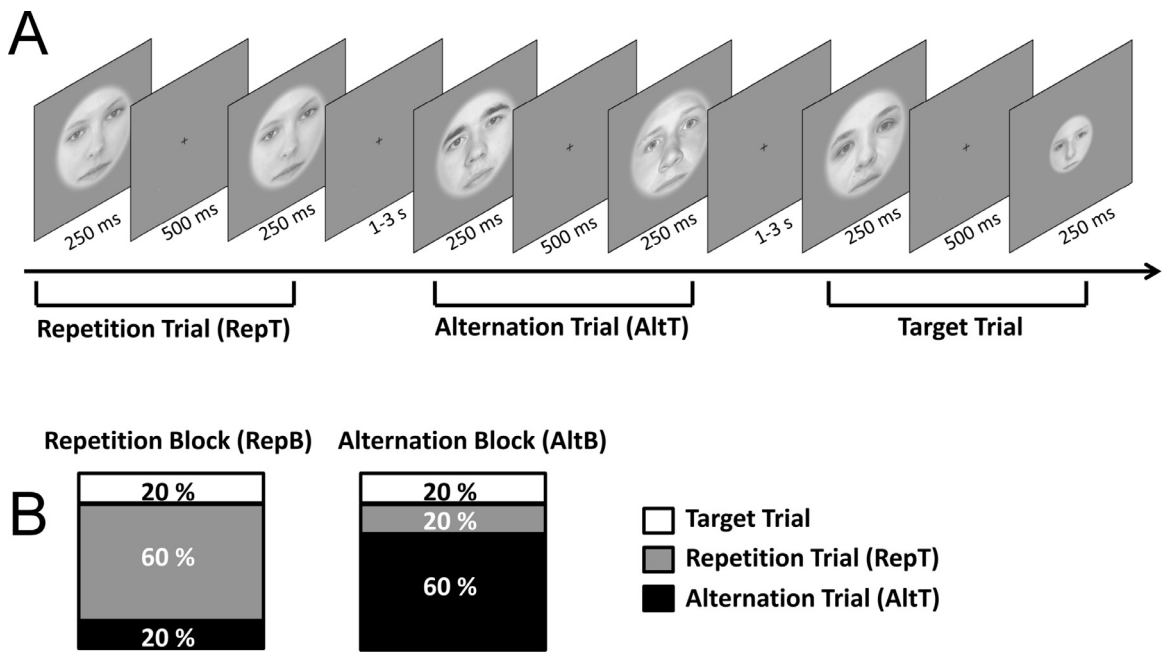

Fig. 1. A. Stimulation parameters and arrangements. A repetition trial (RepT), an alternation (AltT) and a target trial are illustrated. B. The composition of the repetition and alternation blocks. During a run, RepBs and AltBs were each repeated four times.

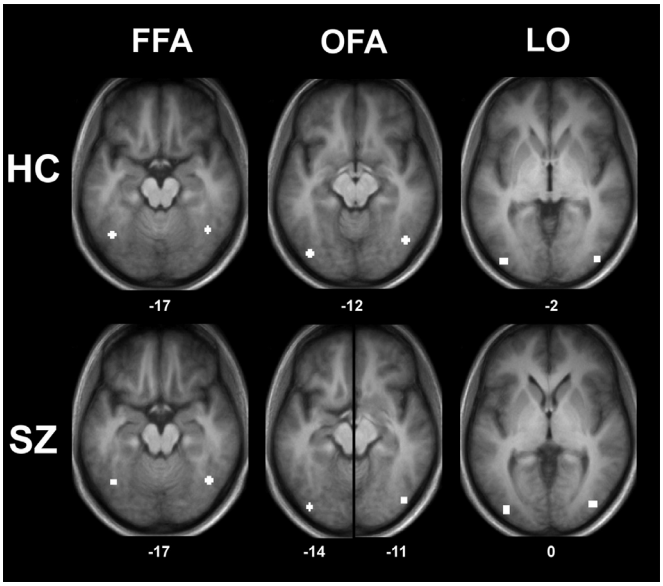

Fig. 2. A. Whole-brain group results of the functional localizer showing the locations of FFA, OFA and LO for control (A) and schizophrenic (B) participants.

T2*-weighted images were acquired (34 slices, 10° tilted relative to axial, T2* weighted EPI sequence, TR = 2000 ms; TE = 30 ms; flip angle = 90°; 64 × 64 matrices; in-plane resolution: 3 × 3 mm; slice thickness: 3 mm). Details of preprocessing and statistical analyses are described elsewhere (Cziraki et al. 2010). Briefly, the functional images were realigned, normalized to the MNI-152 space, resampled to 2 × 2 × 2 mm resolution and spatially smoothed (Gaussian kernel of 8 mm FWHM; SPM8, Welcome Department of Imaging Neuroscience, London, UK). Separate functional localizer runs (480 s long, 20 s epochs of faces, objects and Fourier randomized versions of faces, interleaved with 20 s of blank periods, 2 Hz stimulus repetition rate; 300 ms exposition time; 200 ms blank) were used to determine regions of interest (ROIs; MARSBAR 0.43 Brett et al. 2002). Details of ROI coordinates are given in the supplementary material. ROI size was not significantly different between HC and SZ for either of the areas ($p > 0.25$ for every comparison). The experimental conditions (AltB_AltT, AltB_RepT, RepB_AltT, RepB_RepT) and the target trials were defined as regressors, convoluted with the canonical Haemodynamic Response Function (HRF) of SPM8, for a univariate general linear model (GLM) analysis. We averaged the results of the two runs for each subject and ROI and performed ANOVAs for each area separately; with hemisphere (2), block (2) and trial (2) as within-subject- and group (2, SZ, HC) as between-subject-factors. Post-hoc analyses were performed using Fisher's LSD tests.

To compare the magnitude of RS in SZ and HC directly, we performed the following analysis: First, we calculated a repetition suppression index score (RSI) using the equation $RSI = R_{alt} - R_{rep}$, wherein R_{alt} and R_{rep} are the average responses in the AltT and RepT within a given block. Thereafter, we performed an ANOVA with hemisphere (2) and block (2) as within-subject- and group (2) as between-subject-factors.

3. Results

3.1. Performance

Subjects were not aware of different P(rep), and performance did not differ between groups (see supplementary material for details).

3.2. Fusiform face area (FFA)

3.2.1. Response magnitude and repetition suppression

The response magnitude was similar for HC and SZ (Fig. 3A; non-significant main effect of group: $F(1,32) = 0.39$, $p = 0.53$, $\eta_p^2 = 0.01$). Similarly, both SZ and HC exhibited robust repetition suppression (main effect of trial: $F(1,32) = 3.76$, $p = 0.05$, $\eta_p^2 = 0.15$; non-significant interaction of group x trial: $F(1,32) = 1.01$, $p = 0.32$, $\eta_p^2 = 0.03$). The response was larger over the right compared to the left hemisphere (main effect of hemisphere: $F(1,32) = 6.06$, $p = 0.02$, $\eta_p^2 = 0.16$), and the response reduction due to stimulus repetition was larger over the right compared to the left hemisphere (trial x hemisphere interaction: $F(1,32) = 8.82$, $p = 0.006$, $\eta_p^2 = 0.22$) for both groups (non-significant group x trial x hemisphere interaction: F

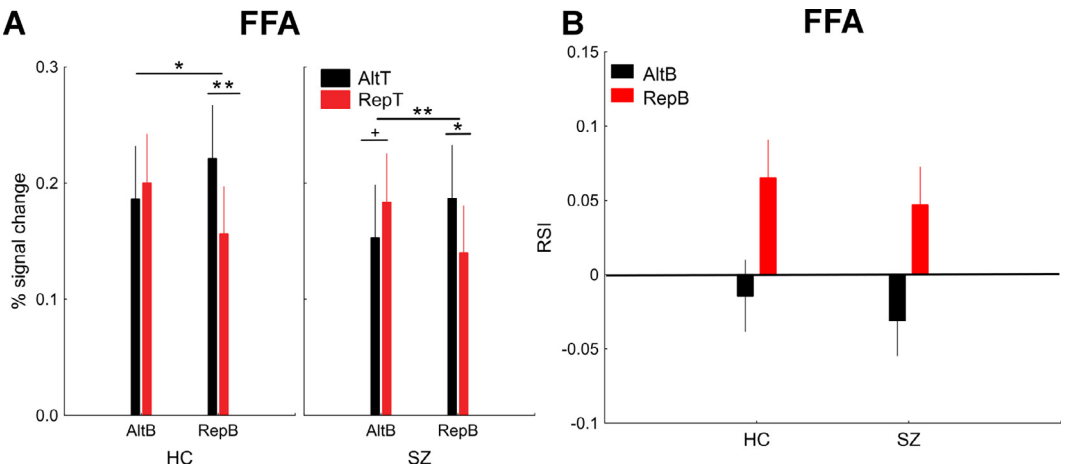

Fig. 3. Average peak activation profiles (± SE) of the FFA, OFA and LO for AltTs and RepTs separately for each block and for the HC and SZ participants, but averaged across hemispheres. Grey crosses represent the individual data.

(1,32) = 0.19, p = 0.66, η_p^2 = 0.006). Altogether, these results suggest that SZ patients have normal response magnitude and RS in the face processing areas.

3.2.2. Repetition probability modulations

The observed RS (Fig. 3A) was dependent on the P(rep) (block x trial interaction: F(1,32) = 19.58, p = 0.0001, η_p^2 = 0.38), as the BOLD signal was significantly lower for RepT than AltT in blocks where repetitions were frequent (RepB; Fisher's post-hoc test: p = 0.0001), but not when they were rare (AltB; p = 0.1). The P(rep) effect on RS was larger over the right compared to the left hemisphere (interaction of hemisphere x block x trial: F(1,32) = 6.64, p = 0.01, η_p^2 = 0.17). The reason for this interaction was that AltB showed no RS over the right hemisphere (p = 0.6), while a significant (p = 0.0001) repetition enhancement (higher response for RepT as compared to AltT) was observed over the left hemisphere. More importantly for the aims of the current study, RS effects were also present in patients (no group x block x trial interaction: F(1,32) = 0.02, p = 0.66, η_p^2 = 0.01). The only difference observed between the response patterns of patients and HC was that - while HC showed no differences of RepT and AltT in the AltB (p = 0.42) - there was a tendency for larger responses (repetition enhancement) in RepT compared to AltT in the AltB for SZ (p = 0.09).

In accordance with the previously presented results, the RSI was larger for RepB compared to AltB (Fig. 3B; F(1,32) = 19.58, p = 0.0001, η_p^2 = 0.38). The direct comparison of the RSIs for patients and HC revealed neither a significant main effect of group (F(1,32) = 1.01, p = 0.32, η_p^2 = 0.03) nor a significant interaction of block type with participant group (F(1,32) = 0.001, p = 0.97, η_p^2 = 0.0005). This analysis further supports the conclusion that there is a significant repetition suppression modulation by P(rep) in SZ. .

3.3. Occipital face area

3.3.1. Response magnitude and repetition suppression

The response magnitude of the occipital face area (OFA) was somewhat lower in patients than in HC (Fig. 4C), but this difference did not reach the level of significance (main effect of group: F(1,30) = 3.57, p = 0.07, η_p^2 = 0.11). The response was also larger over the right compared to the left OFA (main effect of hemisphere: F(1,30) = 15.52, p = 0.0005, η_p^2 = 0.34), but this lateralisation was not present in the SZ patient group (interaction of hemisphere x group: F(1,30) = 5.72, p = 0.02, η_p^2 = 0.16; post-hoc test for right and left OFA activations in SZ group: p = 0.28). Similarly to FFA, SZ patients exhibited RS (main effect of trial: F(1,30) = 3.97, p = 0.05, η_p^2 = 0.15; non-significant interaction of group x trial: F(1,30) = 2.05, p = 0.16, η_p^2 = 0.06). Unlike in FFA, the response reduction due to stimulus repetition was larger over the left compared to the right hemisphere in the HC group (trial x hemisphere x group interaction: F(1,30) = 4.66, p = 0.04, η_p^2 = 0.13; post-hoc tests for the repetition effects in SZ: p = 0.19 and p = 0.96 for the right and left hemispheres, respectively).

3.3.2. Repetition probability modulations

The observed RS depended on the P(rep) (block x trial interaction: F(1,30) = 17.87, p = 0.002, η_p^2 = 0.37), as - in RepB - the signal was lower for RepT than for AltT (Fig. 4; Fisher's post-hoc test: p = 0.0002), but not when they were rare (AltB; p = 0.08). The RS effects were also present in patients within the OFA (non-significant interaction of group x block x trial: F(1,30) = 0.16, p = 0.69, η_p^2 = 0.005).

The analysis of the RSI also showed larger RS for RepB than for AltB (F(1,30) = 17.87, p = 0.0002, η_p^2 = 0.37); without a significant main effect of group (F(1,30) = 2.05, p = 0.16, η_p^2 = 0.06) or an interaction between block type and group (F(1,30) = 0.16, p = 0.69, η_p^2 = 0. 005).

3.4. Lateral occipital cortex (LO)

3.4.1. Response magnitude and repetition suppression

In patients, the response magnitude in LO was very low and significantly different from that of HC (Fig. 5; main effect of group: F(1,30) = 4.57, p = 0.04, η_p^2 = 0.13). The response was also larger over the right compared to the left LO (main effect of hemisphere: F(1,30) = 4.41, p = 0.04, η_p^2 = 0.13).

Both groups exhibited RSs in the LO as well (main effect of trial: F(1,30) = =5.03, p = 0.03, η_p^2 = 0.14; non-significant interaction of group x trial: F(1,30) = 0.87, p = 0.35, η_p^2 = 0.03).

3.4.2. Repetition probability modulations

The observed RS was dependent on P(rep) in LO as well (Fig. 5; block x trial interaction: F(1,30) = 20.2, p = 0.03, η_p^2 = 0.14), and this effect was also due to the lower responses for RepT compared to AltT in the RepB (Fisher's post-hoc test: p = 0.0008) but not the AltB blocks (p = 0.08). The RS effects were also present in SZ patients in the LO (group x block x trial: F(1,30) = 1.85, p = 0.18, η_p^2 = 0.03).

The RSI was larger for RepB compared to AltB (F(1,30) = 20.20, p = 0.0009, η_p^2 = 0.40); without a main effect of group (F(1,30) = 0.87, p = 0.36, η_p^2 = 0.03) or an interaction between block type and group (F(1,30) = 1.85, p = 0.18, η_p^2 = 0.05).

3.5. Whole-brain analyses

Additional whole brain analyses are provided in the supplement

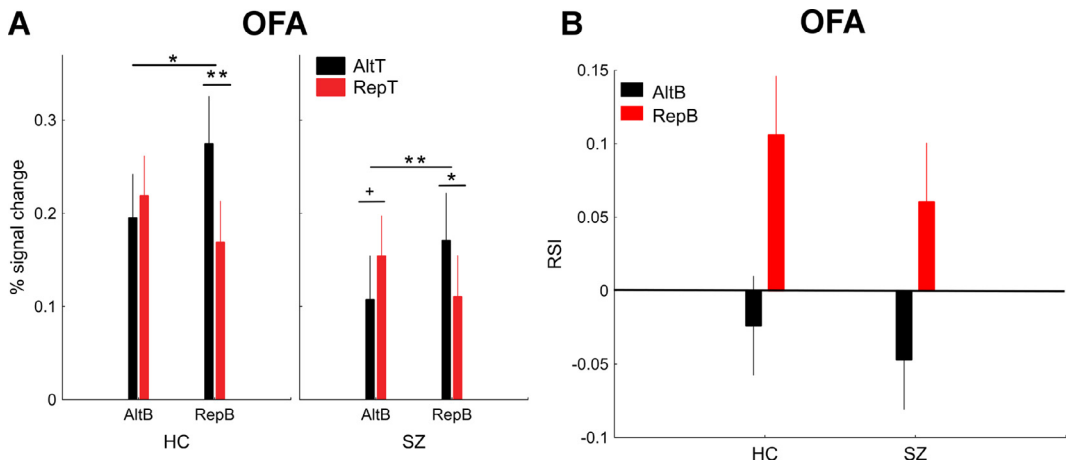

Fig. 4. Results of the whole-brain analysis showing significant activations for the trial and block interaction, signaling P(rep) modulations of RS for HC and SZ participants separately ($p < 0.0001_{uncorrected}$ with a cluster extend of >40 voxels).

section (Fig. 6).

4. Discussion

4.1. Signal magnitude and repetition suppression in SZ patients

To date, there are few fMRI studies testing the effect of stimulus repetition in schizophrenia (SZ). Bleich-Cohen et al. (2009) measured RS within the fusiform gyrus for normal and transfigured faces. They found that controls and SZ patients show similar RS to normal faces, while only SZ patients show RS for transfigured/bizarre faces. More recently, Williams et al. (2013) presented alternating or repeated faces to HC and SZ patients. They found similar response magnitudes and fMRIa in FFA for repeated faces in both groups. Altogether, these results suggest unaffected processing of neutral faces in the fusiform gyrus in schizophrenia (Yoon 2006).

We are not aware of any fMRI study measuring fMRIa in OFA or LO in SZ. The somewhat (OFA) or strongly (LO) reduced BOLD signal is in accordance with those studies that indicate altered processing in LO in schizophrenia (Green et al., 2009; Harvey et al., 2011; Wynn et al., 2008). We did, however, observe significant RS in LO, suggesting normal sensitivity for repetitions. As it was not the aim of the current study to study object processing, more detailed future studies are required to reveal the relationship of reduced LO signal and various aspects of impaired object perception in SZ.

4.2. Repetition probability effects

To our best knowledge, this is the first fMRI study testing stimulus probability effects in SZ patients. Prior studies found a strong modulation of the RS by P(rep) for faces in the occipito-temporal areas of healthy participants (Grotheer et al., 2014; Kovacs et al., 2012; Larsson and Smith, 2012; Summerfield et al., 2008). The magnitude of RS was usually larger in blocks with high compared to low P(rep), and the enhanced RS was interpreted as the reduced ε created through the better fit of bottom-up and top-down information.

Therefore, our results suggest that error detection as well as the estimation of ε are normal in the occipito-temporal cortex of SZ patients. An important aspect of this result is that the correct estimation of ε requires intact top-down connections (Rao and Ballard, 1999). Consequently, our results suggest that connections between occipito-temporal and higher-level areas convey information about ε normally in SZ. Where do the top-down predictions originate? Prior studies related the ε processing to the prefrontal cortex (Fletcher et al., 2001). The disruption of its top-down connection, however, has been suggested to explain positive symptoms of SZ (Fletcher and Frith, 2009). Therefore, it is also possible that the P(rep) modulation effect is not entirely based on these connections in SZ. It is possible that more posterior areas are involved in the estimation of ε. Indeed, Williams et al. (2013) found neither signal enhancement to randomly appearing different faces nor suppression to repeated faces in the hippocampus of SZ. These results

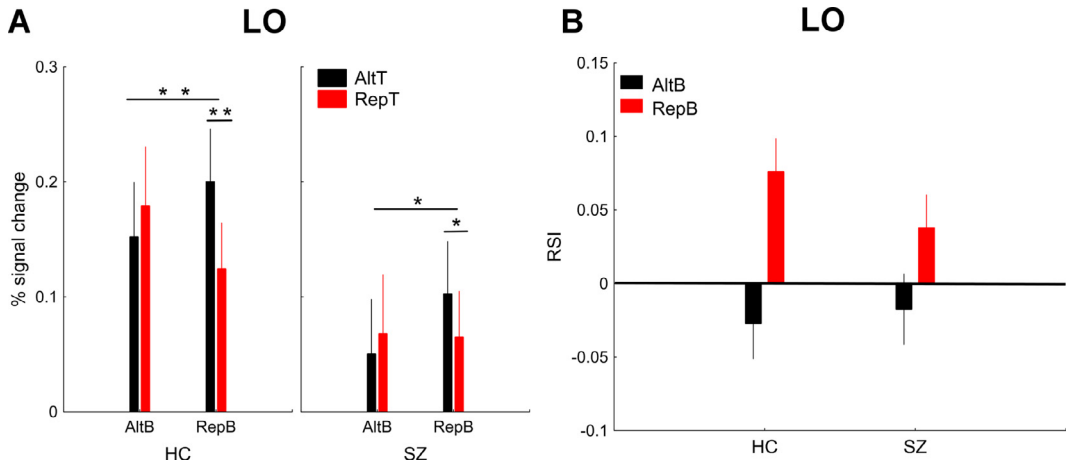

Fig. 5. A. Average peak activation profiles (± SE) of the LO for AltTs and RepTs separately for each block and for the HC and SZ participants, but averaged across hemispheres. *p < 0.05, **p < 0.01 (Fisher's post hoc comparisons). B. The Repetition Suppression Index (RSI, see Methods) of the LO for the Alternation (AltB) and Repetition (RepB) Blocks separately for the HC and SZ participants.

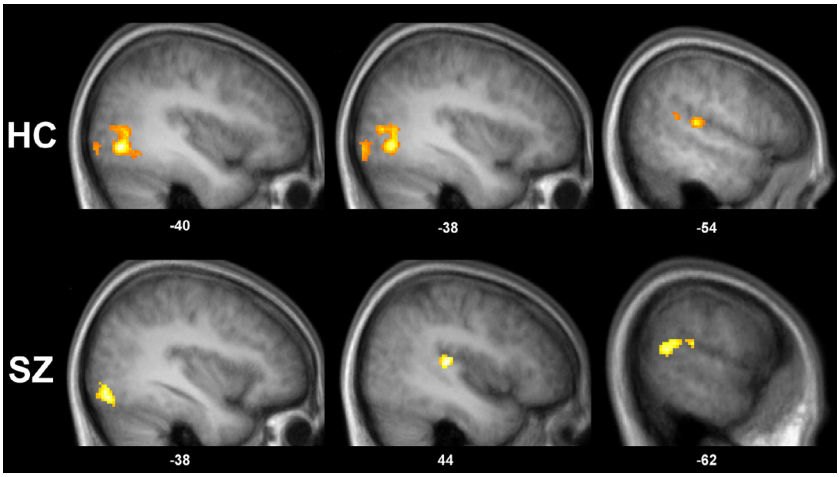

Fig. 6. Results of the whole-brain analysis showing significant activations for the interaction of trial and block for HC and SZ participants separately ($p < 0.0001_{uncorrected}$ with a cluster extend of >40 voxels).

were interpreted as evidence of impaired familiarity/novelty detection in SZ. This study, however, used blocks of identical or different faces; thus, manipulating the probability of identical/different stimuli. In contrast, in the current study, trial-unique stimulus pairs were used, and P(rep) (but not stimulus probability) was manipulated. Therefore, the role of the hippocampus in determining the top-down signals will require further functional connectivity studies.

4.3. Schizophrenia as an impairment of predictive functions

Predictive coding deficits have been associated with SZ in the past. The defective processing of salience and reward value in SZ have been associated by Murray et al. (2008) with PC deficits. Corlett et al. (2007) used fMRI and an associative learning task and connected frontal activations with disrupted ε processing and with positive symptoms of SZ. Blakemore et al. (2000) and Horga et al. (2014) associated hallucinations or self-monitoring with PC. In a similar line of experiments, Voss et al. (2010) related the altered awareness of one's own actions to deficits in predicting action outcomes, while Shergill et al. (2005) linked the impaired sensory attenuation of self-produced stimulation in SZ and concluded that this is due to the dysfunctions of predictions. Lalanne et al. (2012), using a simultaneity-judgement task, found impaired anticipation of upcoming events in SZ. Fogelson et al. (2014) recently found altered top-down connectivity between occipito-temporal areas and attenuated differential responses to predictable/unpredictable stimuli in SZ. In light of these findings, our current study suggests that long-range top-down connections (e.g., those being associated with predictive processes between occipito-temporal and frontal areas; Summerfield et al., 2006) and more local backward connections (e.g., those found to be impaired in SZ between inferior-temporal cortex, V5 and V1; Fogelson et al., 2014) are affected differently by SZ. Finally, neural network simulations indicate that under-connected networks show similar aberrant ε signals to those found in SZ patients (Adams et al. 2013; Yamashita and Tani, 2012). The question regarding the specificities of the cortical networks, their being responsible for carrying intact top-down predictions and whether these are impaired in patients of SZ will have to involve further specific functional connectivity studies.

Several mismatch-negativity (MMN) studies have also connected SZ to failure of predictive processes (Javitt and Freedman, 2015). It has been widely replicated that MMN amplitude is reduced in SZ (Umbricht and Krljes, 2005). MMN is frequently considered a signal of ε (Garrido et al., 2009; Stefanics et al., 2014; Winkler and Czigler, 2012), and its reduction in SZ is interpreted as deficient predictive processing (Baldeweg and Hirsch, 2015; Csukly et al. 2013; Ford and Mathalon, 2012; Friston, 2012; Lakatos et al. 2013; Neuhaus et al.2013; Todd et al. 2012). Furthermore, both SZ (Fletcher and Frith, 2009) and MMN (Deouell et al. 2007; Wacongne et al., 2011) are related to fronto-cortical functions. It is noteworthy, however, that the typical oddball-paradigms of MMN studies and the current P(rep) paradigm differ in several aspects. For example, while oddball paradigms present infrequent stimuli in a continuous stream of stimulation, the current P(rep) paradigm presents pairs of stimuli and modulates P(rep) in short blocks; thus, making comparison of the two paradigms difficult. It is worth mentioning that recent modelling studies have further elaborated on the idea of MMN reflecting Bayesian perceptual learning of sensory regularities and model updating (Lieder et al., 2013), and - at least in an earlier time-window - for the somatosensory modality Bayesian surprise (Ostwald et al., 2012). Such modelling studies, performed on the electrophysiological and neuroimaging correlates of P(rep) modulation of the signal, will be necessary to establish, if similar or different mechanisms underlie these findings as well.

Nonetheless, it is surprising that the current study found a significant P(rep) modulation of RS in SZ; suggesting normal ε estimation. How can these conflicting results be explained? One difference is the applied method: It is possible that the superior temporal resolution of MMN studies reveals mechanisms that are averaged-out in neuroimaging experiments. Indeed, recent results suggest that - while RS effects occur early (40–60 ms for acoustic stimuli) - the effect of expectation only manifests itself later, at around 100–200 ms post stimulus-nset (Todorovic and de Lange, 2012). This is unlikely, however, as (1) neuroimaging studies with oddball paradigms found differences between standard and deviant acoustic stimuli similar to electrophysiological tests (Zevin and McCandliss, 2005), (2) studies using electrophysiological/magnetoencephalographic versions of the current paradigm for visual (Summerfield et al. 2011) or acoustic stimuli (Todorovic et al. 2011) found P(rep) modulations of RS as well and (3) repetition- and expectation-related response suppression has recently been separated, using fMRI (Grotheer and Kovacs, 2015).

Another possibility is that oddball and P(rep) paradigms measure different aspects of stimulus encoding processes. One difference can be the different weight of response reduction for repeated and the enhanced response for unexpected stimuli in determining the net results. On the one hand, a recent study applied oddball paradigms and tested single-cell activity within the inferior temporal cortex of the macaque brain (Kaliukhovich and Vogels, 2014). The authors found larger responses for deviant than for standard responses. But the deviant responses were similar in oddball and equiprobable sequences, suggesting that response suppression for the standard responses - without surprise-related enhancement for deviant responses - is able to explain the

differential responses. Therefore oddball paradigms might dominantly reflect response reduction during repetitions. On the other hand, it has recently been suggested that P(rep) modulations of RS reflect both greater expectation-related suppression and the increased response for unexpected stimuli (Kovács and Vogels, 2014). Therefore, it is possible that a reduced response suppression is responsible for the impaired MMN amplitudes, while normal surprise-related activity-boosts explain the intact P(rep) effects in SZ patients. The inclusion of neutral conditions in MMN and P(rep) paradigms and applying them within the same groups of controls and schizophrenia subjects will be required to test this hypothesis.

Finally, our results also suggest that in the ventral visual unlike in the auditory system (summary in: Todd et al., 2014), somatosensory (Shergill et al., 2013) and dorsal visual systems (Javitt and Freedman, 2015), perceptual inferences are relatively unimpaired in SZ. Indeed, the previously found normal RS in the FFA (Williams et al., 2013) would support this conclusion.

5. Limitations

One limitation of the study lies in the heterogeneity of schizophrenia and the respective relatively small sample size. Recent and similar imaging studies in SZ, however, commonly feature sample sizes ranging from 10 to 25 patients. Thus, the investigated (and compared to carefully matched controls) sample of 17 within the study at hand is not unusual. Also, it is worth noting that the obtained results are rather uniform, as can be seen in the individual data in Fig. 3. The duration of illness in our SZ sample is also comparable to—albeit somewhat shorter as—prior studies (Williams et al., 2013). Furthermore, the previously described subgroups of SZ, identified by concurrent cognitive neuropsychiatric mapping (Szendi et al., 2010), might also be essential in establishing how and when predictive mechanisms are impaired in SZ. Complex future studies with multiple paradigms and methods are required to answer the question, if these different subgroups, having different associative cortical volume deficits (Szendi et al., 2017), differ in the estimation and application of perceptual inferences. Also, it might be important to address effects of acute psychosis (as opposed to stable residual illness) either through correlation in larger patient samples or longitudinal studies, which are more difficult to carry out.

6. Conclusion

In conclusion, the presented data show that P(rep) affects repetition suppression in schizophrenia patients. This suggests that neural mechanisms determining perceptual inferences based on stimulus probabilities remain unimpaired in schizophrenia.

Declaration of Competing Interest

The authors declare no competing financial interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:.

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