Concurrent Functional Magnetic Resonance Imaging and Electroencephalography Assessment of Sensory Gating in Schizophrenia

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Abstract: Schizophrenia is frequently accompanied by deficits in basic information processing, such as sensory gating. The sources behind deficient sensory gating in schizophrenia patients are, however, still largely unclear. The aim of the current study was to identify the brain structures involved in deficient sensory gating in schizophrenia patients. Twenty healthy male volunteers and 23 male schizophrenia patients were initially assessed in a somatosensory P50 suppression paradigm using concurrent electroencephalography (EEG)/functional magnetic resonance imaging (fMRI) methodology. The trials consisted of single stimuli or pairs of identical stimuli with either 500 ms or 1,000 ms interstimulus intervals. Not all subjects showed a P50 waveform as a result of the somatosensory stimuli: It was detected in 13 schizophrenia patients and 15 control subjects. Significant P50 suppression was found in the 500 ms trials in controls only. Region of interest analyses were performed for a priori chosen regions. Significant negative correlations between P50 ratios and the BOLD response were found bilaterally in the hippocampus, thalamus, anterior and posterior superior temporal gyrus (STG), and in the left inferior frontal gyrus pars opercularis. However, significant group differences were found in the hippocampus and the thalamus only. This is the first study in which P50 suppression was assessed in schizophrenia patients with concurrent fMRI/EEG methodology. The data support that the STG, thalamus, inferior frontal gyrus, and the hippocampus are involved in P50 suppression.

However, of these structures only the hippocampus and thalamus appeared involved in the altered sensory processing found in schizophrenia. *Hum Brain Mapp 35:3578–3587, 2014.* © 2013 **Wiley Periodicals, Inc.**

Key words: P50 suppression; fMRI; EEG; sensory gating; concurrent assessment; schizophrenia

INTRODUCTION

The central nervous system constantly receives information about the environment through our senses. The majority of these environmental stimuli never reach consciousness as a result of subconscious processes filtering out irrelevant stimuli. Only relevant information is permitted to pass for further, conscious, processing. The process of subconscious filtering of sensory information is generally called sensory gating. Patients with schizophrenia appear to have disturbed sensory gating (Adler et al., 1982; Bramon et al., 2004; Patterson et al., 2008), which may cause an overload of sensory information reaching cortical areas and theoretically could ultimately lead to formation of psychotic symptoms (Braff and Geyer, 1990; McGhie and Chapman, 1961; Patterson et al., 2008; Venables, 1964).

One way of assessing sensory gating is with a P50 suppression paradigm. In a typical P50 paradigm two identical stimuli (termed S1 and S2 or "conditioning" and "testing" stimulus) are presented with a 500 ms interstimulus interval (ISI) and with an intertrial interval (ITI) of 10 s. Each of these two stimuli generates an event-related brain potential that is assessed with electroencephalography (EEG). In healthy subjects, the P50 amplitude after presentation of S2 is generally reduced compared to the amplitude elicited by S1. Disturbances in sensory gating are thought to be endophenotypic markers of schizophrenia (Braff, 1993; Bredgaard and Glenthoj, 2000). More insight in the brain areas that are involved in (modulation of) sensory gating would greatly enhance our understanding of the disease mechanisms in schizophrenia.

A variety of techniques have been used in previous studies attempting to identify the sources that are involved in sensory gating. The approaches range from inferring the sources based on the neurotransmitters or circuits that seem to be involved (Adler et al., 1998; Carlsson and Carlsson, 1990) to EEG source localization, both from the scalp (Knott et al., 2009; Oranje et al., 2006) and intracranial (e.g., Boutros et al., 2005; Grunwald et al., 2003), MEG source localization (e.g., Reite et al., 1988; Thoma et al., 2003), and functional magnetic resonance imaging (fMRI; Mathiak et al., 2011; Mayer et al., 2009, 2012; Tregellas et al., 2007). Over time, several brain areas have been suggested to be involved in P50 suppression: e.g., the hippocampus (Adler et al., 1992, 1998; Boutros et al., 2005; Grunwald et al., 2003), thalamus (Carlsson, 1988; Carlsson and Carlsson, 1990), superior temporal gyrus (STG; Knott et al., 2009; Korzyukov et al., 2007; Oranje et al., 2006; Reite et al., 1988; Thoma et al., 2003),

both the medial frontal (Jensen et al., 2008; Korzyukov et al., 2007; Oranje et al., 2006; Weisser et al., 2001) and dorsolateral prefrontal cortex (DLPFC; Grunwald et al., 2003; Knight et al., 1989), and the insula (Knott et al., 2009; Mayer et al., 2009) In a study combining these findings Williams et al. (2011) used the STG, the hippocampus, DLPFC, and the thalamus as seed regions in a P50 source localization study. They found a correlation between the hippocampus dipole moment ratio and P50 gating in healthy controls. In schizophrenic patients; however, they found a correlation between the DLPFC dipole moment ratio and P50 gating.

fMRI studies have confirmed the involvement of several of the aforementioned brain regions in P50 gating. Results from Mayer et al. (2009) pointed toward involvement of the prefrontal cortex, thalamus, auditory cortices and the insula in auditory sensory gating. In 2012, the same group investigated schizophrenia patients, where they found significant group differences in their single tone conditions (STG, insula, and ventrolateral prefrontal cortex), but where no statistically significant group differences were found in their paired tones analyses (Mayer et al., 2012). In another study (Tregellas et al., 2007), associations were found between P50 gating and the hippocampus, DLPFC and the thalamus. However, in that study a deviant paradigm was used, in which a train of stimuli was used instead of the classical paired trial. Finally, one study using fMRI (Mathiak et al., 2011) used auditory stimuli and found reduced suppression in auditory cortices and reduced suppression of alpha power in patients. They also found a correlation between the N100m component and the BOLD response in auditory cortices, but no correlation with P50m component. A limitation in all of the above mentioned fMRI studies were that none of them assessed EEG (or MEG) concurrently with fMRI. In a recent study from our laboratory using a somatosensory P50 suppression paradigm with concurrent EEG and fMRI assessment (Bak et al., 2011), we showed that P50 suppression could be reliably assessed inside the MRI scanner. The data pointed toward an involvement of the hippocampus and claustrum in P50 suppression whilst the medial frontal gyrus, and the insula appeared to mediate the P50 amplitude. The aim of the current study was to investigate which brain areas are responsible for the deficient P50 gating as usually found in schizophrenic patients.

MATERIALS AND METHODS

Subjects

The study was approved by the Committee for Biomedical Research Ethics, Copenhagen, with regard to the

ethical principles for medical research involving human subjects as stated in the declaration of Helsinki (amendment of Washington 2002). Written and oral information was given, after which written informed consent was obtained from all subjects.

Twenty-three male patients with schizophrenia were recruited either by advertisement in the community mental health center, or were referred to us by their practitioner. The patients were treated with a variety of antipsychotics: 1 with typical antipsychotics, 3 with clozapine, 11 with other atypicals, and 2 with a combination of a typical and an atypical antipsychotic, whereas 6 were medication free (defined as having received no antipsychotics in the last 3 months preceding the investigation). The average age for the patients was 36.4 [standard deviation (SD): 9.6, range: 21–49], and 12 were smokers ranging from 8 to 25 cigarettes a day. Patients had an average total PANSS score of 71 (SD: 20), and were therefore moderately ill. All patients were interviewed with the Schedule for Clinical Assessment in Neuropsychiatry, version 2.1 (SCAN, Wing et al., 1990) in order to confirm their diagnosis. Substance dependence [as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria] was an exclusion criterion. Datasets from three patients were incomplete so these were excluded from the analyses. This resulted in fMRI data from 20 patients. Of the remaining 20 schizophrenia patients, 7 showed no P50 waveform to the somatosensory stimuli such that the resulting dataset consisted of 13 patients [mean age: 37.7 (SD: 8.5) with an average total PANSS score of 67 (SD: 21)] that were included in the EEG analyses.

Twenty healthy male subjects were recruited through an advertisement on the internet. The subjects' average age was 25.4 years (SD: 4.4, range: 18–35), four were smokers, ranging from 5 to 15 cigarettes per day. All were physically healthy, not abusing alcohol or drugs and did not have a personal history of psychiatric illness, which was confirmed by means of a SCAN interview (Wing et al., 1990). Neither did the healthy subjects have a first-degree relative with a DSM-IV diagnose of psychiatric illness. Furthermore, none of the controls had ever received psychopharmacological medication, nor had they participated in any neurophysiological experiment before. In the fMRI data, three subjects were excluded due to artifacts resulting from excessive movement, resulting in fMRI data from 17 subjects. In the EEG data, five subjects showed no P50 waveform to the somatosensory stimuli. This resulted in 15 subjects (mean age: 25.9, SD: 5.0) with P50 data. Data on the 20 healthy controls has been reported previously in (Bak et al., 2011).

Experimental Design

On a test-day, a sample of the subjects' urine was screened for use of cannabis, cocaine, opiates, and amphetamines (Syva® RapidTest d.a.u® 4). To minimize the effect of caffeine and nicotine, the subjects were asked to abstain from drinking coffee on the test day, and from smoking an hour before testing started. All subjects were instructed to lie still in the scanner, keep their eyes gently closed, and were requested to stay awake. The paradigm was presented by a computer running E-Prime software (v1.1 SP3, Psychology Software Tools, Pittsburgh). The electrical stimuli were presented using Keypoint equipment (v3.25, Medtronic).

P50 Suppression Paradigm

The design of the paradigm has been described in detail before (Bak et al., 2011). Besides a rest condition, three different trial types were used in the paradigm, all using somatosensory stimulation of the left median nerve with identical intensity: (1) a single stimulus with 10 s ITI, (2) two stimuli with 500 ms ISI and 10.5 s ITI, and (3) two stimuli with 1,000 ms ISI and 10 s ITI. The paradigm consisted of six blocks, each consisting of four subblocks with either rest or three trials of one trial type (single, 500 ms or 1,000 ms). The subblocks were presented randomly in each block. The paradigm was run three times, 13 min each, resulting in a total of 54 trials of each type.

The intensity of the somatosensory stimuli was set to 80% of the electric current that was needed to activate the subject's thenar reflex. The intensity of the stimulus was such that it was noticed by the subject, but was not painful. All subjects reported that this was the case. This intensity criterion was also used for six patients of whom it was not possible to elicit the thenar reflex. The intensities in the current study ranged from 2 to 8.4 mA, with an average of 4.9 mA (SD: 1.6) in healthy subjects and an average of 4.9 mA (SD: 1.5) in patients.

EEG Acquisition

EEG was recorded inside the scanner, i.e., concurrent and continuous with the fMRI assessments. Recordings were assessed from 30 scalp sites arranged according to the 10–20 system with a reference located between Fz and Cz and a ground electrode placed at the inion, with sintered Ag/AgCl ring electrodes (EasyCap, Herrsching-Breitbrunn, Germany). The impedance cutoff on Cz was set to 10 kΩ. Two additional electrodes were placed, one on the left mastoid, and one on the left midclavicular line near the fourth intercostal space for ECG recording. EEG was recorded with BrainAmp MR (Brainproducts, Munich, Germany) with a 5,000 Hz sampling rate. The amplifier was synchronized with the scanner clock frequency. Trigger signals from the stimulation computer and the scanner were recorded simultaneously with EEG. During the functional MRI the ECG and the respiratory rate were recorded with the scanner vector cardiogram recorder and a pneumatic thoracic belt, respectively.

P50 Assessment

EEG data was processed with Brain Vision Analyzer (Brainproducts, Munich, Germany) and Matlab (MathWorks, MA) software. Gradient artifacts were corrected by means

of an averaged template subtraction method (Allen et al., 2000). The data were then downsampled to 500 Hz and filtered with a low pass filter set at 70 Hz. Pulse artifact correction was performed semiautomatically, starting with identification of R-peak markers from the scanner vector cardiogram log file (Mullinger et al., 2008). For six subjects, where no vector cardiogram log file was present, Brain Vision Analyzer's intrinsic algorithm was used to locate the R-peaks. Next, the R-peaks were inspected manually and corrected by hand if necessary. The R-peak markers were then used for the Brain Vision Analyzer algorithm as described by Allen et al. (1998) to remove the cardiobalistic artifacts. No removal of eye-blink artifacts was necessary since the subjects had their eyes closed. Data were then epoched between 100 ms prestimulus and 400 ms poststimulus. A combined average of the subjects' response to S1 from the paired trials and the single trials, as well as an average of the responses to each S2 were calculated. P50 amplitude was scored from the electrode of which the maximum amplitude was expected, i.e., electrode Cz (Clementz et al., 1997), with average reference. P50 amplitude was defined as the largest trough to peak amplitude within an interval of 35–75 ms after stimulus onset (Arnfred et al., 2001a, 2001b; Bak et al., 2011). In seven patients and five controls, no peak was observed within our time window of the response to S1. For these subjects no P50 ratio could be determined. The amplitude of S2 was scored as the largest trough to peak amplitude within an interval of ±10 ms of the latency of the maximum P50 amplitude found in S1. To improve reliability, the P50 amplitude was rated in consensus by two researchers. The level of P50 suppression was expressed as the ratio S2/S1; however, in agreement with other studies, ratios greater than 2 were truncated to 2 to avoid the effect of extreme outliers (e.g., Griffith and Freedman, 1995; Nagamoto et al., 1991).

MRI Acquisition

Functional and structural MRI was performed with a Philips Achieva 3.0T whole body MRI scanner (Philips Healthcare, Best, The Netherlands) using an eight-channel sense headcoil (Invivo, Orlando). A structural MRI was made for co-registration of the functional data: 3D T1-weighted TFE with 170 sagittal slices. Repetition time (TR) = 9.8 ms, echo time (TE) = 4.6 ms, flip angle 8°, field of view (FOV) 256 mm × 256 mm, matrix size 240 mm × 200 mm, inplane resolution 1.1 mm × 1.3 mm, slice thickness 1.0 mm. Subsequently, the fMRI was performed: T2*-weighted EPI with 32 slices positioned parallel to the calcarine sulcus. TR = 3,000 ms, TE = 35 ms, flip angle 90°, FOV 230 mm × 230 mm, in plane resolution 2.9 mm × 2.9 mm, slice thickness 4.0 mm, inter slice gap 0.1 mm. For each run 252 volumes were acquired.

fMRI Processing

Statistical analysis was carried out using FSL 4.1 software (Center for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, UK; www.fmrib.ox.ac.uk/fsl). Within FSL, Brain Extraction Tool was applied to all data. Additionally, slice timing correction, Gaussian spatial smoothing with full width at half maximum at 5 mm and high-pass temporal filtering was performed. Each individual functional scan was registered to its high-resolution anatomical scan and transformed to MNI space using MCFLIRT (fMRI linear Image Registration Tool). At first level each scan from the 37 subjects was then analyzed with FEAT within FSL. FEAT uses a general linear model approach. The three types of trials (single stimulus, paired stimuli with 500 ms ISI and paired stimuli with 1,000 ms ISI) of the randomized stimulation paradigm were used as predictors. Motion parameters were added as predictors of no interest in the design matrix. At second level, the contrasts of parameter estimates (COPEs) were determined by analyzing, for each subject, the three runs together. Four second level COPEs were generated at this level: single, 500 ms, 1,000 ms, and 1,000–500 ms. Group statistics were then performed at third level resulting in three contrasts (one for each group and one for group differences) for each of the conditions: single, 500 ms, and 1,000 ms. An additional contrast, 1,000–500 ms was created to evaluate the difference between the two paired trials.

Statistics

A repeated measures analysis of variance (ANOVA) with within subject factor "stimulus amplitude" (S1, S2 from 500 ms trials, or S2 from 1,000 ms trials) and between subject factor "group" (control or patient) was performed on the P50 amplitude data, with age and smoking as covariates. Another repeated measures analysis of covariance (ANCOVA) was performed with between factor "group" (patient or control) and within factor "ratio" (P50 ratio in 500 ms trials or P50 ratio in 1,000 ms trials).

To test whether P50 suppression actually occurred, we analyzed whether the ratios of the two trial types (500 ms and 1,000 ms ISI) differed from 1 for both patients and controls, with a one-sample t test.

To examine the response in each of the four conditions, four group contrasts were generated: patients alone, controls alone, patients > controls, and patients < controls. The contrasts based on the paired trials for each group was used to confirm that relevant areas were activated in response to somatosensory stimulation and thereby used as a control for the validity of the paradigm All voxelwise results were corrected for false positives at $P < 0.05$ using Gaussian random fields theory as implemented in FSL (www.fmrib.ox.ac.uk/fsl). Additionally, region of interest (ROI) analyses were performed for both left and right side of the following areas: the hippocampus, thalamus, inferior frontal gyrus (pars triangularis and pars opercularis), STG (both anterior and posterior part), and insular cortex, adding up to 14 areas in total. Specifically, ROI's were generated from Harvard-Oxford Cortical structural atlas

TABLE I. Mean values (SD) of P50 amplitudes and ratios specified for both patients and healthy controls

P50 data

Stimulus	Controls, $n = 15$, mean (SD)	Sch patients, $n = 13$, mean (SD)
S1 amplitude	1.097 (0.760)	1.809 (1.056)
S2 500 ms amplitude	0.894 (1.076)	1.231 (1.377)
S2 1,000 ms amplitude	1.333 (1.060)	1.599 (1.438)
Ratio 500 ms	0.597 (0.726)	0.803 (0.813)
Ratio 1,000 ms	1.079 (0.811)	0.961 (0.800)

The amplitude for S1 was calculated by averaging the response to S1 stimuli from both the paired trials and the single trials. The P50 ratio was calculated as S2/S1.

and Harvard-Oxford Subcortical structural atlas that are included in FSL. Data from these ROI's were then extracted with the FSL Featquery tool and exported to SPSS. The relationships between P50 suppression in the 500 ms trials and activation in each ROI were explored with Pearson's correlation coefficients in all four conditions (single, 500 ms, 1,000 ms, and 1,000–500 ms). The correlation analyses were performed using all subjects, regardless of group, since we hypothesized that the same brain areas are involved in both patients and controls; we only expect the groups to differ in the level of activation. Additionally, a 3×2 repeated measures ANOVA with within factor "trial" (single, 500 ms or 1,000 ms) and between factor "group" (patient or control) was performed for each ROI.

RESULTS

EEG Data

The repeated measures ANCOVA on P50 amplitudes (see Fig. S1 in Supporting Information for grand average) revealed neither significant effects of smoking ($P = 0.194$) nor of age ($P = 0.454$). Therefore, these factors were excluded as covariates from further analyses. No main effect of "stimulus amplitude" was found for [$F_{(2,26)} = 0.999$, $P = 0.382$] but patients showed higher P50 amplitudes than controls, which reached trend level of significance [$F_{(1,26)} = 4.188$, $P = 0.051$]. Furthermore, no interaction effect was found [$F_{(2,25)} = 0.323$, $P = 0.727$]. In the repeated measures ANCOVA on P50 ratios, no significant effects of "group" [$F_{(1,26)} = 0.040$, $P = 0.842$], "ratio" [$F_{(1,26)} = 2.540$, $P = 0.123$], or group $\times$ ratio" interaction [$F_{(1,26)} = 0.652$, $P = 0.427$] were found (see Table I for amplitude and ratio data). However, the one-sample t test revealed that only the P50 ratios from the controls in the 500 ms trials differed significantly from 1 ($P = 0.049$), indicating significant P50 suppression. No significant differences were found in the 1,000 ms trials for either controls or patients and neither did the P50 ratio differ from 1 in the 500 ms trials of our patients.

fMRI Data

In the voxelwise approach, the paired trial types with controls alone and patients alone revealed similar activation patterns in areas relevant for somatosensory stimulation, including bilateral secondary somatosensory cortex (SII), insula, and primary somatosensory cortex (SI; see Fig. 1A). Significant hemispheric deactivation was only found in the 500 ms contrast in patients. This cluster was located in the ipsilateral premotor cortex, primary motor cortex and SI (see Fig. 1A, see Fig. S2 in Supporting Information for presentation of all calculated contrasts). Significant group differences were only found in the single trial type in the contralateral inferior parietal lobule and SII where controls showed a higher response than patients (see Fig. 1B).

In the ROI analyses, significant ($P < 0.05$, uncorrected) negative correlations between the P50 ratio and ROI activations in the single trial type were found in the hippocampus (L + R), thalamus (L + R), anterior and posterior STG (L + R), and the inferior frontal gyrus pars opercularis (L; see Fig. 2). Activations in the 500 ms, 1,000 ms and the 1,000–500 ms contrast did not significantly correlate with the P50 ratios. The above mentioned cluster with significant group difference from the voxelwise approach (Fig. 1B) was also tested for association with the P50 ratio post hoc with the same procedure, but did not show any significant correlation with P50 ratio.

In the repeated measures ANOVAs, a significant main effect of "trial" was found in the right insula [$F_{(2,35)} = 3.147$, $P = 0.049$]. Furthermore, significant main effects of "group" were found in the left hippocampus [$F_{(1,35)} = 4.232$, $P = 0.047$] and the right STG posterior division; [$F_{(1,35)} = 4.515$, $P = 0.041$], both with higher activation in controls than in patients (see Fig. 3). No interaction effects were found in any of the ROIs. However, based on our amplitude and correlation data, we choose to split on trial type. Significant group differences were found in three areas for the 1,000 ms trial type: the left and right hippocampus ($P = 0.011$ and $P = 0.033$) and the right thalamus ($P = 0.045$). In the 500 ms trial type, a significant group difference was only found in the left hippocampus ($P = 0.039$). In all these cases, controls had significantly higher activation than patients (see Fig. 3).
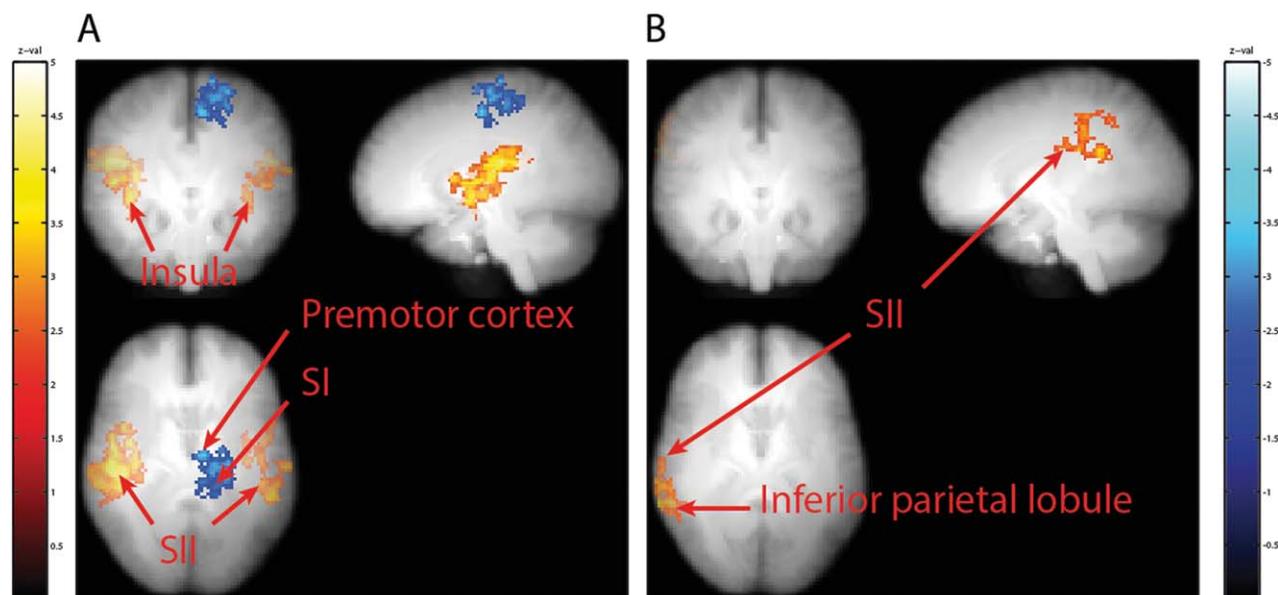
Figure 1.

Whole brain voxelwise analysis. (**A**) Activation in the 500 ms trials in patients. Orange: activation in response to the stimuli, the significant areas include secondary somatosensory cortex (SII) and the insula. Blue: deactivation/inhibition in response to the stimuli, significantly deactivated areas include the premotor cortex, primary motor cortex and primary somatosensory cortex (SI). (**B**) Areas where schizophrenia patients respond significantly different from controls in the single trial type (controls > patients), significant areas include the inferior parietal lobule and SII.

DISCUSSION

To our knowledge, this is the first study in which source localization of deficient P50 suppression was performed in schizophrenia patients with concurrent fMRI and EEG methodology. With this multimodality approach it was possible to confirm in which of our two trial types P50 suppression actually occurred during the fMRI scanning, rather than having to assume it, as was the case in similar previous studies reported in literature. Additionally, we used a typical P50 suppression paradigm (with 500 ms ISI and 10 s ITI), albeit with somatosensory stimulation instead of auditory stimulation, due to the noisy MRI scanner. This enabled easier comparison of our results with the P50 suppression literature as assessed in EEG settings.

As expected, significant P50 suppression was only found in the trials with 500 ms ISI and in control subjects only. The voxelwise whole brain analyses revealed significant activation in areas relevant for somatosensory stimulation during the paired trials regardless of group, yet revealed significant group differences in the single trial type only. In the ROI approach, we found negative correlations between P50 ratio and the activation in the single trials in the hippocampus, thalamus, STG, and in the left frontal gyrus. However, no correlations were found between P50 ratio and the activations in the 500 ms, 1,000 ms, or 1,000–500 conditions. In addition to these correlations, the ROI approach showed significantly lower activation in the right insula in the single trial type compared to the paired trials, regardless of group. Furthermore, patients showed significantly lower activation than controls in the left hippocampus and the right STG, regardless of trial type. Finally, significant group differences in activation were found in the 500 ms (left hippocampus) and in the 1,000 ms (left and right hippocampus, and right thalamus) trial types, where controls activated the areas while patients deactivated (inhibited) them.

In line with a previous study by Mayer et al. (2012) no significant group differences were found in the voxelwise analyses of the paired trials. This absence could be due to the fact that the hemodynamic response is a summation of the entire response to both stimuli in the paired trials: It is unlikely that the summation of these paired stimulus trials will reflect solely the P50 waveform; it will additionally reflect processes that are represented by, for instance, the P200 amplitude, which may be influenced differently than the P50 amplitude by paired stimuli. Alternatively, the group differences could be too small to be detected with a two stimulus approach as suggested by Mayer et al. (2012). The group difference found in the single condition in the somatosensory cortex might be modality specific. It suggests a basic difference in the processing or registration of a single stimulus between patients and controls contralateral inferior parietal lobule and SII.
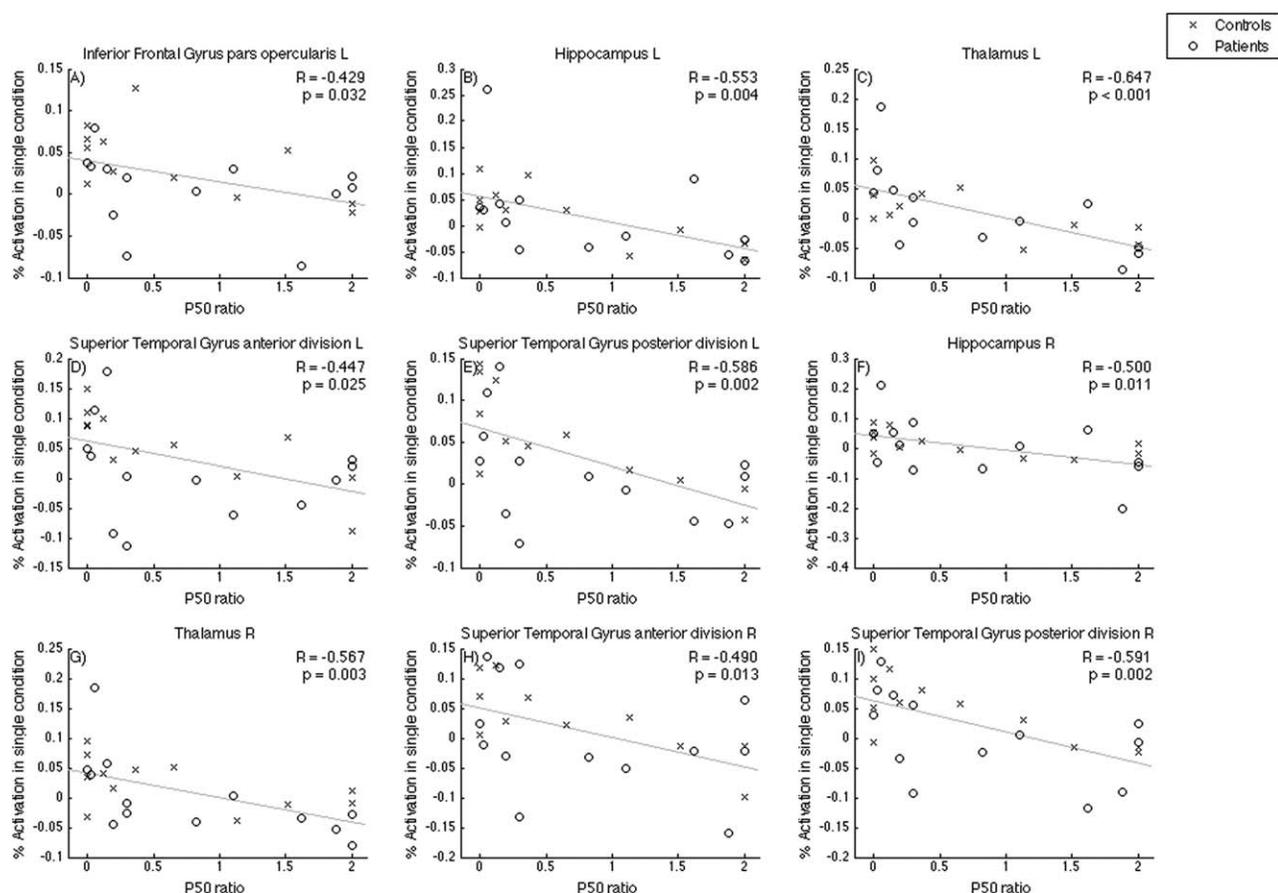
Figure 2.

Graphic representation of correlations between the P50 ratios from the 500 ms trials and the activation in the ROIs. The correlations were made on the total dataset and thus included both patients and controls.

In the ROI analyses, significant correlations between P50 ratios and the activation in the single trial type suggests that the response to the first (conditioning) stimulus (in hippocampus, thalamus, STG, and the left frontal gyrus) determines the P50 amplitude to the second stimulus and thereby the P50 ratio. Areas with a significant positive or negative correlation should, therefore, be involved in generation or regulation of the P50 waveform. Similar to the voxelwise approach, no significant results were found in the paired trial types, probably for comparable reasons as the ones explained above. Our current findings of correlations with P50 ratios in the STG and the left inferior gyrus pars opercularis, supports previous studies in which EEG methodologies were used (Knott et al., 2009; Korzyukov et al., 2007; Reite et al., 1988; Thoma et al., 2003). The indication of hippocampal involvement is in agreement with many P50 suppression studies (Adler et al., 1992, 1998; Adler and Waldo, 1991; Tregellas et al., 2007; Williams et al., 2011), while the involvement of the thalamus also supports previous literature (Carlsson and Carlsson, 1990;

Mayer et al., 2009; Tregellas et al., 2007). A previous fMRI study by Tregellas et al. (2007) found significant positive correlations between P50 ratios and fMRI data in hippocampus and thalamus. This was accompanied by a hyperactivation in patients, which is the opposite of the current data. However, Tregellas et al. (2007) used a rather atypical P50 in which auditory click trains were compared to a single click. In addition, they used clustered MRI acquisition as opposed to continuous acquisition in the current study. Whether the conflicting results between their and our study are due to differences in methodology (i.e., paradigm or modality) or that a paired paradigm triggers other properties of sensory processing than click trains, cannot be determined from the current data.

A main effect of trial in our ROI data, i.e., a difference in activation between the three different trial types, was found in the right insula only. Usually in fMRI BOLD imaging, it is expected that presentation of two stimuli in close proximity of each other results in a doubling of the BOLD response; therefore, we expected to find such an
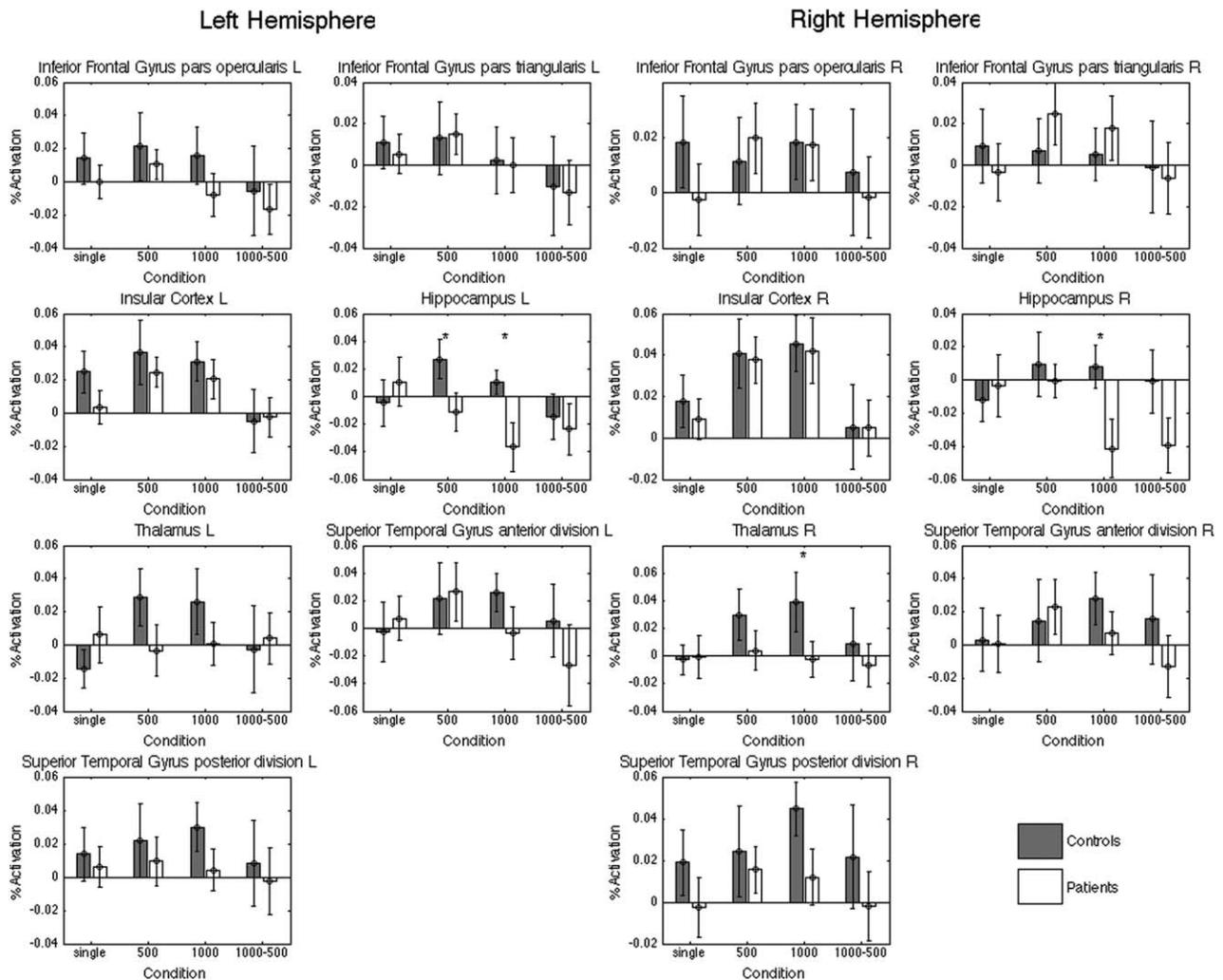
Figure 3.

Mean activations of the ROIs (with SEM, all left side regions are presented to the left). A significant group difference was found in the left and right hippocampus and the right thalamus in the 1,000 ms trials, while in the 500 ms trials a significant group difference was only found in the right hippocampus. *: $P < 0.05$.

effect in all of our ROIs. Our results may, therefore, demonstrate the non linearity of this paradigm and the complex nature of sensory processing.

Significant group differences in activation were found in SI and SII with the voxel wise approach; however, these areas could be modality specific and has not been, to our knowledge, suggested to be involved in P50 suppression before. With the ROI approach, we found significant group differences in activation of the hippocampus and the thalamus in the 500 ms and 1,000 ms trial types. The fact that our data indicated both significant correlations between hippocampal and thalamic activations and the P50 ratios as well as significant group differences in these two structures strengthen the notion that these areas are most

relevant for P50 suppression deficits in schizophrenia patients. These results support many other studies in which these two structures were implicated in P50 suppression in general, and in the deficient gating in schizophrenia patients in specific, like in the many studies supporting hippocampal involvement by Freedman and his group (summarized in Adler et al., 1998) and the theories of the "thalamic filter" by Carlsson et al. (1988).

There are some caveats in our study that should be mentioned. In the EEG dataset, P50 ratios are missing for 12 subjects since they showed no identifiable P50 waveform. In our previous paper (Bak et al., 2011), we found the same in an EEG alone setting, which suggests that somatosensory stimulation is less ideal for assessing P50

gating than auditory stimulation. We reasoned however that the noisy environment of the MRI scanner would make auditory assessment of P50 gating with a traditional paradigm unreliable. Although we, much as expected, found significant P50 suppression in controls in the 500 ms trials only, we did not find a significant group difference in P50 ratio. Our results should therefore be interpreted with the necessary caution, and should be confirmed and extended in a larger subject population.

CONCLUSIONS

Summarized, this is the first source localization study on deficient P50 suppression in patients with schizophrenia, using concurrent EEG and fMRI methodology. The EEG data confirmed that, as expected, the control subjects showed P50 suppression while the schizophrenia patients did not. Our results indicate that sensory gating of somatosensory stimuli involves several brain structures, among which the inferior frontal gyrus, STG, thalamus, and hippocampus. Furthermore, our data indicated that of these structures the hippocampus and thalamus appear to be involved in the altered sensory processing found in schizophrenia.

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