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Spectral EEG abnormalities during vibrotactile encoding and quantitative working memory processing in schizophrenia

Simon Ludwig[a,b,*], Bernhard Spitzer[a], Arthur M. Jacobs[c], Maria Sekutowicz[d], Philipp Sterzer[d,e], Felix Blankenburg[a,b,e]

[a] Neurocomputation and Neuroimaging Unit, Freie Universität Berlin, Germany
[b] Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Germany
[c] Department of Experimental and Neurocognitive Psychology, Freie Universität Berlin, Germany
[d] Klinik für Psychiatrie und Psychotherapie, Charité - Universitätsmedizin Berlin, Germany
[e] Bernstein Center for Computational Neuroscience, Berlin, Germany

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ABSTRACT

Schizophrenia is associated with a number of cognitive impairments such as deficient sensory encoding or working memory processing. However, it is largely unclear how dysfunctions on these various levels of cortical processing contribute to alterations of stimulus-specific information representation. To test this, we used a well-established sequential frequency comparison paradigm, in which sensory encoding of vibrotactile stimuli can be assessed via frequency-specific steady-state evoked potentials (SSEPs) over primary somatosensory cortex (S1). Further, we investigated the maintenance of frequency information in working memory (WM) in terms of parametric power modulations of induced beta-band EEG oscillations. In the present study schizophrenic patients showed significantly less pronounced SSEPs during vibrotactile stimulation than healthy controls. In particular, inter-trial phase coherence was reduced. While maintaining vibrotactile frequencies in WM, patients showed a significantly weaker prefrontal beta-power modulation compared to healthy controls. Crucially, patients exhibited no general disturbances in attention, as inferred from a behavioral test and from alpha-band event-related synchronization. Together, our results provide novel evidence that patients with schizophrenia show altered neural correlates of stimulus-specific sensory encoding and WM maintenance, suggesting an early somatosensory impairment as well as alterations in the formation of abstract representations of task-relevant stimulus information.

1. Introduction

Schizophrenia is a psychiatric disorder associated with a number of positive and negative symptoms. One core negative symptom is cognitive impairment, which may affect various levels of cognitive processing. On the lowest level, this can manifest in early sensory deficits. For example, patients diagnosed with schizophrenia show impairments in object- or visuospatial discrimination (O'Donnell et al., 1996; Tek et al., 2002), motion- (Chen et al., 1999) or form perception (Brenner et al., 2003), visual context processing (Seymour et al., 2013; Tibber et al., 2013; Yang et al., 2013), as well as slowed visual encoding (Hartman et al., 2003; see also Javitt, 2009). These early sensory deficits have been substantiated by reports of lowered amplitudes in steady-state evoked potentials (SSEPs, i.e., rapidly repeating stimuli such as visual flicker, auditory click trains or tactile flutter evoke a frequency-specific neural entrainment in early sensory cortices; e.g., Regan, 1966; Mäkelä and Hari, 1987; Kelly et al., 1997) or differences in inter-trial coherence (ITC, i.e., a measure of phase-locking of a particular frequency over trials; e.g. Makeig et al., 2004) using electroencephalography (EEG). In patients with schizophrenia, SSEPs (Kwon et al., 1999) as well as ITC (Light et al., 2006) were significantly reduced in response to auditory click trains or visual flicker (Krishnan et al., 2005; for a review see Brenner et al., 2009) as compared to healthy controls. (See Table 1.)

Beyond early sensory deficits, cognitive impairments in schizophrenia also include higher-level processes such as working memory (WM) (Goldman-Rakic, 1994; Silver et al., 2003; for a meta-analysis see Lee and Park, 2005). WM subserves the short-term maintenance of internal and external action-related information (Baddeley, 1992). While some behavioral and neurophysiological studies suggest that such higher-level impairments are possibly caused by aforementioned sensory dysfunctions (Tek et al., 2002; Hartman et al., 2003; Haenschel et al., 2007), other studies have provided evidence that beyond early sensory impairments, schizophrenic patients also show deficits in WM processing per

* Corresponding author at: Freie Universität Berlin, FB Erziehungswissenschaften und Psychologie, Habelschwerdter Allee 45, Raum JK 25/212, 14195 Berlin, Germany.
E-mail address: simon.ludwig@fu-berlin.de (S. Ludwig).

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se (e.g., Tek et al., 2002; Haenschel et al., 2007; Haenschel and Linden, 2011). Together, these studies imply that schizophrenia is associated with a symptomatology of altered WM-related cognitive processing as a result of cortical hypo- and hyperactivity (Haenschel et al., 2009) as well as disturbed occipital to frontal (Bittner et al., 2015) and frontal to parietal connectivity (Deserno et al., 2012). However, from these studies it remains largely unclear how stimulus-specific information is perturbed during sensory encoding and WM maintenance in patients with schizophrenia.

Sensory encoding and WM maintenance of such intrinsic stimulus features (e.g. the frequency of a vibration on the skin) have been studied in a vibrotactile sequential frequency comparison (SFC) task in non-human primates (Romo et al., 1999; Romo and Salinas, 2003) and in humans (Spitzer et al., 2010; Spitzer and Blankenburg, 2011, 2012). During the SFC task, the frequency of a first stimulus (f1) has to be encoded and maintained in WM during the retention interval until it is compared to the frequency of a second stimulus (f2) in order to decide whether the f2-frequency was higher or lower than the f1-frequency. Romo et al. (1999) recorded single cell activity from neurons in primary somatosensory (S1) and prefrontal cortices (PFC) of monkeys performing this task. S1 neurons showed periodic spike trains in synchrony with the vibrotactile stimulation, as well as parametrically increasing firing rates with higher stimulus frequencies. In the retention interval, the firing rate of PFC neurons parametrically in- or decreased as a function of the f1-frequency maintained in WM. Spitzer et al. (2010) transferred this paradigm to humans by investigating evoked (i.e. phase-locked) and induced (i.e. ongoing or non-phase-locked) oscillatory power evolutions in the EEG signal during a similar vibrotactile frequency comparison task. The authors observed SSEPs over S1 during stimulation. In the retention interval, in contrast, induced beta-power (20–25 Hz) over right frontal electrodes was parametrically increased as a function of f1-frequency. Additional studies showed that, beyond encoding vibrotactile stimulus frequencies, this prefrontal power modulation during WM maintenance can be generalized to other sensory modalities (vision and audition; Spitzer and Blankenburg, 2012) and other quantitative stimulus properties (intensity and duration; Spitzer et al., 2014) and therefore might indicate a prefrontal correlate of abstract (i.e. unspecific with regard to the stimulus feature or modality) quantity information in human WM (Spitzer et al., 2014).

Studying vibrotactile frequency processing in patients with schizophrenia may generalize and complement previous findings in at least two ways. First, tactile vibrations can be regarded as a somatosensory equivalent to visual flicker or auditory click trains, which were previously used to assess deficits in early sensory encoding in schizophrenia (Krishnan et al., 2005; Kwon et al., 1999; Light et al., 2006; for review see Brenner et al., 2009). Thus far, there have been no studies in schizophrenic patients investigating analogous neural responses to vibrotactile stimuli across multiple frequencies (cf. Teale et al., 2013). Second, it was previously shown that patients with schizophrenia show deficits in deducing abstract stimulus categories from visual stimuli (Glahn et al., 2000). However, the neural processing of such abstract stimulus features (e.g. stimulus frequency; cf. Spitzer et al., 2010, 2014) in WM has not yet been studied in patients.

In the present study, patients with schizophrenia and healthy control subjects performed a vibrotactile SFC task while EEG was recorded. Somatosensory SSEPs and ITC were measured during the presentation of the stimuli as a proxy for tactile sensory encoding. On the basis of previous studies, we hypothesized that patients with schizophrenia would show reduced SSEPs and ITC. Furthermore, the power of induced beta-band oscillations was analyzed in the retention interval (during maintenance of the first stimulus). We hypothesized that if patients suffer from impairments in WM maintenance, they should show a relatively weaker parametric modulation of prefrontal beta-oscillations. Lastly, we analyzed the power evolution of overall induced alpha-activity as an indicator for the extent to which subjects attend to the task (Haegens et al., 2010; Spitzer and Blankenburg, 2012).

2. Materials and methods

2.1. Participants

Twelve patients diagnosed with schizophrenia (11 male, 25–37 years old, mean $age_{patients} = 31$) and nine healthy control subjects (mean $age_{controls} = 32$) matched in age, gender, and level of formal education took part in the study (for participant details, see Table 1). Three patients were excluded from the analysis, two due to poor task performance (<50% correct responses), and one because of insufficient EEG signal quality. Informed consent was obtained from every participant prior to the experiment and the study was approved by the local ethics committee at the Charité University Hospital, Berlin.

Patients with paranoid schizophrenia (ICD10: F20.0; World Health Organization) were recruited at the outpatient clinic of the Psychiatry Department of the Charité University Hospital, Berlin. The *Positive and Negative Syndrome Scale* (PANSS) (Kay et al., 1987) was used to assess the patients' current clinical symptoms. Patients with acute psychosis or any signs of an upcoming psychotic episode were not included in the study. At the time of the study, all but one patient were on stable doses of atypical antipsychotic medication (Olanzapine, 3; Risperidone, 1; Aripiprazole, 1; Amisulpride, 2; Quetiapine, 2). One patient also received a selective serotonin reuptake inhibitor and Methimazole, another patient received Pregabalin.

Healthy control subjects were recruited via online advertisements and telephone interviews. Exclusion criteria for control participants were any previous diagnosis of a psychiatric disorder or any psychopharmacological medication. Exclusion criteria in both groups were neurological disorders and drug abuse up to seven days before testing.

2.2. Task and procedure

Prior to the main experiment, subjects performed a standard computerized n-back task (Kirchner, 1958) in order to assess each participant's performance in a traditional WM task. The task included two conditions, the '0-back' and the '2-back' condition. In both conditions, a stream of serially presented numbers with an inter-stimulus interval of 900 ms was displayed in the center of the screen. In the '0-back' condition subjects were asked to only identify the target number '0'. In the '2-back' condition, targets were defined as those numbers that had appeared already two numbers earlier in the stream. Subjects

Table 1
Sample characteristics. Subject, group (SCZ: patients with schizophrenia; HC: healthy control subjects), Gender (m: male; f: female), education (HSD: high school diploma; CVT: completed vocational training; TD: technical diploma; GQUE: general qualification for university entrance; BA: Bachelor of Arts), PANSS (Pos: positive symptom scale; Neg: negative symptom scale; GPS: general psychopathology scale).

Subject	Group	Age	Gender	Education	PANSS		
					Pos	Neg	GPS
1	SCZ	26	m	HSD	12	9	16
2	SCZ	30	m	CVT	21	14	34
3	SCZ	29	m	HSD	7	9	16
5	SCZ	29	m	HSD	14	8	22
6	SCZ	25	m	HSD	14	7	18
9	SCZ	36	m	GQUE	–	–	–
10	SCZ	37	m	TD	7	7	16
11	SCZ	33	m	HSD	7	19	18
12	SCZ	30	m	GQUE	17	15	25
13	HC	32	m	CVT			
14	HC	38	m	TD			
15	HC	35	m	HSD			
16	HC	25	m	HSD			
17	HC	28	m	BA	–		
18	HC	32	m	HSD			
19	HC	28	m	HSD			
20	HC	37	m	TD			
21	HC	31	m	GQUE			

responded by pressing the 'space' bar of a computer keyboard. Each run contained six targets. Participants completed three runs per condition.

Subsequently, subjects performed the SFC task during EEG recording. Vibrotactile stimuli were presented at the left index finger using a 16-dot piezoelectric Braille display (4 × 4 quadratic matrix; 2.5 mm spacing) controlled by a programmable stimulator (Piezostimulator; Quaerosys). The stimulus set for the first vibrotactile frequency (f1) contained six different frequencies in the flutter range (i.e., 16, 19, 22, 25, 28, and 31 Hz); the second frequency (f2) was always 3 Hz higher or lower than f1. The driving signals of the stimuli were generated by fixed sinusoidal amplitude modulation of a constant carrier frequency of 133 Hz in order to reduce EEG artifacts in the frequency spectrum of interest. Importantly, subjects perceive the trial-specific modulating frequency which corresponds to the envelope curve of the stimulus function (Tobimatsu et al., 1999). The sound of the braille display was masked by white noise (~90 dB), which was constantly presented through loudspeakers during the whole experiment.

After a variable inter-stimulus interval (1500–2000 ms) the first vibrotactile stimulus (base frequency, f1, 500 ms) was presented. Following a 3000 ms retention interval, the second stimulus (comparison frequency, f2, 500 ms) was applied. Subjects were asked to respond within 2000 ms after f2 offset whether the second stimulus had a lower or higher frequency compared to the first one. Participants pressed the 'space' bar once for "f1 > f2" or twice for "f2 > f1" (cf. Spitzer et al., 2010). Visual feedback in the form of '+' symbols for correct responses or '−' symbols for incorrect responses was displayed left and right of the fixation cross. To avoid eye movement artifacts in the EEG, participants were asked to fixate a black cross presented in the center of the screen during the entire duration of the trial. In each experimental block, each of the twelve possible stimulus pairs occurred six times in total and in a random order. Overall, there were six blocks, resulting in a total number of 12 (stimulus pairs) × 6 (repetitions per block) × 6 (blocks) = 432 trials. The whole session including EEG preparation lasted for 2.5 h. After the experiment, participants' general ability to attend to a task was assessed using the '*d2 test of attention*' (Brickenkamp, 1962; for validity measures see Bates and Lemay, 2004).

2.3. EEG recording

EEG was recorded using a 64-channel active electrode system (ActiveTwo; BioSemi) with electrodes placed according to the extended 10–20 system. Four additional electrodes were used to record blinks and eye movements. Single electrode locations were registered using a stereotactic electrode positioning system (Zebris Medical).

2.4. Behavioral analysis

Performance in the n-back task was assessed using sensitivity measure *d-prime* (Swets, 1964). In the d2 test we computed the GZ-f value, a measure of overall performance, representing the total number of treated items corrected for number of mistakes.

Behavioral group differences in the n-back and the d2 task were tested for significance using two-tailed two sample *t*-tests for independent measures. To test for group differences and a potential frequency-specific effect on performance accuracy or reaction times in the SFC-task we computed, for each dependent variable, a two-factorial (2 [groups, between subject factor] × 6 [frequencies, within subject factor]) ANOVA. As an additional behavioral measure we computed the performance accuracy across ratios of stimulus frequency-difference to the frequency of f1 (i.e., [f2 − f1] / f1). This ratio represents a corrected estimate of the stimulus frequency difference with respect to Weber's law (Fechner, 1966), which would predict an increasing discrimination difficulty with increasing stimulus frequency.

2.5. EEG analysis

EEG analyses were performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/) and custom MATLAB code (The MathWorks).

2.5.1. Preprocessing

Preprocessing included co-registration of the channels to the individual electrode positions, rejection of noisy channels, average referencing, adaptive spatial filtering to correct for eye-blink artifacts, as well as high- (0.5 Hz) and low-pass (45 Hz) filtering. The continuous recordings were segmented into epochs from 1000 ms before f1-onset to 1000 ms after f2-offset. Epochs with amplitudes greater than 80 mV were rejected. Remaining artifacts were excluded after careful visual inspection.

2.5.2. Steady-state evoked potentials (SSEPs)

For evoked responses, epochs were averaged for each f1 condition. These data were transformed into the time–frequency domain using Morlet wavelet-transformation (seven cycles, 5–45 Hz). Baseline correction of the time–frequency data was done with respect to a 500 ms pre-stimulus interval (−600 ms to −100 ms). For SSEP analysis, we extracted for each subject the narrowband power in the frequency of stimulation for each f1 and the same f2 conditions. We averaged these signals over all f1 and f2 conditions, respectively.

2.5.3. Inter-trial coherence (ITC)

To analyze the coherence of the EEG signal phase in the stimulation frequency over trials (phase locking), we again used a Morlet wavelet-transformation (seven cycles, 5–45 Hz) but applied it on every single trial epoch. We calculated the circular average of the phases for each f1 and corresponding f2 conditions, respectively. For each condition we extracted the ITC at the frequency of stimulation and averaged those values over conditions to get a grand mean estimate for each subject.

2.5.4. Parametric induced responses

To examine induced, i.e. non-phase locked responses, the mean event-related potential (ERP) associated with each condition was subtracted from every trial before Morlet wavelet-transformation was performed on a single trials basis. Changes in spectral power in certain frequency bands are reported as event-related (de)synchronization (ERD/ERS; Pfurtscheller and Aranibar, 1977). Thus, values are in percentage signal change compared to a pre-stimulus baseline (−600 ms to −100 ms). To reduce inter-trial variability, time frequency data were convolved using a 3 (Hz) × 500 (ms) Gaussian smoothing kernel (Kilner et al., 2005). The single trial power spectra were then averaged for each f1 frequency. For parametric effects of the stimulus frequency (f1) on the induced beta-power during the maintenance period, we first computed the average ERS for every f1 over the whole retention interval. We fitted a linear trend for the power of the ERS over the six f1 conditions using a least-squares algorithm. Slopes of the linear regression line were used as a measure of the strength of the parametric effect.

2.5.5. Overall induced responses

Overall changes in the induced spectral power were computed by averaging the time frequency data across all conditions. In particular, as described above, we focused on potential changes in the alpha-band (8–12 Hz).

2.5.6. Statistical analysis

First, electrodes that showed SSEP signals ($p < 0.05$, uncorrected) for both, patients and controls, were identified. Group differences for the SSEP and ITC were then calculated by the average of this subset of electrodes (i.e., Fz, F2, F4, FC2, FC4, C6, CP6, P2, P4 and P6). For SSEPs, two-sample *t*-tests for independent measures were performed for every

time point during f1 and f2. For statistical analysis of ITC values, we used the Wilcoxon rank sum test to account for non-normal distributed data. For overall induced alpha-power we identified electrodes which showed an ERS in patients as well as in controls (Pz and POz). To test for group differences, we computed two-sample *t*-tests for independent measures for every time point of the whole trial. Based on previous work, statistical tests for a parametric effect was performed for a priori selected electrodes (i.e., F2, FC2, F4 and FC4) and frequencies of interest (i.e., beta-band: 20–25 Hz; Spitzer et al., 2010). To test if parametric effects in induced beta-band responses were significantly different from zero, we computed a one-sample *t*-test over the individual slopes for each of the a priori selected electrodes and each group. Group differences in the parametric modulation of prefrontal beta-power in each electrode of interest were then compared using two-sample *t*-tests for independent measures. All of the above *t*-tests were one-tailed given the strong a priori hypotheses that controls show higher values for measures of SSEPs, ITC as well as the parametric beta-modulation compared to patients. To correct for multiple comparisons for each of the above analyses, the respective p-values were adjusted by false discovery rate (FDR) correction (Benjamini and Hochberg, 1995). Given the small sample size of this study and to increase the interpretability of the data, we determined effect sizes and conducted formal power analyses (G*Power; Faul et al., 2007) for the central statistical tests within our study. Hence, we can estimate the probability to which our observations describe true positive effects.

To test for the impact of SSEPs and the parametric modulation on behavioral performance we additionally analyzed both of these measures for incorrect trials. Within-group comparisons of correct vs. incorrect trials were computed by two-sample *t*-tests for dependent measures.

2.5.7. Source reconstruction

For supplementary source modeling, we used the source reconstruction techniques as implemented in SPM8 (Friston et al., 2006). A forward model was constructed for each participant using a template cortical mesh of 8196 points, incorporating the participant's individual electrode positions. The lead field of this forward model was computed using the three-shell BEM EEG head model (Phillips et al., 2007). Before model inversion, the data were band-pass filtered in the respective frequency band of interest. Using multiple sparse priors (Friston et al., 2008) the locations of condition-specific sources were estimated under group constraints (Litvak and Friston, 2008). 3D images were computed for each subject to summarize oscillatory source power for a given frequency at a given time. On the group level effects were estimated in a flexible factorial design.

3. Results

3.1. Behavioral results

3.1.1. N-back

For the group statistics of the n-back task one of the control subjects was excluded because of an extreme response strategy producing an immense false alarm (FA) — rate of 22.22% ($mean_{FA}$ = 5.24%; 95% CI_{FA} [2.78, 7.69]). Control subjects performed the task with an average sensitivity of $d' = 2.41$ (standard error of the mean (SEM) = 0.33) and patients with a sensitivity of $d' = 2.34$ (SEM = 0.12). These values were statistically indistinguishable ($t(15) = -0.29$, n.s.).

3.1.2. d2 test of attention

In the d2 test control subjects performed with an average GZ-f value of mean = 454 (SEM = 39.3). This value did not differ significantly from the average performance (m = 443; SEM = 20.3) of patients with schizophrenia ($t(16) = 0.25$, n.s.).

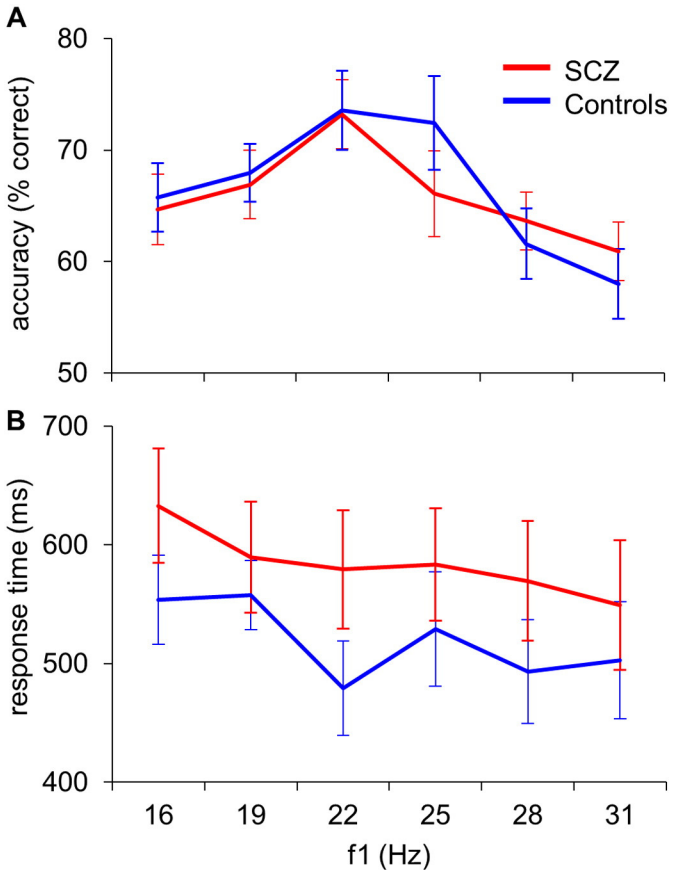

Fig. 1. Performance measures in the sequential frequency comparison (SFC) task. Subjects had to indicate whether the second stimulus (f2) had a higher or a lower frequency compared to the first stimulus (f1). The stimulus set consisted of six frequencies for f1. F2 was 3 Hz higher or lower compared to f1. Average accuracies (A) and response times (B) of healthy controls (blue) and patients with schizophrenia (Scz, red) sorted by f1-frequency. Error bars indicate standard errors of the mean. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.1.3. Vibrotactile SFC task

Fig. 1 shows the accuracies and response times for individual f1 frequencies for both groups. On average, control subjects responded correctly in 66.55% (SEM = 7) and patients with schizophrenia in 65.9% (SEM = 8) of the trials. This difference was not significant ($F(1, 16) = 0.33$, n.s.). The ANOVA revealed only a significant main effect for the within-subject factor *f1 frequency* ($F(5, 80) = 10.08$, $p < 0.01$). On average, subjects tend to perform better at medium f1 frequencies (22 and 25 Hz). For higher and lower f1 frequencies performance levels decreased in both groups. Control subjects responded on average 536 ms, (SEM = 49 ms) and patients 584 ms (SEM = 42 ms) after the offset of f2. In the response time analysis, only the main effect of f1-frequency was significant ($F(5, 80) = 3.49$, $p < 0.01$). Patients did not respond significantly slower than controls ($F(1, 16) = 0.12$), but on average, subjects tended to respond faster for higher f1 frequencies. The interaction *group × f1 frequency* was not statistically significant ($F(5, 80) = 0.8$, n.s.). Response accuracy tended to decrease with decreasing f2–f1 to f1 ratio in healthy controls (slope = 0.65) as well as in patients (slope = 0.34). However, a linear trend analysis revealed no significant effect for neither group ($p_{controls} = 0.15$; $p_{patients} = 0.42$).

Performance in the n-back task and performance in the vibrotactile FC task were significantly positively correlated, $r = 0.87$ ($p < 0.01$) for healthy controls, and positively but insignificantly correlated, $r = 0.4$ ($p = 0.4$) for patients. Patients' measures of negative symptoms

surveyed with the PANSS showed no significant correlation with task performances (all $p > 0.3$).

3.2. EEG results

3.2.1. SSEPs

Fig. 2 B shows average f1- and f2-SSEPs for patients and control subjects, respectively. Frequency-following steady-state evoked responses were prominent in both groups and were source-localized to the right primary somatosensory cortex S1 (Fig. 2 D, source cluster includes Brodmann areas 3a, 3b, 1 and 2 both in patients and control subjects, illustrated at a level of $p < 0.05$ FWE-corrected for multiple comparisons). For f1-SSEPs control subjects showed a significantly higher ($p < 0.05$, $d = 1.14$; one-tailed; FDR-corrected) change in evoked power between 88 and 283 ms after f1-stimulus onset. For f2-SSEPs control subjects showed a significantly higher ($p < 0.05$, $d = 1.27$; one-tailed, FDR-corrected) change in evoked power between 104 and 201 ms after f2-stimulus onset.

3.2.2. ITC

Average f1- and f2-ITCs are shown in Fig. 2 C for patients and control subjects, respectively. For f1 there was a trend for higher ITC values for controls compared to patients ($p = 0.09$, $d = 0.96$; one-tailed; FDR-corrected) from 137–234 ms after f1-stimulus onset. During f2 ITC was significantly higher ($p < 0.05$, $d = 1.42$; one-tailed; FDR-corrected) in controls than in patients from 104 to 201 ms and at 299 ms after f2-stimulus onset.

3.2.3. Parametric induced responses

Parametric modulations of spectral activity during the retention interval are displayed in Fig. 3. Statistical tests of the linear relationship of average induced power changes in the beta-band (20–25 Hz) revealed a significant parametric effect for control subjects ($p < 0.05$; one-tailed; FDR-corrected) in electrodes F4, FC4 and FC2 but not in F2. For patients with schizophrenia there was no significant effect at any electrode. The parametric effects measured by the slopes of the linear fit were significantly different ($p < 0.05$; $d = 1.01$; one-tailed; FDR-corrected) between patients and controls in electrodes F4 and FC4. There was a trend of a difference in FC2 ($p = 0.069$; $d = .85$; one-tailed; FDR-corrected). Importantly, overall baseline beta-band activity was equally variable in patients compared to controls. Thus, unspecific group differences in overall beta-band activity appear unlikely to explain this effect.

3.2.4. Overall induced responses

Time–frequency maps of induced spectral power changes are shown in Fig. 4. To illustrate the most prominent (post-central to occipital) effects, we show time–frequency maps of the EEG signal in electrode Pz. For both groups, a prominent increase in oscillatory power in the alpha-band (8–12 Hz) was observed, starting during f1 stimulation and most pronounced during the retention interval. Source reconstruction analyses yielded the largest source cluster in early visual areas (BA 17, 18) for both groups illustrated at a level of $p < 0.05$ uncorrected. Controls seem to have a slightly steeper increase of alpha-power during the first 500 ms of the retention interval (Fig. 4 B), but all group differences

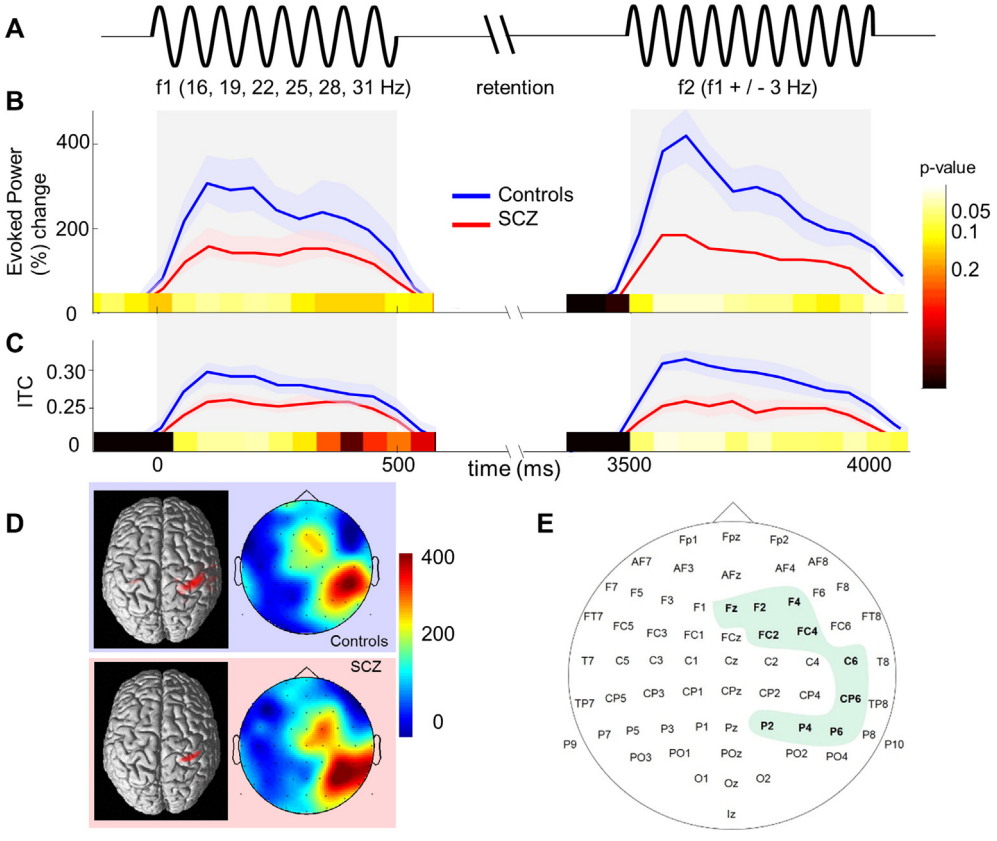

Fig. 2. Trial design, steady-state evoked potentials (SSEP) and inter-trial coherence (ITC). Grey shadings indicate the stimulus presentation time. *A*, Exemplary trial, starting with 500 ms of vibrotactile stimulation (f1) in one of six frequencies (16, 19, 22, 25, 28, and 31 Hz). Followed by a 3 s retention interval, and subsequently a second 500 ms stimulation (f2) 3 Hz higher or lower compared f1. *B*, Left graph: Mean evoked frequency-specific power changes for healthy control subjects (blue) and patients with schizophrenia (red) averaged across all f1 conditions and over representative electrodes (see E). Right graph: same as in the left graph, for the f2 conditions (16, 19, 22, 25, 28, and 31 Hz). *C*, Left graph: mean values of inter trial coherence (ITC) for healthy control subjects (blue) and patients with schizophrenia (SCZ, red) averaged over all f1-frequencies and over representative electrodes (see E). Right graph: same as in the left graph, for f2 conditions (16, 19, 22, 25, 28, and 31 Hz). *D*, Left, SPM source reconstruction and right, scalp topographies of the steady-state response over all f1 conditions. Blue background for healthy controls, red background for patients with schizophrenia. E, Subset of electrodes used for the analysis of SSEPs and ITC (see Section 2). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

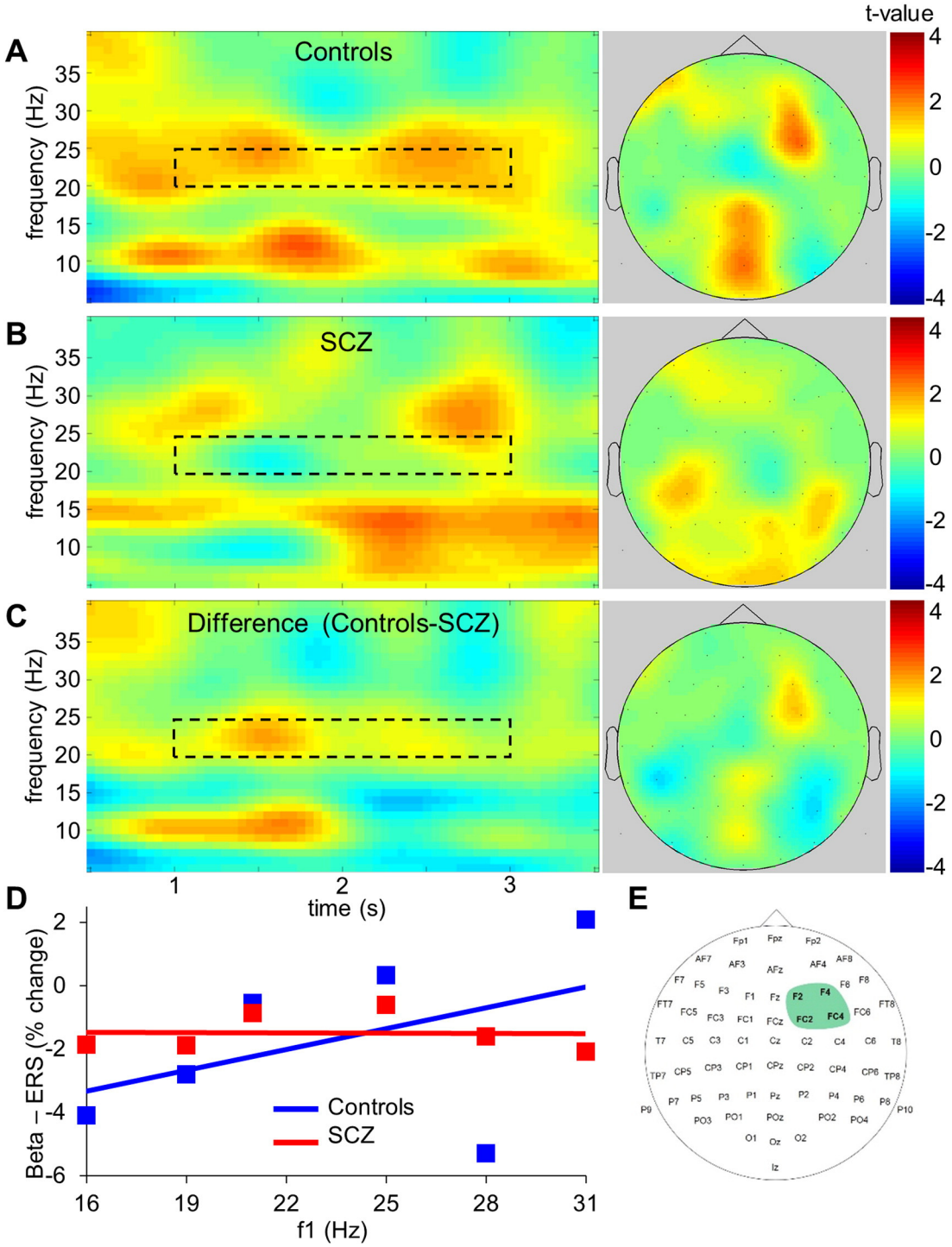

Fig. 3. Parametric modulations of induced power. *A*, Strength of the parametric relationship between induced power and f1 stimulation frequency control subjects averaged over electrodes of interest F2, F4, FC2 and FC4. Right panel: Scalp topographies of the parametric power modulation for time–frequency windows indicated by the dashed rectangle. *B*, Same as *A*, for patients with schizophrenia. *C*, Difference contrast of the parametric effect (Control subjects − patients with schizophrenia). *D*, Induced ERS in the time–frequency window of interest (1000–3000 ms retention interval; 20–25 Hz) for each of the six f1 conditions in both groups. Lines show the linear fit using a least-squares method. *E*, A priori selected set of electrodes for the parametric analysis.

in alpha-power during the whole trial were far from significant (all $p > 0.38$). During f1 presentation, a slight decrease in spectral activity in the beta-band (15–25 Hz) was evident, with a characteristic topographical distribution over bilateral sensorimotor areas. At the end of the trial average power in a broad frequency range (5–30 Hz) decreased, mostly over sensorimotor areas.

3.2.5. Correct vs. incorrect trials

Control subjects' SSEPs showed a significantly higher evoked power in correct trials than in incorrect trials during f1 ($t(8) = 2.74$, $p < 0.05$) and f2 ($t(8) = 4.13$, $p < 0.01$). For patients with schizophrenia this difference was only significant for f1-SSEPs ($t(8) = 2.34$, $p < 0.05$). Mean slopes of the linear fit were significantly different for correct versus

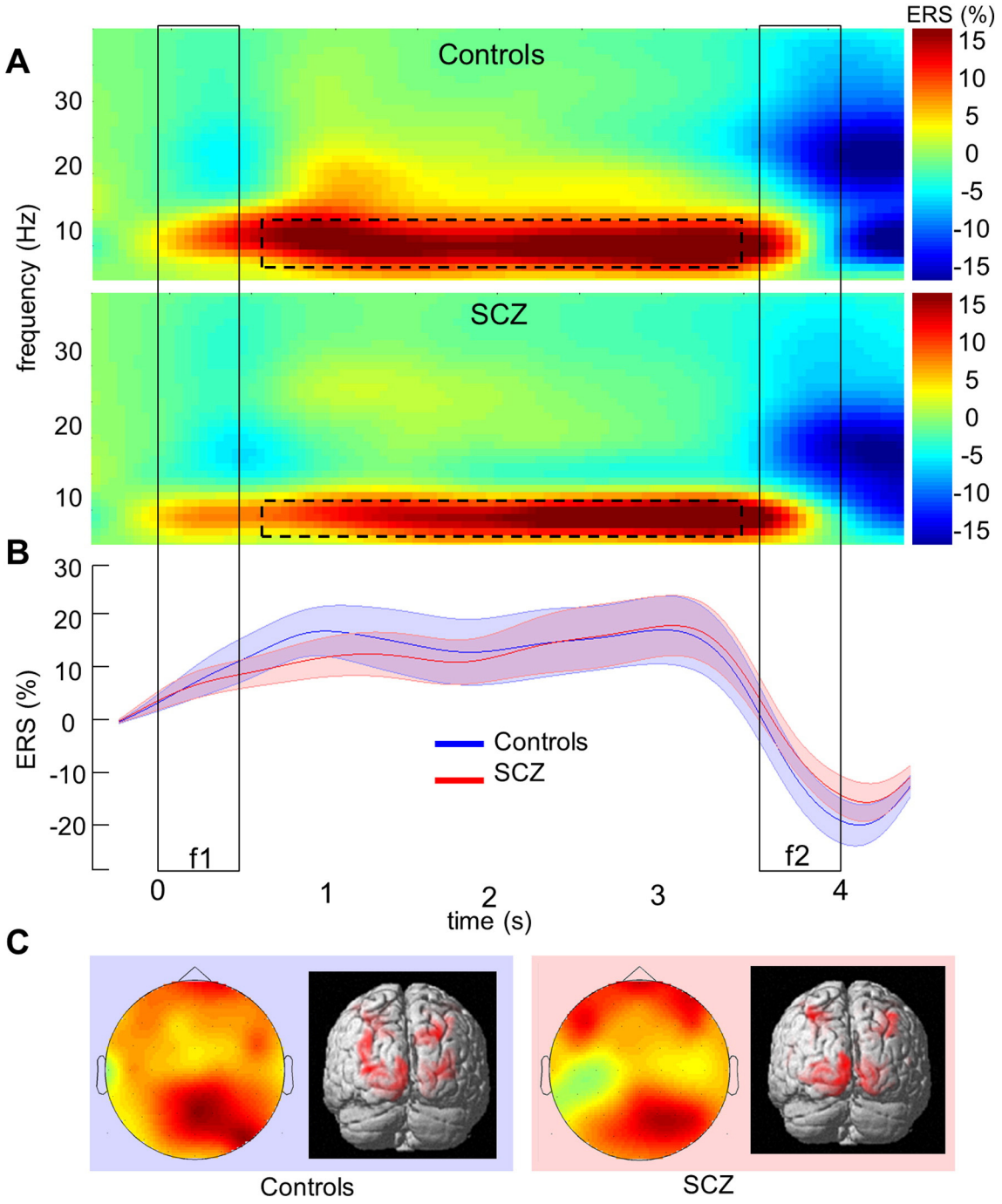

Fig. 4. Overall induced power changes. *A*, Time–frequency plots of induced power changes (ERS) for healthy controls (upper panel) and patients with schizophrenia (lower panel) averaged over all conditions (data from a representative electrode Pz). *B*, Mean alpha-ERS (8–12 Hz) for healthy controls (blue) and patients with schizophrenia (SCZ, red). Colored shadings show the standard error of the mean. *C*, Scalp topography (color scale as in A) plots and SPM source reconstruction of the time–frequency windows delineated in A. Blue background is for healthy controls, red background is for patients with schizophrenia. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

incorrect trials in the control group ($t(8) = 2.36$, $p < 0.05$). No significant difference was observed in patients.

3.3. Correlational results

Across the patient sample, scores from the negative symptom scale of the PANSS correlated negatively with the peak steady-state evoked response ($r = -.81$, $p = 0.018$). There was no significant correlation of the scores in the negative symptom scale and measures of ITC ($r = -0.32$, n.s.). Peak SSEPs showed no significant correlation with behavioral performance either in control subjects ($r = 0.44$, n.s.) or in patients ($r = -.40$, n.s.). In healthy controls the linear trend (slope) of accuracy across ratios of f2–f1 to f1 showed a slightly positive correlation ($r = 0.31$, n.s.) with individual slopes in prefrontal beta-power across f1 frequencies, which was, however, not significant. For patients there was a significant negative correlation between these measures ($r = -.78$; $p = 0.013$).

4. Discussion

We studied patients with schizophrenia and healthy control subjects in a well-established (Romo and Salinas, 2003; Spitzer et al., 2010)

vibrotactile sequential frequency comparison (SFC) task to assess vibrotactile sensory encoding and parametric WM. Somatosensory steady-state evoked potentials (SSEPs) during f1 and f2 as well as inter-trial coherence (ITC) during f2 and by trend during f1, in response to periodic tactile stimuli were significantly reduced in patients. Further, compared to healthy control subjects, patients showed a significantly reduced parametric modulation of prefrontal beta-oscillations by the stimulus frequency. Interestingly, patients with schizophrenia and healthy controls differed neither in behavioral task performance nor in behavioral or electrophysiological measures of attention allocation.

More specifically, we evaluated the primary somatosensory encoding of stimulus frequencies by means of the power of the somatosensory SSEPs and more specifically ITC of these frequencies in the primary somatosensory cortex. We found significantly weaker SSEPs during f1 and f2 presentation as well as a significant reduction of ITC during f2 in patients compared to control subjects. Our results indicate that patients with schizophrenia have an impaired sensory representation of the applied stimuli. This finding is well in line with other behavioral and neurophysiological studies reporting general sensory or perceptual impairments in schizophrenia (Chen et al., 1999; Hartman et al., 2003; Javitt, 2009; Leitman et al., 2010; Seymour et al., 2013; Tek et al., 2002). Additionally, steady-state evoked responses to visual or auditory periodic stimulations were previously studied to examine sensory functioning in patients with schizophrenia. Several studies consistently found reduced SSEPs as well as reduced phase-locking (i.e. ITC) in schizophrenic patients (Krishnan et al., 2005; Kwon et al., 1999; Light et al., 2006; for a review see Brenner et al., 2009). Our study extends these previous results to the tactile domain by reporting similar findings (reduced SSEPs and ITC in schizophrenic patients) with respect to vibrotactile stimulation at multiple frequencies, and thus enriches the existing understanding of impaired neural synchronization in schizophrenia (see also Teale et al., 2013). Currently, alterations in gamma-aminobutyric-acid (GABA) inter-neuronal networks in association with glutamatergic input are discussed as a potential explanation for these impairments in neural entrainment (e.g. Uhlhaas and Singer, 2010). Due to minimal task demands and its replicability across modalities, a reduction of neural responses to periodic stimulations has already been considered as a potential biomarker that might be relevant for diagnosis of this disease in the future (Brenner et al., 2009).

We moreover analyzed the oscillatory correlates of WM content, i.e. of the stimulus frequency, maintained during the retention interval. Healthy control subjects, as expected, showed a significant parametric increase of induced beta-band (20–25 Hz) ERS as a function of f1 stimulus frequency in our a priori selected electrodes (Fig. 3). For patients, in contrast, we found a reduced parametric power modulation by f1 frequency in the same frequency band and electrodes. Monotonic increases in neural firing rates varying with the concurrently maintained frequency of a previously presented stimulus were originally found in monkey PFC (Romo et al., 1999). The authors argued that these neurons encode an analogue measure of a continuous quantity, i.e. in this case the stimulus frequency (high firing rates for high stimulus frequencies and low firing rates for low stimulus frequencies). In humans, by analyzing time–frequency transformed EEG responses, recorded during the same task, an equivalent of this effect was reported in form of a parametric power modulation in the beta-band (Spitzer et al., 2010). This modulation indicated an internal top-down WM updating modulated by the stimulus frequency (Spitzer and Blankenburg, 2011) and has been further generalized to periodic stimuli in the visual and auditory modality (Spitzer and Blankenburg, 2012) as well as to different stimulus features such as intensity and duration of tactile stimuli (Spitzer et al., 2014). Thus, the modulation of prefrontal beta-oscillations is likely to reflect an abstract representation of quantity information about the relevant stimulus attribute (Spitzer et al., 2014). In line with these reports control subjects in the present study showed a significant parametric effect which was significantly reduced in patients. Further, in the control group, but not in patients, the parametric effect was stronger for correct than for incorrect trials. Although this points to the behavioral relevance of the prefrontal beta-modulation by stimulus frequency, patients showed no such parametric effect in the beta-power despite a sustained level of behavioral performance. Together, these findings indicate that parametric beta-modulations can manifest as a result of an abstract quantity representation during WM updating, but might not be essential for solving the task. Our results indicate that patients do not form as strong abstract representations of stimulus information (i.e. less parametric modulation in the beta-band by the stimulus frequency) as healthy controls, but might instead use a different strategy that still allows for a similar level of discrimination accuracy. This appears reasonable in the light of evidence from behavioral studies investigating stimulus feature abstraction (Glahn et al., 2000; Weickert et al., 2014). In these studies, results indicated that patients with schizophrenia show impaired capabilities in inferring a stimulus category on the basis of low-level stimulus features. Interestingly, individual slopes of the linear trend of decreasing accuracy with decreasing Weber-adjusted stimulus differences were negatively correlated with the slopes of prefrontal beta-band modulation in patients. That is, they show a reduced dependency of prefrontal beta-power modulation if they are actually sensitive to changes within the task. As before, this might hint to the conclusion that patients use different strategies in order to solve the task while avoiding higher-level abstract representations of WM content. However, as discussed later, this alternative explanation remains speculative due to the limited sample size of this study. In sum, our results complement former studies with schizophrenic patients which reported, e.g., hyperactivity during WM maintenance as apparent by high power of gamma oscillations in a visual DMTS-task (e.g. Haenschel et al., 2009) as well as other studies showing alterations of neural activity specifically during WM maintenance and mostly in areas within the prefrontal cortex (Cannon et al., 2005; Perlstein et al., 2001; see also Manoach, 2003). Beyond these reports of altered cortical activation, we provide evidence that patients with schizophrenia show reduced sensory encoding of stimulus-specific information as well as altered neural representations of WM content during maintenance.

To interpret our results, however, it is crucial to consider the effect of potential attentional impairments which are prevalent in schizophrenic patients (Heinrichs and Zakzanis, 1998; Nuechterlein et al., 2004). Fundamental attentional deficits in patients could influence the cognitive processes in demand for the present task. However, our different control analyses speak against this objection: First, we consider overall changes in induced oscillatory power (see Fig. 4) which were mainly expressed in a parietal to occipital ERS in the alpha-band (8–12 Hz). Importantly, patients showed similar ERS as control subjects. This increase in alpha activity might be largely explained by a general top-town focus favoring internal over external processing, as potential external input might interfere with ongoing WM processing (Klimesch et al., 2007; Spitzer and Blankenburg, 2012). Moreover, since visual input is irrelevant in this specific vibrotactile task, a modality-specific inhibitory effect of alpha-activity on task-irrelevant brain areas, as here on the visual cortex, might add to this global effect (Haegens et al., 2010; Spitzer and Blankenburg, 2012; Tuladhar et al., 2007; see Klimesch et al., 2007 for a review). In this regard, patients in our study do not seem to display obvious disturbances (see also Gold et al., 2006). Second, Giabbiconi et al. (2004) investigated the effect of attention on the power and on phase-locking of stimulus-following frequencies in the EEG in response to periodic tactile stimuli. Importantly, attended compared to unattended tactile vibrations elicited an increased amplitude of the stimulation frequency in the EEG. In contrast, ITC was not affected by different levels of attention. This is noteworthy, because the power of averaged EEG signals (ERP or SSEP), depends on the amplitude of this specific frequency in the single trial epochs as well as on the amount of phase-locking or inter-trial (phase) coherence of this frequency across trials (Makeig et al., 2004). Thus, SSEP and ITC are by no means independent measures. Rather, ITC represents one factor which

influences the power of an SSEP. Our results indicate a reduction in the power of the overall SSEPs and in particular reduced ITC for patients compared to control subjects. Thus, we assume that patients with schizophrenia indeed show impairments in the neural entrainment of the stimulation frequency beyond potential attentional deficits. Third, both groups did not show significant performance differences in the n-back task or the d2 test of attention. Hence, the reported findings are very likely to reflect differences in the specific neurophysiological basis underlying the considered sensory and cognitive processes, and not mere attentional effects. We are aware of the fact that similar levels in measures of attention in both groups cannot be interpreted as a significant null-effect. However, given that multiple tests and analyses (n-back, d2-test of attention, accuracy in the SFC-task & alpha-activity) show not even trends in differences between groups, major confounding factors like, e.g., differences in the level of attention or impaired task performance are rather unlikely to explain the findings.

Finally, the relatively small sample size should be mentioned as a potential limitation of the present study, which led us to restrict our analysis to a priori specified effects of interest, rather than performing explorative analyses of potential other effects that might have occurred in the patient group only. Further, our observed effects showing significant differences between patients and controls achieve a statistical power between 64 and 90%. These values describe the probability to which our observed test results can be considered true effects. This appears reasonable given that a power of 80% has been suggested as a sensible value in the behavioral sciences (Cohen, 1988). Furthermore, many studies in the neurosciences show a much lower level of statistical power (median = 21%; Button et al., 2013).

To summarize, we studied patients with schizophrenia and healthy control subjects in a WM task, which enables researchers to examine primary somatosensory encoding of vibrotactile stimuli as well as abstract representations of stimulus features during WM maintenance. Our results provide evidence that the neural entrainment of vibrotactile stimuli in primary somatosensory cortex is impaired in schizophrenic patients. Furthermore, neural oscillatory correlates of abstract stimulus information were reduced in patients during WM maintenance. Our study for the first time provides evidence for altered neural responses of stimulus-specific information during sensory encoding as well as WM maintenance, and thus contributes to the overall understanding of altered oscillatory signals in schizophrenia.

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