Isn’t it ironic? Neural Correlates of Irony Comprehension in Schizophrenia

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Abstract

Irony is a frequent form of social cognition. Increasing evidence indicates a deficit in comprehension in schizophrenia. Several models for defective comprehension have been proposed, including possible roles of the medial prefrontal lobe, default mode network, inferior frontal gyri, mirror neurons, right cerebral hemisphere and a possible mediating role of schizotypal personality traits. We investigated the neural correlates of irony comprehension in schizophrenia by using event-related functional magnetic resonance imaging (fMRI). In a prosody-free reading paradigm, 15 female patients with schizophrenia and 15 healthy female controls silently read ironic and literal text vignettes during fMRI. Each text vignette ended in either an ironic (n = 22) or literal (n = 22) statement. Ironic and literal text vignettes were matched for word frequency, length, grammatical complexity, and syntax. After fMRI, the subjects performed an off-line test to detect error rate. In this test, the subjects indicated by button press whether the target sentence has ironic, literal, or meaningless content. Schizotypal personality traits were assessed using the German version of the schizotypal personality questionnaire (SPQ). Patients with schizophrenia made significantly more errors than did the controls (correct answers, 85.3% vs. 96.3%) on a behavioural level. Patients showed attenuated blood oxygen level-dependent (BOLD) response during irony comprehension mainly in right hemisphere temporal regions (ironic>literal contrast) and in posterior medial prefrontal and left anterior insula regions (for ironic>visual baseline, but not for literal>visual baseline). In patients with schizophrenia, the parahippocampal gyrus showed increased activation. Across all subjects, BOLD response in the medial prefrontal area was negatively correlated with the SPQ score. These results highlight the role of the posterior medial prefrontal and right temporal regions in defective irony comprehension in schizophrenia and the mediating role of schizotypal personality traits.

Introduction

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has been previously demonstrated that medial prefrontal cortex dysfunction may underlie impaired affective mentalizing in schizophrenia [35,36,37].

Several theoretical models have been proposed for brain dysfunction during irony comprehension in schizophrenia. Perhaps, the most commonly proposed model is that the defective irony and sarcasm (that is, irony with hurtful intentions) comprehension in individuals with schizophrenia is due to deficits in TOM and perspective taking [9,38]. Indeed, TOM is one of a number of essential cognitive steps required for irony comprehension [31,39]. This model assumes that the TOM is the key problem and implies that the functional neuroanatomical deficits are present in brain regions crucial for TOM, such as the medial prefrontal cortex.

Misinterpretation of ironic remarks may also contribute to developing or worsening positive symptoms such as persecutory delusions. The cognitive model proposed by Salvatore et al. [27] assumes misinterpretation of “ambiguous and hard-to-interpret communicative signals” such as “ironic comments” in co-occurrence with the factors above may induce delusions. Thus, investigating the (mis)understanding of ironic remarks in schizophrenia will provide insights into an important aspect of schizophrenic psychopathology.

Leitman and colleagues [40] proposed a model that deficits in prosody and speech melody perception are important for sarcasm detection deficits in schizophrenia. This model suggests a deficit in the brain regions associated with comprehension of prosody, such as the right superior temporal cortex [41,42]. Further, this would mirror fMRI findings in autism, where prosody interacts with fMRI correlates during irony comprehension [43]. Nevertheless, the importance of prosody for irony comprehension is controversial because it is only one of a number of markers for irony [44]. Irony without speech melody is not only possible [45], but is actually very frequent in written language [2,3,46]. In fact, patients with schizophrenia show abnormalities in tasks with written irony [15,16].

Another model states that dysfunction of the right cerebral hemisphere and/or defective interaction between the cerebral hemispheres may underlie difficulties in deciphering irony and sarcasm in schizophrenia [23,47]. Traditionally, comprehension of non-literal stimuli is ascribed to the right cerebral hemisphere ([48]; see [20,49] for a critical discussion). Indeed, there is sufficient evidence that the right hemisphere is involved in the comprehension of irony. Both the left and right hemispheres are more involved in comprehension of ironic remarks than in lower linguistic functions [18,22,33]. The hypothesis that the comprehension difficulties in schizophrenia represent a right hemisphere deficit is, therefore, plausible, but currently lacks functional support. The functional lateralisation of irony comprehension in schizophrenia is also interesting from another point of view; increasing evidence indicates that language lateralisation is reduced in schizophrenia [50], i.e., in schizophrenia, language is shifted to the right cerebral hemisphere to a higher extent. It has been proposed that language functions previously outperformed by the right hemisphere might, in a similar manner, shift to the left hemisphere [25], particularly in patients with severe thought disorder [24,47,51]. The latter assumption is supported by findings of studies in patients with severe thought disorders and language production tasks [52,53], and in patients with difficulties in literal language comprehension [54,55,56].

Dysfunction of the brain language system is crucial for another model of disturbed irony comprehension that was recently proposed by our group [19,57], in which we assumed a role of the frontotemporal language semantic comprehension network for disturbed irony comprehension in schizophrenia and adopted a model put forward by Siever and Davis. Siever and Davis [50] suggested a model that strengthens the role for schizotypal personality traits in schizophrenia. Briefly, they suggested that individuals with elevated schizotypal traits and patients with schizophrenia share a temporal lobe deficit, which is compensated for by lateral prefrontal overactivation in schizophrenic, not in schizophrenia. Nonliteral language comprehension highly relies on frontotemporal interaction [20]; moreover, underactivation in left prefrontal regions has been reported for another type of nonliteral language, metaphors, in schizophrenia [51,59]. Therefore, language paradigms represent good paradigms to test the hypothesis. Indeed, in our previous publication, we showed that higher degrees of schizotypal personality traits in a non-clinical population resulted in reduced lateral temporal activation, but increased left lateral prefrontal activation, as detected using fMRI [19]. Following Siever and Davis [50], we hypothesize reduced activation in both these regions in schizophrenia.

To our knowledge, no fMRI studies on irony comprehension in schizophrenia have been reported. The aim of this work is to provide the first insights into the functional neuroanatomy of irony comprehension in schizophrenia using fMRI. Our hypotheses for activation abnormalities in schizophrenia are based on the functional models outlined above. We hypothesize a functional deficit in the brain fronto-temporal semantic language system in both cerebral hemispheres. Based on our previous study in non-clinical schizotypal individuals, we think that the strength of the deficit will correlate with the degree of schizotypal traits. Further, we expect that as an alternative, or in addition to, the abnormalities in the frontotemporal system, functional deficit will be observed in TOM regions, including the medial prefrontal cortex and the temporoparietal junction, both of which play a role in irony comprehension in healthy subjects [20]. Prosody may likewise interact with the functional deficits in schizophrenia. Thus, in this investigation, we chose a prosody-free task to limit influencing factors. Deficits in both the medial prefrontal and temporal lobe systems are expected to mirror the findings for irony comprehension in autism [43,60]. Further, we hypothesize that compensatory activation (fMRI signals greater in schizophrenia patients versus controls), equivalent to literal language perception in schizophrenia [56], may occur in brain regions adjacent to the classical semantic system, such as the premotor cortex.

Materials and Methods

Subjects

This study included 15 right-handed probands with DSM-IV schizophrenia and 15 healthy control subjects matched for age, years of education, and verbal intelligence [61]. All study participants were female. The recruitment process and results for the control group were published previously in detail [19]. Patients were recruited from the Department of Psychiatry, University of Tübingen, Germany. All patients were acute or subacute inpatients, were native German speakers, had no other past or present medical illness, and had sufficient reading skills. All patients were on stable medication, mainly with atypical antipsychotics (mean dosis [62] 516 (SD: 237) chlorpromazine equivalents). Among the 15 patients, four patients showed concreteness. Among the 15 patients, four patients showed concreteness. Schizotypal personality traits (SPQ total score) showed a range between 14 and 70 in patients (range 1–44
in controls [19]). Further group characteristics are shown in table 1.

Procedure
The study was approved by the local ethical committee (University of Tuebingen, Germany). First, all subjects received complete information about the study and ability to consent was ensured in an interview with an experienced psychiatrist (A.R.). Afterwards, subjects underwent a practice session with stimuli not used in the experiment and provided written informed consent. Then, the subjects completed the schizotypal personality questionnaire (German version, [63]) and underwent functional magnetic resonance imaging. During the fMRI scanning procedure, subjects lay supine in the MR-scanner, their head secured by foam rubber to minimize movement artefacts. Stimuli were presented as whole sentences visually on a translucent screen viewed by the subjects via a mirror. To reduce the difficulty of the task, the context scenarios were additionally presented acoustically using a tape-recorded version with a female voice. To avoid influences of an ironic tone of voice on brain activation [43,64], only visual presentation was used in the case of target sentences. During the scanning session, task instruction was to attend to the stimuli and assess if intention of the target sentences was ironic or not. However, to avoid effects of motor response on brain activation, no motor response was requested. Instead, subjects read all sentences silently and performed an attention task during which they pressed a button with their right index finger any time a particular picture appeared on the screen. Stimulus sequence was unforeseeable for the subject and optimised using optseq software (http://surfer.nmr.mgh.harvard.edu/optseq/).

Experimental Stimuli
A set of 56 German stimuli, each consisting of context scenarios and target sentences, was used in the experiment. Exact description of the stimuli and evaluation process was given previously [19,57]. In brief, the context scenarios consisted of 2 sentences (8–12 words), each with 2 protagonists. The target sentences always consisted of 1 statement made by one of the protagonists and had, in the context, either an ironic or a literal meaning. The number of words and sentences, grammatical complexity, and word frequency were counterbalanced between literal, ironic, and meaningless context scenarios. Corresponding literal and ironic target sentences were identical.

Functional MRI Acquisition
Imaging was performed on a 3-T Scanner (Siemens, TIM TRIO). Functional images were acquired with an echoplanar image sequence which is sensitive to BOLD-contrast (TE 40 ms, TR 2 s, 32 slices, slice thickness 3 mm, gap 1 mm, FoV 192×192 mm², pixel size 3×3 mm²). One run consisting of 390 volumes was acquired during the experiment. After the functional task, structural images of the whole brain were acquired using a T1-weighted MPRAGE sequence (TR 2200 ms, TI 900 ms, TE 2.92 ms, voxel size 1×1×1 mm³).

Data Analysis
First level processing parameters for the imaging data were identical with [19]. For image processing and all statistical analysis, SPM5 (Wellcome Department of Imaging Neuroscience, London) was used. The functional images of each subject were slice time corrected to the middle slice and were corrected for motion and

| Table 1. Clinical and sociodemographic characteristics of patient and control group. |
|------------------------------------|
|                                   |
|                                   |
| **patients**                      |
|                                   |
| n = 15                            |
|                                   |
| **control subjects**              |
|                                   |
| n = 15                            |
|                                   |
| **significance**                  |
|                                   |
| p                                 |
|                                   |
| age (years)                       |
| 28.1                              |
|                                   |
| years of fulltime education       |
| 15.9                              |
|                                   |
| verbal intelligence (score)¹      |
| 31.6                              |
|                                   |
| HAWIE picture sequencing test²    |
| 30.7                              |
|                                   |
| CPT                               |
| 0.3                               |
|                                   |
| SPQ cognitive perceptual³         |
| 7.3                               |
|                                   |
| SPQ interpersonal³                |
| 3.6                               |
|                                   |
| SPQ total                         |
| 14.6                              |
|                                   |
| SAPS total score                  |
| 33.0                              |
|                                   |
| SAPS hallucinations               |
| 6.9                               |
|                                   |
| SAPS delusions                    |
| 17.5                              |
|                                   |
| SANS total score                  |
| 29.3                              |
|                                   |
| PANSS total score                 |
| 69.9                              |
|                                   |
| PANSS positive                    |
| 17.4                              |
|                                   |
| PANSS negative                    |
| 16.0                              |
|                                   |
| PANSS general                     |
| 36.5                              |
|                                   |
| Global Assessment of Functioning Scale |
| 39.0                              |
|                                   |
| Chlorpromazine equivalents⁴       |
| 516.0                             |
|                                   |
|¹Multiple choice vocabulary test [61]. |
|²Subtest 2 from [72].              |
|³As defined by [63].               |
|⁴As defined by [62].               |
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realigned by using the first scan of the block as reference. T1 anatomical images were coregistered to the mean of the functional scans and spatial normalized to the MNI space by the combined segmentation, bias correction and spatial normalization tool in SPM5. The calculated nonlinear transformation was applied to all functional images. Finally, the functional images were smoothed with an 8-mm full-width, half-maximum (FWHM) Gaussian filter. A general linear model (GLM) was constructed for each participant to analyze the hemodynamic response function. In each GLM, regressors were generated by convolving a box car function with the hemodynamic function. Separate regressors were used to model the hemodynamic responses during presentation of target textoids, ironic sentences, literal sentences and the visual baseline condition. Moreover, a high-pass filter (1/128 Hz) was applied to remove low-frequency drifts.

For each subject, several T-Test contrasts were calculated separately for (1) the ironic target sentences (“irony”) and (2) literal target sentences (“literal”) conditions versus visual baseline and (3) ironic versus literal target sentences. Random effects analyses on group level were calculated for each of these contrasts. Then, between group comparisons were calculated for each of these contrasts using two sample T-Tests.

Effect of Psychopathology and Schizotypal Personality Traits on Brain Activation

To investigate the influence of psychometric schizotypy and psychopathology on brain activation, simple regression analyses of SPM data were applied. In this type of analysis, each single voxel in the brain is individually examined with respect to whether the size of the BOLD response is correlated with a variable over subjects.

Effects of schizotypal personality traits were calculated using the total score of the schizotypy questionnaire ([65], German version [63]) as regressor. These analyses were calculated for all participants together, following the rationale that schizotypal traits represent a continuum [66,67,68]. The result of this analysis is a brain map, which depicts the voxels with which there is a significant correlation between the variables. Because of the exploratory character of our pilot-study, we chose a liberal threshold of p < 0.001 uncorrected and an extent threshold of 5 voxels for these analyses. In each analysis, separate tests were performed to detect positive correlation (that means the higher the score of the individual score of the study subject, the stronger the BOLD response) and negative correlation (the higher the score of the individual score of the study subject, the weaker the BOLD response) were calculated.

Effects of psychopathological parameters were calculated within the schizophrenia group. Due to computer hardware failure, psychopathological data for 2 patients was lost. Therefore, regression analyses were performed using data from only 13 patients. In separate subanalyses, SAPS (positive symptoms, [69]) total score, SANS (negative symptoms, [70]) total score and SAPS formal thought disorder subscale were used as regressors.

Off-line Testing

After fMRI, the subjects performed an off-line test to detect error rate. In this test, the subjects indicated by button press whether the target sentence has ironic, literal, or meaningless content [19,57]. Subjects were seated in front of a computer screen. A total of 54 stimuli was used for this experiment (22 ironic and 22 literal textoids identical to the fMRI experiment, 10 textoids with similar structure and content followed by a nonsense statement by one of the two protagonists). The task was to indicate by pressing one out of three buttons whether the target sentence was in this context most likely ironic, literally meaningful, or meaningless. Afterwards, subjects completed a short test battery (verbal intelligence [61], digit span [71], subtest picture sequencing from the HAWIE-R intelligence test [72]). Then, subjects were clinically assessed (by A.R.) using the SAPS [69], SANS [70] and PANSS [73].

Results

Results of the attention task inside the MR scanner indicate good performance with no significant difference between patients and controls (mean error rate 0.1 errors in healthy controls, 0.8 errors in schizophrenia, p = 0.33).

Off-line Data

Immediately after the fMRI session, subjects completed the off-line irony test. Off-line performance in the irony comprehension task showed substantial performance in both control subjects (mean 96.3% correct answers, SD 3.4) and schizophrenia (85.3% correct, SD 15.3), however with a significant difference (p = 0.02, ANOVA). A significant correlation was found between psychometric schizotypy (total score of the schizotypal personality questionnaire) and and percentage of correct responses (r = −0.55, p = 0.004).

Brain Activation

Main effects for reading priming sentences, ironic targets, and literal targets showed robust activations in a predominantly left lateralized network including visual cortices, temporal lobe, and prefrontal cortex in the study participants.

Differences between Control and Patient Group

Results for differential contrasts between control subjects and schizophrenia patients are shown in table 2, figure 1, figure 2 and figure S1.

In brief, differential contrasts between ironic and literal target sentences showed diminished activation in right hemisphere temporal and parietal regions in schizophrenia. Further, during processing of ironic, but not literal, target sentences, BOLD response in schizophrenia was decreased in a network including the posterior medial prefrontal cortex (MNI maximum at −3 18 27, Brodmann area 32/24) and left hemisphere (LH) insula. In the reverse contrast (schizophrenia>controls) patients showed enhanced BOLD response in the posterior temporal lobe bilaterally (table 2). Again, this difference was only detectable for ironic, but not literal target sentences.

Influence of Schizotypal Personality Traits on Brain Activation

Influences of schizotypal personality traits, as measured with the total score of the SPQ [63] were calculated across all study participants. As positive and negative correlations indicate different processes, they were calculated separately. A negative correlation was found, that is the higher the degree of psychometric schizotypy, the lesser the BOLD response, in the posterior medial prefrontal cortex (anterior cingulate, MNI x, y, z: 3, 18, 33; z = 3.34) for reading ironic sentences>visual baseline in the same regions previously found underactivated in schizophrenia patients in the differential contrast (figure 3). Reading ironic sentences>visual baseline contrasts showed no positive correlation with the SPQ total score. Further, the contrasts for ironic>literal target sentences or literal sentences>visual baseline did not show significant correlations (either positive or negative).
Table 2. Group comparison between healthy controls and schizophrenia. p<0.001, ext. 5 voxels.

| region                        | hemisphere | extent       | MNI coordinates | z     |
|-------------------------------|------------|--------------|-----------------|-------|
| ironic sentences>literal target sentences controls > patients | RH         | 5            | 51 – 54 15      | 3.39  |
| middle temporal gyrus         | RH         | 8            | 57 – 12 18      | 3.29  |
| rolandic operculum            | RH         | 6            | 48 – 12 33      | 3.25  |
| postcentral gyrus             | RH         | 6            | 57 – 9 30       | 3.19  |
| patients>controls             | No activated clusters |
| ironi sentences>visual baseline controls > patients | LH         | 60           | – 3 18 27       | 4.02  |
| anterior/middle cingulate gyrus | LH        | 41           | –36 9 0        | 3.75  |
| insula                        | LH         | –45 12 0     |                | 3.55  |
| postcentral gyrus             | LH         | 15           | –42 – 12 33     | 3.59  |
| postcentral gyrus             | RH         | 11           | 48 – 15 33      | 3.44  |
| supramarginal gyrus           | RH         | 5            | 54 – 36 30      | 3.39  |
| patients>controls             | No activated clusters |
| parahippocampal gyrus         | LH         | 26           | –24 – 36 – 12   | 4.40  |
| brainstem                     | LH         | 5            | –6 – 27 – 9     | 3.74  |
| fusiform gyrus                | RH         | 6            | 24 – 39 – 15    | 3.70  |

Results from further correlations between cognitive-perceptual and interpersonal subscales of the German schizotypal personality questionnaire are shown in table S4. We could not investigate an association with the disorganised factor since, in contrast to the original version, the German version of the SPQ has no disorganised factor [74,75]. Within the schizophrenia group, there was no significant correlation between the SPQ and PANSS [73] total score (r = 0.08; p = 0.79) or the global assessment of functioning score (r = –0.17; p = 0.58).

Influence of Psychopathology within the Patient Group

Correlations with symptom dimensions within the patient group were detectable in both cerebral hemispheres as shown in table 3.

Discussion

We investigated the comprehension of ironic and literal text vignettes in female patients with schizophrenia by using event-related fMRI. In a prosody-free reading task, subjects processed text vignettes that ended in either a literal or an ironic statement made by one of the protagonists. As expected, we were able to detect robust differences between patients and subjects in a control group, which was matched for age and educational level (control group results previously published [19]). Differences were detectable both for ironic versus literal, as well as for ironic sentences versus visual baseline, between the groups. However, no differences were detected for reading literal target sentences vs. visual baseline. This lack of difference is in line with a number of MRI studies on literal language in schizophrenia [56].

In this pilot study, we had several hypotheses concerning the results, which were partially confirmed. Most investigations in healthy subjects (see [20]), as well as those with brain lesions (see [19]), indicate that both cerebral hemispheres are involved in the comprehension of ironic remarks. In healthy individuals, the contribution of the right hemisphere seems to be more prominent for irony than for literal language [20,21,22,33]. Based on these and other studies, we hypothesised that impairment in irony comprehension in both schizophrenia and autism may be caused by right hemisphere dysfunction [10,76]. However, our results have been mixed in terms of cerebral lateralization. Indeed, contrasts for ironic vs. literal (Table 2) indicate a deficit in the right cerebral hemisphere; however, contrasts between ironic target sentences vs. visual baseline and correlations with symptomatology (Table 3) indicate that the left hemisphere also contributes to the deficit.

Our main hypothesis was that dysfunction of the brain’s frontotemporal language system may be crucial in the pathophysiology of the difficulties experienced by patients with schizophrenia in interpreting ironic remarks, and that schizotypal personality traits might mediate the magnitude of these difficulties. As expected, patients showed attenuated activation in the RH middle temporal gyrus (table 2, figure S1).

Moreover, BOLD response in the RH temporal lobe showed correlations with both positive and negative symptoms (table 3). The right hemisphere temporal lobe is part of the brains semantic system [20,77]. Our finding of decreased activation during a language task in schizophrenia therefore supports other evidence of impairment of this system in schizophrenia [47,56,78]. However, in contrast to our expectation [19], and in contrast to other MRI findings for figurative language in schizophrenia [51,59], there was no activation difference in the left inferior frontal gyrus.

The cognitive model for delusions by Salvatore et al. [27,79] assumes that ambiguous intersubjective interactions, such as ironic remarks, are relevant for the development of positive symptoms in schizophrenia and may be caused by mirror neuron dysfunction. The brain regions typically associated with mirror neurons are the ventral premotor cortex and the inferior parietal lobule [80], and these regions did not show the most prominent differences between patients and controls in our study, although they are known to be involved in irony comprehension in healthy subjects [19,20]. However, the human mirror neuron system may extend into other brains regions as well [80].

The most prominent differences between healthy controls and patients with schizophrenia have been found in the posterior medial prefrontal cortex, as well as the LH insula, RH middle temporal gyrus, and bilateral postcentral gyrus (Table 2). As hypothesised, medial prefrontal brain activation was attenuated in patients with schizophrenia (table 2, table S1). However, activation was localised more posterior than that suggested by the “classical” theory of mind regions [81,82] in the dorsal part of the anterior cingulate and more posterior than activations found in previous studies on irony comprehension (see [20]). This more posterior part of the anterior cingulate is thought to play a role in conflict monitoring and action monitoring [81] and in making judgements about the external world [82]. Therefore, activation in this part might represent a correlate of the difficulties of patients with schizophrenia to simulate the social situation during the decision
process and to determine if a sentence is ironic or not. The medial prefrontal cortex is also ascribed the function to suppress the incorrect alternative literal meaning during comprehension of nonliteral stimuli [20,83], so attenuated activation in this area could possibly reflect the tendency of patients with schizophrenia to literally interpret nonliteral stimuli (“concretism”).

In the present study, the degree of attenuation of the BOLD response in this region correlated with psychometric measures of schizotypy across all subjects, i.e., the higher the SPQ score, the lesser the BOLD response exhibited by the subject during the processing of ironic sentences, irrespective of diagnostic group. Thus, our results further strengthen previous assumptions of a continuum between schizotypal traits in nonclinical subjects and symptoms manifested in patients with schizophrenia [67,68]. Our data are also compatible with previously made assumptions according to which the interaction between medial prefrontal and lateral temporal brain areas might be determined by the magnitude of schizotypy expression and other subclinical psychot-
ic symptoms. For example, based on their research on schizotypy in nonclinical adolescent subjects, Lagioa et al. [84] suggested that schizotypy is associated with “inefficient connectivity” between medial prefrontal and language areas [84]. Similarly, Brent et al. [85] suggested, on the basis of fMRI research on subclinical psychotic symptoms in their nonclinical population, that “aberrant connectivity” between frontal and lateral temporal areas may play a role in the pathophysiology of psychosis.

Another region found to be underactivated in schizophrenia was the LH insula. The insula is involved in perceptual decision making [86, 87, 88] and in the comprehension of irony [89] and other nonliteral stimuli in healthy subjects [20, 90, 91]. The insula shows structural and functional abnormalities in schizophrenia [92]. Underactivation of the insula in fMRI studies has been previously reported during social cognition tasks [93] and language comprehension on sentence level in schizophrenia [56, 59, 94].

Patients showed stronger BOLD response than controls in the left hemisphere parahippocampal gyrus. This region frequently shows activation during the comprehension of nonliteral stimuli, which could possibly represent ambiguity processing and analyzing/ascribing emotional connotation to nonliteral stimuli [20]. It could also represent “integrating context” [90, 95] or “recognizing the importance of social cues” during irony comprehension [90]. A growing body of evidence suggests that the parahippocampal gyrus may play a significant role in schizophrenia. For example, in fMRI studies, aberrant activation of the parahippocampal gyrus has been shown to be associated with positive symptoms in patients with schizophrenia [96, 97, 98, 99]. Rankin et al. [90] speculated that defective “top-down influence on the parahippocampal gyrus” from the dorsomedial prefrontal and insular cortex may play a role in the pathophysiology of defective sarcasm detection in neurodegenerative diseases, arguing that these brain regions are functionally interconnected. The same mechanism may also play a role in the pathophysiology of defective irony comprehension in schizophrenia, as we found impaired activation in the dorsomedial prefrontal cortex and insula, and increased activation in parahippocampal regions.

Limitations
We are aware of several limitations in our study. First, the number of subjects is rather low, especially when considering that correlation analyses were performed. This gives our investigation more of the character of a pilot study. Future research is therefore needed to confirm the reliability of the findings in a larger sample. On the other hand, stable and replicable correlations with personality traits and psychopathology have been shown in studies with roughly the same number of subjects [100, 101, 102]. Furthermore, conference proceedings with data from an additional fMRI study on irony comprehension in schizophrenia confirm the underactivation of the insula in schizophrenia [103].

Affective connotation is a further limitation. In our task, ironic statements were predominantly negative. However, irony with positive connotations may have different neural correlates [104]. Furthermore, we studied only female individuals. This point is of possible importance because gender differences have been reported for irony comprehension [105, 106]. Furthermore, gender differences have been reported for schizotypy [107] and schizophrenia [108]. Future research is therefore encouraged to evaluate how irony comprehension in schizophrenia interacts with gender [109].

Previous fMRI studies have showed that irony comprehension may be related to motor cortex function. To avoid confounding with button press or motor response, our subjects had to indicate whether the sentence was ironic or not only in the offline task. Thus, we cannot be certain that subjects performed the task in the scanner correctly. Nevertheless, good performance in the attention task, the quality of movement parameters during the imaging
### Table 3. Correlation analysis between fMRI signal during irony comprehension and psychopathology dimensions.

|                | Positive correlation | Negative correlation |
|----------------|----------------------|----------------------|
|                | region               | hemisphere | size | MNI  | z    | region               | hemisphere | size | MNI  | z    |
| **Irony sentences > literal target sentences** |                       |            |      |      |      |                       |            |      |      |      |
| positive symptoms (SAPS total score) | no activated clusters | RH         | 21   | 60–27 0 | 3.56 | insula/superior temporal gyrus | RH         | 21   | 60–27 0 | 3.56 |
| Thought disorder (SAPS Thought disorder) | no activated clusters | no activated clusters |            |      |      | no activated clusters | no activated clusters |            |      |      |      |
| negative symptoms (SANS total score) | no activated clusters | no activated clusters |            |      |      | no activated clusters | no activated clusters |            |      |      |      |
| **Irony sentences > visual baseline** |                       |            |      |      |      |                       |            |      |      |      |
| positive symptoms (SAPS total score) | inferior frontal gyrus | LH         | 6    | −42 30 12 | 3.59 | no activated clusters | no activated clusters |            |      |      |      |
| Thought disorder (SAPS Thought disorder) | posterior cingulate | LH         | 21   | −6 −54 6 | 3.71 | no activated clusters | no activated clusters |            |      |      |      |
| Thalamus | LH | 7 | −21−30−3 | 3.69 |             |      |      |      |      |      |      |      |
| superior temporal gyrus | RH | 7 | 60−27 0  | 3.56 |             |      |      |      |      |      |      |      |
| negative symptoms (SANS total score) | middle temporal gyrus | LH | 18   | −54 −42 −6 | 3.51 | rolandic operculum | RH | 5 | 57 −6 12 | 4.45 |
| | | | | | | corpus callosum | LH | 30 | −9 6 24 | 3.97 |
| | | | | | | | LH | −6 −3 30 | 3.44 |
| | | | | | | | LH | −18 12 24 | 3.11 |
| | | | | | | | middle temporal gyrus | RH | 8 | 51 −57 9 | 3.50 |
| | | | | | | | corpus callosum | RH | 45 −60 15 | 3.39 |
| | | | | | | | frontal lobe | LH | 7 | −24 33 15 | 3.49 |
| | | | | | | | cerebellum | LH | 7 | −3 −42 −30 | 3.46 |
| | | | | | | | corpus callosum | RH | 6 | 6 18 18 | 3.41 |
| **Literal target sentences > visual baseline** |                       |            |      |      |      |                       |            |      |      |      |
| positive symptoms (SAPS total score) | no activated clusters | no activated clusters |            |      |      | no activated clusters | no activated clusters |            |      |      |      |
| Thought disorder (SAPS Thought disorder) | no activated clusters | no activated clusters |            |      |      | no activated clusters | no activated clusters |            |      |      |      |
| negative symptoms (SANS total score) | inferior frontal gyrus | RH | 10   | 39 27 −15 | 4.05 | precuneus | RH | 5 | 6 −72 33 | 3.74 |

Correlations are shown within the schizophrenia group (n = 13). A negative correlation indicates that the higher the degree of psychopathology, the lower is the BOLD response. p < 0.001, ext. 5 voxels. doi:10.1371/journal.pone.0074224.t003
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session, and stable activation in the brain’s language system in each individual subject do indicate that subjects complied with the instructions.

Several limitations relate to the nature of our irony comprehension task. Irony is a complex phenomenon and can have various linguistic forms. In our irony comprehension test, most stimuli characteristics were paralleled between ironic and literal text vignettes. In the target sentences, a protagonist made an ironic or literal statement. Our task was explicit (i.e., subjects were aware that ironic utterances may occur during the task), and ironic statements were made concerning others (not relating to the study participants). It is possible that patients with schizophrenia might show aberrant responses when dealing with issues pertaining to them personally, but this was not the case here. In a more general sense, it is very likely that social cognition in a real world setting might be different [19,110,111]. In interpersonal communication which is not in written form (which was used here), it is postulated that subjects include information from facial affect, prosody, larger context, information about the speaker, momentary affect, general world knowledge, and other factors when trying to decide whether a statement is ironic or not. All of these factors have been shown to undergo altered processing in schizophrenia, and aberrant activation of various brain regions has been confirmed in functional imaging studies in connection with most of these factors in patients with schizophrenia. Thus, it is obvious that our study represents only the beginning in this investigation, and future research must clarify how these other factors interrelate with schizophrenic psychopathology during irony appreciation.

Supporting Information

Figure S1 Group comparison between healthy controls and schizophrenia for ironic sentences>visual baseline. Slice view. p<0.001, ext. 5 voxels. Controls>schizophrenia activation is marked red, Strongest maxima in the posterior part of the anterior cingulate (ACC) and the LH anterior insula. Schizophrenia>controls is marked blue, strongest activation is in the LH parahippocampal gyrus. (PSD)

Table S1 Correlation analysis between fMRI signal during irony comprehension and schizotypal personality traits. Correlations are shown across all study participants independent of diagnosis. p<0.001, ext. 5 voxels. Table shows correlations with “interpersonal” and “cognitive perceptual” subscales of the schizotypal personality questionnaire, German version [67]. A negative correlation indicates that the higher the degree of psychometric schizotypy, the lower is the BOLD response. Total score of the schizotypal personality questionnaire showed negative correlation in the posterior medial prefrontal cortex (MNI 3 18 33, z = 3,34, extent 5 vox) for reading ironic sentences>visual baseline, all other correlations were not significant. (DOC)

Author Contributions

Conceived and designed the experiments: AMR KL DEM BW ME. Performed the experiments: AMR KL DEM ME. Analyzed the data: AMR KL DEM ME. Contributed reagents/materials/analysis tools: ME. Wrote the paper: AMR KL DEM SK BW ME.

References

1. Gibbs RWJ (2000) Irony in talk among friends. Metaphor and Symbol 15: 5–27.
2. Whalen JM, Pexman PM, Gill AJ, Nowson S (2012) Verbal irony use in personal blogs. Behav Inf Technol: 1–12.
3. Whalen JM PP, Alastair JG (2009) ’’Should Be Fun Not!’’: Incidence and Marking of Nonliterator Language in E-mail. Journal of Language and Social Psychology 28: 263–290.
4. Pexman PM (2008) It’s fascinating research: The cognition of verbal irony. Current Directions in Psychological Science 17: 296–299.
5. Giora R (2001) Irony and its discontents. In: Bich E, Steen,G, Schram, D., eds. The Psychology & Sociology of Literature. Amsterdam: John Benjamins.
6. Harris M, Pexman PM (2003) Children’s perceptions of the social functions of verbal irony. Discourse Processes 36: 147–165.
7. Kreuz R, Long D, Church M (1991) On being ironic: Pragmatic and mnemonic implications. Metaphor and Symbolic Activity 6: 149–162.
8. Gibbs RWJ, Colston HL (2012) Interpreting figurative meaning. Cambridge, New York, Melbourne, Madrid: Cambridge University Press.
9. Herold R, Tenyi V, Lenard K, Trider M (2002) Theory of mind deficit in people with schizophrenia during remission. Psychological Medicine 32: 1125–1129.
10. Landgen R, Coltheart M, Ward PB, Cats SV (2002) Disturbed communica-
tion in schizophrenia: the role of poor pragmatics and poor mind-reading. Psychological Medicine 32: 1273–1284.
11. Kosmidis MH, Arvoudi E, Boukas VP, Giannakou M, Ioannides P (2008) Studying social cognition in patients with schizophrenia and patients with frontotemporal dementia: theory of mind and the perception of sarcasm. Behavioural neurology 19: 65–69.
12. Mo S, Su Y, Chan RC, Lui J (2008) Comprehension of metaphor and irony in schizophrenia during remission: the role of theory of mind and IQ. Psychiatry Research 157: 21–29.
13. Sparks A, McDonald S, Lino B, O’Donnell M, Green MJ (2010) Social cognition, empathy and functional outcome in schizophrenia. Schizophrenia Research 122: 172–179.
14. Ziv I, Leiser D, Levine J (2011) Social cognition in schizophrenia: cognitive and affective factors. Cognitive Neuropsychiatry 16: 71–91.
15. Champagne-Lavau M, Charast E, Anselmo K, Rodriguez JP, Blouin G (2012) Theory of mind and context processing in schizophrenia: the role of cognitive flexibility. Psychiatry Research 206: 184–192.
16. Hereser MM (2009) Sind konkretnische Denkstorungen eine homogene Entität? Untersuchungen zum Verständnis nicht-würdlicher Sprache bei schizophrenen Patienten. [thesis]. Tuebingen, Germany: University of Tuebingen. http://nbn-resolving.de/urn:nbn:de:bsz:21-opus-40670.
17. Channon S, Rule A, Maudgal D, Martins M, Pellige A, et al. (2007) Interpretation of mentalistic actions and sarcastic remarks: Effects of frontal and posterior lesions on mentalising. Neuropsychologia 45: 1723–1734.
18. Giora R, Zaidel E, Soroker N, Batori G, Kasher A (2000) Differential effects of right- and left-hemisphere damage on understanding sarcasm and metaphor. Metaphor and Symbol 1: 63–83.
19. Rapp AM, Mutscherl DE, Wild B, Erb M, Lengfeld I, et al. (2010) Neural correlates of irony comprehension: the role of schizotypal personality traits. Brain and Language 115: 1–12.
20. Rapp AM, Mutscherl DE, Erb M (2012) Where in the brain is nonliteral language? A coordinate-based meta-analysis of functional magnetic resonance imaging studies. Neuroimage 63: 600–610.
21. Winner E, Brownell H, Happe F, Blam A, Pincus D (1998) Distinguishing lies from jokes: Theory of mind deficits and discourse interpretation in right hemisphere brain-damaged patients. Brain and Language 62: 89–106.
22. Zaidel E, Kasher A, Soroker N, Batori G (2002) Effects of right and left hemisphere damage on performance of the “right hemisphere communication battery”. Brain and Language 80: 510–535.
23. Mitchell KL, Crosw T (2005) Right hemisphere language functions and schizophrenia: the forgotten hemisphere? Brain 129: 963–978.
24. Rapp AM (2009) The role of the right hemisphere for language in schizophrenia. In: Sommer IE, Kahn RS, editors. Language Lateralization and Psychosis. Cambridge: Cambridge University Press. 147–156.
25. Mehta UM, Basar-EE, RR, Tharillall J, Gangasohan BN (2012) Mirror neuron dysfunction-a neuro-marker for social cognition deficits in drug naive schizophrenia. Schizophrenia Research 141: 281–283.
26. Leube D, Straube B, Green A, Blumel I, Prinz S, et al. (2012): A possible brain network for representation of cooperative behavior and its implications for the psychopathology of schizophrenia. Neuropsychopharmacology 66: 24–32.
27. Salvatore G, Lyasker PH, Popolo R, Proacci M, Carcione A, et al. (2012) Vulnerable self, poor understanding of others’ minds, threat anticipation and cognitive biases as triggers for delusional experience in schizophrenia: a theoretical model. Clin Psychol Psychother 19: 247–259.
28. Whiffen-Gabriel S, Themerson HV, Milánov S, Tsuang MT, Farkone SV, et al. (2009) Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci U S A 106: 1279–1284.
29. Whiffen-Gabriel S, Ford JG (2012) Default mode network activity and connectivity in psychopathology. Amnu Rev Clin Psychol 8: 49–76.
58. Siever LJ, Davis KL (2004) The pathophysiology of schizophrenia disorders: A lesson study. Neuropsychology 45: 167–180.

59. Meshal N, Vishne T, Laor N, Tzite D (2013) Enhanced left frontal involvement during novel metaphor comprehension in schizophrenia: evidence from functional neuroimaging. Brain and Language 124: 64–74.

60. Golich NL, Wang AT, Rudiea JD, Hernandez LM, Beckerliner SY, et al. (2013) Antipsychotic neural processing of ironic and sincere remarks in children and adolescents with autism spectrum disorders. Metaphor & Symbol 27: 70–92.

61. Lehr S, Treibig G, Fischer B (1995) Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurol Scand 91: 229–235.

62. Andreasen NC, Persller M, Nopoulos P, Miller D, Ho BC (2010) Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biological Psychiatry 67: 255–262.

63. Klein C, Andreasen R, Jahn T (1997) Erfassung der schizophrenen Persönlichkeit nach DSM-III-R: Psychometrische Eigenschaften einer autoritierenden deutschsprachigen Übersetzung des “schizotypal personality questionnaire” (SPQ) von Raine: Diagnostica 34: 347–369.

64. Wang AT, Lee SS, Sigmun M, Dagetto M (2006) Developmental changes in the neural basis of interpreting communicative intent. Social cognitive and affective neuroscience 1: 107–121.

65. Raine A (2003) The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophrenia Bulletin 17: 555–564.

66. Cochrane M, Petch I, Pickering AD (2012) Aspects of cognitive functioning in schizotypy and schizophrenia: evidence for a continuum model. Psychiatry Research 196: 230–234.

67. Lenzenweger M (2011) Schizotypy and schizophrenia. New York: Guilford Press.

68. Nelson MT, Seal ML, Pantels C, Phillips LJ (2013) Evidence of a dimensional relationship between schizotypy and schizophrenia: A systematic review. Neuroscience and Biobehavioral Reviews 37: 317–327.

69. Andreasen NC (1986) Scale for the Assessment of Positive Symptoms (SAPS). Iowa city: University of Iowa.

70. Andreasen NC (1982) Negative symptoms in schizophrenia. Definition and reliability. Archives of General Psychiatry 39: 709–724.

71. Wechsler S (1981) Wechsler Adult Intelligence Scale - Revised WAIS-R. UK: London: The Psychological Corporation.

72. Trives U (1994) Habeve-R: Hamburg-Wechsler Intelligenztest fu¨r Erwachsene, Revision 1991. Go¨ttingen, Hoger.

73. Kay SR, Fishein A, Olper LA (1987) The positive and negative syndrome scale (PANSS). Schizophrenia Bulletin 13: 261–276.

74. Dillmann J (2005) Priming as a kognitive Vulneribilitätsmarker bei Personen mit Schizotypie und Bas-Faktor- und clusteranalytisch ermittelten multidimensionalen Merkmalen. [Thesis]. Jena: University of Jena.

75. Klein C, Andreasen R, Jahn T (2001) Konstruktualisierung der deutschsprachigen Adaptation des Schizotypality Questionnaires (SPQ) von Raine (1991). In: Andreasen R, Mail R, editors. Schizotypie: Psychometrische Entwicklungen und biopsychologische Forschungsansätze. Go¨ttingen: Hogrefe. 349–378.

76. Langdon R, Colheam M (2004) Recognition of metaphor and irony in young adults: the impact of schizotypal personality traits. Psychiatry Res 125: 9–20.

77. Binder JR, Desai RH, Graves WW, Conant LL (2009) Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 19: 2767–2796.

78. Delisi LL (2004) Speech comprehension in schizophrenia: review of the literature and the new study of the relation to uniquely human capacity for language. Schizophrenia Bulletin 27: 481–496.

79. Salvador G, Dimaggio G, Lysaker PH (2007) An intersubjective perspective on negative symptoms of schizophrenia: implications of simulation theory. Cognitive Neuropsychiatry 12: 144–164.

80. Keysers C, Gazzola V (2009) Expanding the mirror: vicarious activity for actions, emotions, and sensations. Current Opinion in Neurobiology 19: 666–671.

81. Amoldio DM, Frith C.D. (2006) Meeting of minds: the medial frontal cortex and social cognition. Nature Reviews Neuroscience 7: 268–277.

82. Denny BT, Kober H, Wager TD, Ochsner KN (2012) A meta-analysis of functional neuroimaging studies of self and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. Journal of Cognitive Neuroscience 24: 1742–1752.

83. Papagno C, Romero-Lauro LJ (2010) The neural basis of idiom processing: implications of simulation theory. Cognitive Neuropsychiatry 13: 380–345.

84. Streter P, Kleinschmidt A (2010) Anterior insula activations in perceptual paradigms: often observed but barely understood. Brain Stuct Funct 214: 611–622.
9. Spotorno N, Koun E, Prado J, Van Der Henst JB, Noveck IA (2012) Neural evidence that utterance-processing entails mentalizing: the case of irony. Neuroimage 63: 25–39.

10. Rankin KP, Salazar A, Gorno-Tempini ML, Sollberger M, Wilson SM, et al. (2009) Detecting sarcasm from paralinguistic cues: anatomic and cognitive correlates in neurodegenerative disease. Neuroimage 47: 2005–2015.

11. Shibata M, Toyomura A, Itoh H, Abe J (2010) Neural substrates of irony comprehension: A functional MRI study. Brain Research 1308: 114–123.

12. Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. (2008) The anatomy of first-frame and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. American Journal of Psychiatry 165: 1015–1023.

13. Russell TA, Rubia K, Bullmore ET, Soni W, Sackling J, et al. (2006) Exploring the social brain in schizophrenia: left prefrontal underactivation during mental state attribution. American Journal of Psychiatry 157: 2040–2042.

14. Grosselin A, Royer A, Schneider FC, Brouillet D, Martin S, et al. (2010) Inhibition des réponses automatiques au test du Hayling dans la schizophrénie. Encephale 36: 277–284.

15. Diana RA, Yonelinas AP, Ranganath C (2007) Imaging recollection and familiarity in the medial temporal lobe: a three-component model. Trends Cogn Sci 11: 379–386.

16. Behrendt RP (2010) Contribution of hippocampal region CA3 to consciousness and schizophrenic hallucinations. Neurosci Biobehav Rev 34: 1121–1136.

17. Diederen KM, Neggers SF, Daalman K, Blom JD, Goekoop R, et al. (2010) Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. American Journal of Psychiatry 167: 427–435.

18. Sommer IE, Clos M, Meijering AL, Diederen KM, Eckhoff SB (2012) Resting state functional connectivity in patients with chronic hallucinations. PLoS One 7: e43516.

19. Jardri R, Pouchet A, Pans D, Thomas P (2011) Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. American Journal of Psychiatry 168: 73–81.

20. Canni T, Sivers H, Whitefield SL, Godih IH, Gabrieli JD. (2002) Amygdala response to happy faces as a function of extraversion. Science 296 (5576): 2191–2193.

21. Kumari V, Floythe D, Williams S, Gray J (2004) Personality predicts brain responses to cognitive demands. Journal of Neuroscience 24: 10636–10641.

22. Rapp AM, Wild B, Erb M, Rodden FA, Ruch W, et al. (2008) Trait cheerfulness modulates bold response in lateral cortical but not limbic brain areas – a pilot fMRI study. Neuroscience letters 445: 242–245.

23. Varga E, Hajnal A, Schnell Z, Orsi G, Tényi T, et al. (2010) Exploration of irony appreciation in schizophrenia: a functional MRI study. European Psychiatry 25: 1572.

24. Shumay-Toosey SG, Tibi-Elhanany Y, Aharon-Peretz J (2006) The ventromedial prefrontal cortex is involved in understanding affective but not cognitive theory of mind stories. Social Neuroscience 1: 149–166.

25. Colston HL, Lee SY (2004) Gender Differences in Verbal Irony Use. Metaphor & Symbol 19: 209–306.

26. Ivusko SL, Pexman PM, Olineck KM (2004) How sarcastic are you? Individual differences and verbal irony. Journal of Language and Social Psychology 23: 244–271.

27. Reynolds CA, Raine A, Mellingen K, Venables PH, Mednick SA (2000) Three factor model of schizotypal personality: invariance across culture, gender, religious affiliation, family adversity, and psychopathology. Schizophrenia Bulletin 26: 603–618.

28. Sommer IE, Ramsey NF, Mandl RC, Kahn RS (2003) Language lateralization in female patients with schizophrenia: an fMRI study. Schizophr Res 60: 163–190.

29. Schofield K, Mohr C (2013) Schizotypy and hemispheric asymmetry: results from two Chapman scales, The O-Life questionnaire, and two laterality measures. Laterality DOI: 10.1080/1357650X.2013.789813.

30. Dimaggio G, Popolo R, Salvatore G, Lysaker PH (2013) Mentalizing in schizophrenia is more than just solving theory of mind tasks. Front Psychol 4. doi: 10.3389/fpsyg.2013.00883.

31. Rapp AM, Wild B (2011) Nonliteral language in Alzheimer dementia: a review. J Int Neuropsychol Soc 17: 207–218.