Hyperactivation balances sensory processing deficits during mood induction in schizophrenia

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While impairments in emotion recognition are consistently reported in schizophrenia, there is some debate on the experience of emotion. Only few studies investigated neural correlates of emotional experience in schizophrenia. The present functional magnetic resonance imaging study compared a standard visual mood induction paradigm with an audiovisual method aimed at eliciting emotions more automatically. To investigate the interplay of sensory, cognitive and emotional mechanisms during emotion experience, we examined connectivity patterns between brain areas. Sixteen schizophrenia patients and sixteen healthy subjects participated in two different mood inductions (visual and audiovisual) that were administered for different emotions (happiness, sadness and neutral). Confirming the dissociation of behavioral and neural correlates of emotion experience, patients rated their mood similarly to healthy subjects but showed differences in neural activations. Sensory brain areas were activated less, increased activity emerged in higher cortical areas, particularly during audiovisual stimulation. Connectivity was increased between primary and secondary sensory processing areas in schizophrenia. These findings support the hypothesis of a deficit in filtering and processing sensory information alongside increased higher-order cognitive effort compensating for perception deficits in the affective domain. This may suffice to recover emotion experience in ratings of clinically stable patients but may fail during acute psychosis.

Keywords: schizophrenia; fMRI; emotion; music; mood induction; connectivity

INTRODUCTION

Disturbances in emotional processing are a prominent clinical feature of schizophrenia. On a behavioral level, there is consensus that schizophrenia patients show a reduced ability to recognize facial emotions [see Kohler et al. (2009) for a review]. As a paradox, several studies indicated that the immediate experience of an emotion in response to different stimuli is generally preserved [compare Kring and Moran (2008) for a review]. A recent meta-analysis reported that schizophrenia patients do not differ from healthy subjects in their subjective rating of negative emotion, although they do report more negative experience of positive or neutral stimuli (Cohen et al., 2010). Furthermore, experience sampling studies have documented increased experience of negative emotional states in schizophrenia (Myin-Germeyns et al., 2000).

Even though subjective ratings of emotional experience may not differ between patients and healthy subjects, neural activations may diverge. However, there are only a small number of studies that directly investigated neural correlates of emotional experience in schizophrenia with functional magnetic resonance imaging (fMRI). Some studies reported hypoactivations in the amygdala as well as in areas of visual processing in patients (Schneider et al., 1998); however, the meta-analysis of Taylor et al. (2012) could not confirm differences in amygdala activation between patients and healthy subjects. Activity in the occipital region, in contrast, was shown to be consistently reduced in schizophrenia during tasks reflecting emotional experience.

Mechanisms underlying this dissociation of adequate subjective ratings of mood and altered brain activation are poorly understood. To better understand this dissociation, it is important to examine the way in which mood was elicited in previous studies. The most common paradigm is the presentation of emotional faces. This technique of watching facial emotional expressions is supposed to mainly target ‘a cognitive road to mood’ (Phillips et al., 2003) because subjects reported afterwards that they used cognitive strategies of mood induction such as autobiographical memory recall or the imagination of sad situations. Hypoactivations in the amygdala may have been caused by inhibitory projections of frontal brain areas being implicated in cognitive processing. Baumgartner et al. (2006) and Dyck et al. (2011) compared the neural correlates of visual and audiovisual mood induction procedures in healthy subjects and found increased activation in areas related to emotion processing in the audiovisual as compared to the visual condition. We concluded that the audiovisual induction of mood relies less on cognitive reflection and represents ‘a more automatic road to mood’. To better understand mechanisms contributing to emotion experience in schizophrenia, it may help to compare the widely used visual mood induction and our novel audiovisual mood induction paradigm.

In the current study, we investigated brain activation in schizophrenia patients and healthy subjects by inducing mood with an audiovisual as compared to a visual mood induction while blood oxygen level-dependant (BOLD) imaging was acquired. In accordance with previous studies, we expected successful mood induction in healthy subjects and schizophrenia patients as indicated by similar emotional ratings. In reference to the meta-analysis of Cohen et al. (2010), we hypothesized similar ratings of negative emotional stimuli but more negative experience of positive and neutral stimuli in patients with
schizophrenia. In accordance with the recent meta-analysis of Taylor et al. (2012), we assumed deficits mainly in brain areas of sensory processing (visual and auditory cortices) that may represent deficits in emotion perception and in areas of cognitive processing during both mood inductions that may reflect compensatory processes.

The audiovisual mood induction may elicit emotions more automatically. There are studies indicating differences in conscious and unconscious emotion processing in schizophrenia (Holt et al., 2006; Rauch et al., 2010). In contrast to hypoaivation of the amygdala in response to conscious and controlled processing of emotion, hyper-responsiveness of the amygdala was indicated when emotional faces were processed at an unconscious level. Therefore, we expected increased activation in areas of emotion processing, particularly in the amygdala, during the audiovisual induction in patients with schizophrenia as compared to healthy subjects (Holt et al., 2006; Rauch et al., 2010). To further investigate the interplay of sensory, emotional and cognitively controlled mechanisms during emotion experience, we examined connectivity patterns between brain areas corresponding to sensory, emotional and cognitive processing, respectively. Previous studies observed various patterns of altered connectivity in schizophrenia during emotion processing (Das et al., 2007; Leitman et al., 2008, 2010; Mukherjee et al., 2012). We aimed at investigating functional connectivity from primary to secondary sensory areas as well as from sensory to cognitive and affective areas—as the latter was suggested to be reduced in schizophrenia (Das et al., 2007; Leitman et al., 2008; Mukherjee et al., 2012).

METHODS

Participants

Sixteen patients (10 males, 6 females) with a diagnosis of schizophrenia that were all receiving ambulant treatment at the Department of Psychiatry, Psychotherapy and Psychosomatics of the RWTH Aachen University participated in the study. Sixteen healthy subjects with no prior history of any psychiatric or neurological disorder were recruited in the same clinic and matched to the patient group by gender, age and education. All participants were right-handed as indicated by a minimal score of 6 out of 10 on the Edinburgh Handedness Inventory (Oldfield, 1971). There were no significant differences between groups on these demographic variables (Table 1).

All patients were diagnosed with paranoid schizophrenia by an experienced psychologist according to the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I; Wittchen et al., 1997). Patients did not have any other psychiatric or neurological disorders. All patients were in a stable phase of the disease, which was confirmed by low scores on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and all received second-generation antipsychotic medication with 69.93 ± 28.92% of the daily defined maximal dose (DDD, WHO Collaborating Centre for Drug Statistics Methodology, 2012). Four patients were additionally taking anti-depressive medication (DDD = 100.13 ± 20.41%).

To control for cognitive impairments, all subjects were administered the Multiple-Choice Vocabulary Intelligence Test (Mehrfachwahl-Wortschatz-Intelligenztest) (MWT-B), a German test measuring verbal crystallized intelligence (Merz et al., 1975). All subjects achieved a verbal intelligence quotient (IQ) above 96 and the mean IQ did not differ between the groups.

The study was approved by the Local Ethics Committee and performed according to the Declaration of Helsinki. All participants gave written informed consent after having received a full description of the study and were paid an allowance at the end of their participation.

Table 1 Descriptive information of the sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy controls</th>
<th>SZ patients</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.25 (8.51)</td>
<td>35.94 (8.98)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Own education (years)</td>
<td>14.00 (3.10)</td>
<td>13.00 (3.23)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Parental education (years)</td>
<td>10.56 (4.63)</td>
<td>10.44 (3.44)</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>IQ (MWT-B)</td>
<td>104.69 (42.72)</td>
<td>107.19 (32.65)</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>PANSS positive</td>
<td>10.13 (2.80)</td>
<td>10.13 (2.80)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PANSS negative</td>
<td>12.69 (5.26)</td>
<td>12.69 (5.26)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PANSS psychopathology</td>
<td>25.06 (5.32)</td>
<td>25.06 (5.32)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>DDD for antipsychotic medication (%)</td>
<td>96.93 (28.92)</td>
<td>96.93 (28.92)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>DDD for anti-depressive medication (%)</td>
<td>100.00 (20.41)</td>
<td>100.00 (20.41)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Stimuli

Emotional face stimuli

Seventy-two color photographs of actors expressing happiness, sadness or no emotion were taken from a standardized stimulus set (Gur et al., 2002). All facial stimuli were validated in a prior study to confirm target emotion recognition rates above 80% (Dyck et al., 2008). The faces were balanced for gender and no actor appeared more than once within a session.

Emotional music stimuli

The music stimuli were selected excerpts from classical orchestral pieces and did not contain vocals. Three unique excerpts were chosen for happy and sad emotion and each excerpt was adjusted to a length of 44 s. All stimuli were shown to reliably evoke happiness or sadness in healthy subjects, respectively (Baumgartner et al., 2006; Etzel et al., 2006). Due to technical problems, we collected ratings of the presented music from only 12 of the 16 patients. Ratings showed that patients correctly perceived the core emotion expressed by the music. The music was selected on the criterion that it reliably induced the target emotions; we did not match tempo, mode or pitch. Because the emotional neutrality of musical excerpts is subject dependent (Krumhansl, 1997; Peretz et al., 1998), we elected to present pink noise as the neutral auditory stimulus.

Mood induction procedure

In a blocked fMRI design, happiness, sadness and neutrality were induced using two mood inductions paradigms: (i) visual and (ii) audiovisual. The visual mood induction was carried out with visual stimuli alone. For the audiovisual mood induction, the faces were complemented with classical music. The emotional content of the musical excerpt was always congruent to the emotions expressed by the faces. This task setup resulted in a three (emotions: happiness, sadness or neutrality) by two (modality: visual or audiovisual) design, which was presented in six different mood induction runs. Within each run, one target mood was induced in three alternating blocks of mood induction and resting baseline. For more details of the mood induction procedure see Dyck et al. (2011) (see Figure 1 for an example of experimental setup). Subjects were instructed to watch the stimuli and experience the emotion that was expressed by the faces. After every mood induction block, subjects rated valence and arousal of their emotional experience (‘How do you feel right now? How aroused are you right now?’) on a bipolar non-verbal rating scale, the Self-Assessment Manikin (SAM) ranking from 1 = very negative/weak to 5 = very positive/strong. Bipolar scales may mask the potential coactivation of hedonic and aversive emotions (Cohen and Minor, 2008) and therefore we included a second rating with separate unipolar
assessments at the end of every mood induction (Emotional Self-Rating, ESR, Schneider et al., 1994). Mood ratings of one patient were missing due to technical problems. To wash out the mood induction effect before the subsequent run, a short attention task was completed by the subjects.

fMRI procedures
Earplugs were fitted to dampen scanner noise and subjects’ heads were fixated with a foam-rubber device mounted on the head coil. Visual stimuli were displayed via MRI-compatible video goggles and musical excerpts were presented binaurally through MRI-compatible 30-dB noise attenuation headphones that reduce distracting gradient noise [VisuaStimDigital, Resonance Technology (RT, Northridge, CA, USA)]. To individually adjust the volume of the music to a comfortable listening level, additional music excerpts were played during dummy sessions at the beginning of the experiment.

fMRI data acquisition
Data were acquired on a 3T Magnetom Trio MR scanner (Siemens Medical Solutions, Erlangen, Germany) using a 12-channel head coil. Functional data were acquired in the axial plane with an echo-planar imaging sequence [interleaved acquisition of 34 slices, repetition time (TR) = 2000 ms, echo time (TE) = 28 ms, flip angle (FA) = 77°, slice thickness = 3 mm, matrix size = 64 × 64 mm², field-of-view (FOV) = 192 × 192 mm², voxel size = 3 × 3 × 3 mm³]. The slices were positioned oblique-transversally to achieve maximal brain coverage. After an automated shimming, pilot echo-planar images were obtained and visually inspected to insure good image quality in subcortical regions. After the functional runs, structural images were acquired for each participant using a high-resolution T1-weighted imaging sequence (TR = 1900 ms; TI = 900 ms; TE = 2.52 ms; FA = 9°; FOV = 256 × 256 mm²; 176 3D partitions with an isotropic resolution of 1 mm).

Data analysis
MR images were analyzed using Statistical Parametric Mapping (SPM5, www.fil.ion.ucl.ac.uk) implemented in MATLAB 7.0 (Mathworks, Sherborn, MA, USA). The first three volumes of every run were discarded from the analysis to allow the MR signal to reach a steady state. All images in a session were realigned to the mean image of a run to correct for head movement, and normalized into the Montreal Neurological Institute (MNI) stereotaxic space. The normalized data with resliced voxel sizes of 2 × 2 × 2 mm³ were spatially smoothed with an 8-mm isotropic Gaussian kernel to account for inter-subject variability in brain anatomy.

Whole-brain analysis
The six experimental conditions (three emotions: happy, sad and neutral × two modalities: visual and audiovisual) were separately modeled with a boxcar function convolved with the canonical hemodynamic response function. The period during which subjects rated their mood was modeled additionally to separate it from the pure baseline condition. At the individual level, contrast images were calculated comparing the six conditions with the baseline condition. To explore general activation patterns in the visual and audiovisual conditions, the resulting contrast images were entered into a mixed-effects analysis with ‘condition’ as the fixed factor and ‘subject’ (healthy subjects, schizophrenia patients) as the random factor. We adopted unequal variances for the subject factor because we expected large inter-subject variability during mood induction. First analyses investigated the main effect of modality and the interactions of modality by group as well as emotion by group. To decompose interactions, t-contrasts were computed for the different conditions. Results are reported at an adaptive threshold for an expected false discovery rate (FDR) of P < 0.05 (Genovese et al., 2002), only for clusters with a minimal size of 120 µl (15 voxels).

Connectivity analysis
Functional connectivity was assessed for predefined regions-of-interest (ROIs). According to the anatomic atlas for automatic labeling of structural brain images (Tzourio-Mazoyer et al., 2002), center coordinates were chosen from bilateral primary and secondary visual cortices (V1 and V2), primary and secondary auditory cortices (A1 and A2), amygdala and inferior frontal gyrus (for a specification of coordinates, see Table 2). Pair-wise correlation coefficients were calculated after time-series extraction for both hemispheres separately and Fisher-transformed. A mixed-model analysis of variance (ANOVA) analyzed the fixed factors ‘modality’ (visual and audiovisual), ‘emotion’ (happy, sad and neutral) and ‘group’ (healthy subjects and schizophrenia patients) in addition to subject as a nested random-effects variable. This procedure is equivalent to connectivity analysis of the AFNI package (http://afni.nimh.nih.gov/) and takes only differences between correlation coefficients into account to suppress physiological artifacts. Bonferroni-Holm correction was applied to correct for multiple testing for all pair-wise comparisons.
Inferior frontal cortex L
Primary auditory cortex L

Moreover, both groups showed a significant difference in their emotional responses. Patients experienced increased happiness, although this effect was more pronounced in the healthy group. A repeated measures ANOVA revealed a significant main effect of mood induction. During sadness induction, patients reported less happiness than healthy controls. However, during happy induction, patients reported increased happiness compared to the neutral condition.

Table 2: MNI coordinates of anatomically predefined ROIs in the connectivity analysis

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Hemisphere</th>
<th>MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x   y   z</td>
</tr>
<tr>
<td>Amygdala</td>
<td>L</td>
<td>-24  -2  -19</td>
</tr>
<tr>
<td>Primary visual cortex</td>
<td>L</td>
<td>-10  -91  13</td>
</tr>
<tr>
<td>Secondary visual cortex</td>
<td>L</td>
<td>-7   -80  5</td>
</tr>
<tr>
<td>Primary auditory cortex</td>
<td>L</td>
<td>-42  -20  9</td>
</tr>
<tr>
<td>Secondary auditory cortex</td>
<td>L</td>
<td>-53  -22  6</td>
</tr>
<tr>
<td>Inferior frontal cortex</td>
<td>L</td>
<td>-43  26   5</td>
</tr>
</tbody>
</table>

L = left; R = right.

Analysis of behavioral performance

To evaluate subjective ratings, repeated measures ANOVAs were computed with PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). All P-values are reported at a significance level of α < 0.05.

RESULTS

Behavioral results

The effectiveness of the mood induction procedure was confirmed in the repeated measures ANOVA, revealing a significant main effect of mood for the whole group [F(1,54.67) = 54.62, P < 0.001] and both groups separately [healthy controls (HC): F(1,15) = 37.65, P < 0.001; schizophrenia patients (SZ): F(1,15) = 18.24, P < 0.001]. During sadness induction, valence of self-perceived emotion was rated more negative than during neutral mood induction, and during happiness induction experienced valence was rated more positive than during the neutral conditions (Figure 2A). There was no significant main effect of modality or time. The interaction of group x mood just failed significance [F(1,54.67) = 3.30, P = 0.054]. Post hoc t-tests, however, revealed that there was a trend in patients to experience less happiness than healthy subjects [t(29) = 1.99, P = 0.055]. No significant differences emerged between the groups for the experience of sadness [t(29) = 1.50, P = 0.144] and neutrality [t(29) = 0.36, P = 0.72]. Ratings on the unipolar ESR scales confirmed results of successful mood induction in both groups from the bipolar valence ratings. With respect to the induction of happiness, patients as compared to controls indicated slightly increased experience of fear [t(15) = 2.16, P = 0.05] in addition to their comparatively increased rating of happiness.

Regarding the arousal ratings, a significant main effect of mood emerged for the whole group [F(1,88,54.61) = 18.01, P < 0.001] and both groups separately [HC: F(1,15) = 9.82, P = 0.001; SZ: F(1,14) = 10.23, P = 0.001] with arousal differing between the emotional and neutral inductions. Moreover, both groups showed a significant effect of modality with audiovisual conditions being more arousing than visual conditions [HC: F(1,15) = 9.29, P = 0.008; SZ: F(1,14) = 14.58, P = 0.002]. There was no main effect of group [F(1,29) < 1] but a significant group x modality interaction [F(1,29) = 4.61, P = 0.001]. Patients’ arousal ratings showed a trend toward a larger difference between visual and audiovisual conditions than it was seen in healthy controls [t(19.67) = 1.86, P = 0.073; Figure 2B]. The rating given at the beginning of the experiment confirmed that all subjects were reporting a neutral mood when starting the mood induction.

fMRI results

Analysis of variance

The F-test revealed a significant main effect of modality (visual and audiovisual) in a widespread network extending from occipital to temporal, parietal and frontal areas (thresholded at an F-value of 11.36 corresponding to P < 0.01, Supplementary Table S1). The interaction of interest between modality and group showed significant clusters in the bilateral superior temporal gyrus, right cingulate cortex, right lingual and right precentral gyrus as well as the left postcentral gyrus and left precuneus (thresholded at an F-value of 14.47 corresponding to P < 0.05, Supplementary Table S2). The main effect of emotion (happy, sad and neutral) was significant at a family-wise error correction of P < 0.05 thresholded at an F-value of 14.67 (Supplementary Table S3). Especially the bilateral superior temporal gyrus, bilateral cerebellum as well as bilateral amygdala and hippocampus were shown to be most activated during the happy conditions and least activated during the neutral conditions. At a threshold of P < 0.05 corrected according to FDR, there was no significant interaction of group by emotion. To increase statistical power, sad and happy conditions were combined for further analysis. Decomposing the modality by group interaction we examined group differences in the visual and audiovisual conditions separately by computing difference contrasts with two sample t-tests.

Visual mood induction: healthy subjects > schizophrenia patients. During the visual mood induction, healthy subjects showed increased activations that were constrained to the left lingual gyrus (Figure 3A).

Visual mood induction: schizophrenia patients > healthy subjects. No increased activation could be found in patients as compared to healthy controls at a level of P < 0.05 (FDR corrected). At an exploratory and uncorrected level, patients showed greater activation in bilateral inferior frontal gyri and two small clusters in the lingual gyrus (Figure 3B).

Audiovisual mood induction: healthy subjects > schizophrenia patients. When examining the audiovisual mood inductions, healthy subjects showed increased activation in the right superior temporal gyrus (Figure 3C).

Audiovisual mood induction: schizophrenia patients > healthy subjects. In contrast to the visual mood inductions, patients revealed increased activations in an extended network including bilateral inferior frontal cortex, bilateral precuneus, left fusiform gyrus, left supramarginal gyrus, superior parietal gyrus, separate small clusters of the occipital gyrus, right precentral gyrus and bilateral postcentral gyrus during the audiovisual mood inductions (Figure 3D). For details of activated brain regions see Supplementary Table S4.

Connectivity analysis

Reflecting audiovisual processing, modality emerged as a significant predictor for connectivity across groups between right-hemispheric visual and auditory areas, i.e. V1–A1 [F(1,62) = 36.45, P < 10^{-3}] and V1–A2 [F(1,62) = 41.92, P < 10^{-6}], but also within the auditory modality, i.e. right A1–A2 [F(1,62) = 34.74, P < 10^{-3}] and as a trend left A1–A2 [F(1,62) = 11.10, P < 0.005 uncorrected]. Across groups emotion modulated connectivity between left V1 and the amygdala [F(2,62) = 9.38, P < 10^{-3}] as well as left V2 and the amygdala [F(2,62) = 6.12, P < 0.005; Figure 4A]. This is in accordance with time-locked processing of the emotional stimuli. Regarding the connectivity of interest schizophrenia patients in contrast to healthy
subjects exhibited increased connectivity between early and late processing areas within the visual as well as a trend within the auditory cortex [left V1–V2: F(1,62) = 12.21, P < 0.0015; right A1–A2: F(1,62) = 9.53, P < 0.005 uncorrected; Figure 4B and C]. No significant effects on correlations were found between the inferior frontal cortex (cognitive regions) and any of the other ROIs.

**DISCUSSION**

The current study compared brain activation patterns between schizophrenia patients and healthy controls during visual and audiovisual mood induction. Furthermore, we examined the interplay between sensory, cognitive and emotional processes during mood by means of functional connectivity. Consistent with previous studies, our results confirm that visual mood induction leads to similar subjective ratings of mood in patients with schizophrenia and healthy subjects (Schneider et al., 1998; Habel et al., 2004). Our data extend previous work in that, first, audiovisual mood induction was shown to be just as effective in eliciting emotions in patients and healthy subjects. Second, the brain responses to both mood inductions revealed hypoactivations in sensory areas and hyperactivations in higher cortical areas in patients with schizophrenia. Responses in brain areas related to emotion processing did not differ between patients and healthy subjects. Third, connectivity analysis revealed increased connectivity between primary and secondary sensory areas conceivably reflecting impaired sensory filtering in schizophrenia patients. Hyperactivations in higher cognitive areas may reflect higher effort adduced by patients and function as a compensation for hypoactivity and impaired filtering in sensory processing.

**Deficits in sensory processing**

Hypoactivation in patients was prominent in the occipital lobe and the supratemporal plane reflecting deficits in sensory processing. The
mood induction paradigm required a certain degree of sensory processing for emotion perception, which is well documented to be impaired in schizophrenia (Taylor et al., 2012; Li et al., 2010). The deficits in the perception of emotion may possibly reflect an impaired ability to process physical features of the emotional stimulus (i.e. face) rather than specific deficits in emotion circuits. In support of this hypothesis, studies reported deficits in schizophrenia in early visual (Turetsky et al., 2007; Martinez et al., 2008; Butler et al., 2009; Norton et al., 2009) and auditory processing (Kircher et al., 2004; Leitman et al., 2004, 2010; Salisbury et al., 2005) across a wide range of stimuli. The severity of these deficits in early sensory processing was additionally correlated with the extent of deficits in emotion perception. As a further evidence for deficient sensory processing, brain-volumetric studies have shown reduced grey matter volumes in the occipital lobe (Davatzikos et al., 2005; Dorph-Petersen et al., 2007; Onitsuka et al., 2007) and the superior temporal gyrus (Sun et al., 2009). Sensory hypoactivation further supports the classical hypothesis by McGhee and Chapman (1961) that assumes that patients with schizophrenia have a deficit in directing their attention and filtering incoming information. The resulting overflow of input then leads to a cognitive overload.

Our connectivity analysis provides further evidence for a deficit in sensory processing. Schizophrenia patients showed increased connectivity only within the sensory system, i.e. connectivity between primary and secondary sensory processing areas was higher in patients than in control subjects, in the visual as well as in the auditory stream. An increase in connectivity between two brain areas reflects similar activations in these areas of interest and points to less differentiated processing. Thus, in patients with schizophrenia incoming information may be forwarded within the sensory stream without differentiated filtering or processing.

**Hyperactivations in schizophrenia**

In contrast to these early perceptual deficits, patients showed higher activations in brain areas that are related to higher-order cognitive processing. Increased activation in the inferior frontal gyrus, the precuneus and in parietal areas was seen in earlier studies investigating emotion processing with various tasks (Reske et al., 2009; Habel et al., 2010; Salgado-Pineda et al., 2010). Based on a meta-analysis of 26 functional imaging studies, Taylor et al. (2012) speculated ‘that schizophrenia patients recruited non-emotional regions as a compensatory process, for example, greater cognitive effort to encode emotional stimuli, more ambivalent interpretation...’ (p. 143). Compensatory or regulatory processes may counterbalance deficits in emotion recognition and face processing. This may hold for mood induction as well. Hyperactivation in premotor and motor areas during facial affect recognition for example were postulated as a compensatory mechanism of the mirror neuron system (Quintana et al., 2001). The current study extents these findings in that the extent of hyperactivations in frontal and parietal areas increased during the audiovisual as compared to the purely visual condition. The additional inclusion of music resulted in an increased neural effort for patients to process the emotional information. In a similar vein, research examining working memory performance in schizophrenia reported similar hyperactivations in patients that were dependent on increasing task demands (Quintana et al., 2003; Kim et al., 2010). A change from low-to-moderate memory...
load in an item recognition paradigm resulted in exaggerated hyperactivations in the BOLD signal of schizophrenia patients. Authors interpret this pattern as a cortical inefficiency. Due to compensatory processes, nevertheless, similar behavioral outcomes were achieved in the patients and healthy subjects. Similarly, in the current study, patients reported adequate affective experience in the behavioral ratings despite deficits in perceptual processes of emotion and inefficient processing of higher-order brain areas.

Patients showed a trend to experience positive emotion as less positive than healthy subjects. During the experience of negative emotion they showed no differences when compared with healthy subjects. Cohen and Minor (2008) suggested that positive stimuli induced hedonic and aversive emotions at the same time in patients with schizophrenia. Ambivalent emotions or a deficit to inhibit negative emotions in patients are consistent with a model of increased cognitive resources to obtain the same level of positive feeling. Thus, even in clinically stable patients, compensatory efforts may lead to an altered quality of emotion experience. We further hypothesize that during increased stress or situations with higher demand, reported hyperactivation in frontal and parietal regions may lead to a further overload of the system. In turn, compensation mechanisms may fail and further overload may then lead to stronger deficits in emotion experience as specifically seen in acute psychosis. Future studies are needed that compare neural activations of emotion experience in patients that are in an acute and a stable phase of the disease to further understand the association between ratings of emotion experience and corresponding brain activations. Furthermore, it would be worthwhile to explore the possible different mechanisms that may underlie transition from stable phases of the disease to acute psychosis.

Limitations
Our study did not apply a pure auditory condition as a mood induction strategy. Therefore, we cannot completely rule out that the observed differences in brain activation between healthy subjects and patients in the audiovisual mood induction could have been produced at least partly by musical stimuli alone. However, the activation seen during the audiovisual condition in healthy subjects resembles activation indicated during audiovisual mood induction in previous studies (compare Baumgartner et al., 2006). Moreover, the main goal of this study was not to explore particularly the effect of unimodal and multimodal brain processing but rather to compare two different mood induction methods, which were never compared in schizophrenia using neuroimaging methods. Nevertheless, future studies comparing the neural correlates of music perception and its effects on mood in schizophrenia and healthy subjects should be conducted to exclude the possibility that differences indicated here are specific to the presentation of musical stimuli.

Emotion perception and mood induction may not be considered separate processes. On the one hand, contagion and empathic feelings may lead in any kind of emotion perception task to a certain degree of mood induction. On the other hand, our mood induction paradigm required also a certain degree of emotion perception. The current study was steered to emphasize the mood induction by (i) using prolonged presentation of unambiguous stimuli, (ii) the task instructions and (iii) the ratings of own experience. However, the involvement of sensory networks confirms contributions from perception to mood induction. Future studies should design experiments to investigate the differential effect of pure emotion perception vs emotion experience within one paradigm.

The small number of repetitions within our paradigm is another limitation with respect to the power of the design. However, a higher number of mood induction cycles may also have led to habituation and attention effects. In particular, schizophrenia patients may be more prone to difficulties in maintaining prolonged concentration on the task.

Medication as a possible confounder on activation in neural substrates in schizophrenia is a longstanding debate. Some authors do not
find general effects of antipsychotic medication on neural processes in schizophrenia (Schneider et al., 1998, Röder et al., 2010) while others reported at least short-term effects (Lui et al., 2010) or effects on subjective experience (de Haan et al., 2004). Generally, there is the possibility that differences in brain activation between patients and healthy subjects within the current study are partly due to medication effects. In the same manner, differences in brain activity may be more profound in drug-naïve patients. To minimize effects of medication, all patients recruited in our study were all in a stable phase of the disease and were taking the same antipsychotic medication for at least 4 months.

CONCLUSIONS

During both mood inductions, visual and audiovisual, patients with schizophrenia demonstrated visual and cognitive deficits, which were manifested in hypoactivation of early sensory processing areas and hyperactivation in areas of higher cognitive processing. When two modalities were involved, the hyperactivations were stronger and more widespread. These findings support the hypothesis of a deficit in filtering and processing incoming information and concurrent increased higher-order cognitive effort compensating for these sensory deficits during emotion perception. This compensation may further allow for adequate emotion experience as seen in behavioral ratings of clinically stable patients.

SUPPLEMENTARY DATA

Supplementary data are available at SCAN online.

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Conflict of Interest

None declared.

REFERENCES


