



Neural basis of altered physical and social causality judgements in schizophrenia



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ABSTRACT

Patients with schizophrenia (SZ) often make aberrant cause and effect inferences in non-social and social situations. Likewise, patients may perceive cause-and-effect relationships abnormally as a result of an alteration in the physiology of perception. The neural basis for dysfunctions in causality judgements in the context of both physical motion and social motion is unknown. The current study used functional magnetic resonance imaging (fMRI) to investigate a group of patients with SZ and a group of control subjects performing judgements of causality on animated collision sequences (launch-events, Michotte, 1963) and comparable “social” motion stimuli. In both types of animations, similar motion trajectories of the affected object were configured, using parametrical variations of space (angle deviation) and time (delay).

At the behavioural level, SZ patients made more physical and less social causal judgements than control subjects, and their judgements were less influenced by motion attributes (angle/time delay). In the patients group, fMRI revealed greater BOLD-responses, during both physical and social causality judgements (group × task interaction), in the left inferior frontal gyrus (LIFG). Across conditions (main effect), LIFG-interconnectivity with bilateral occipital cortex was reduced in the patient group.

This study provides the first insight into the neural correlates of altered causal judgements in SZ. Patients with SZ tended to over-estimate physical and under-estimate social causality. In both physical and social contexts, patients are influenced less by motion parameters (space and time) than control subjects. Imaging findings of LIFG-disconnectivity and task-related hyper-activation in the patient group could indicate common dysfunctions in the neural activations needed to integrate external cue-information (space/time) with explicit (top-down) cause–effect judgements of object motions in physical and social settings.

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1. Introduction

Patients with schizophrenia (SZ) often have aberrant views of causality, observed in delusional ideation or in ideas of reference. At the level of cognition, deviant causal inferences occur in biased (Moritz and Woodward, 2005) and impaired reasoning (Kruck et al., 2011), as well as altered inferences about other people's mental states and social interactions (Horan et al., 2009; Herrington et al., 2011). At the level of perception, psychotic patients might also experience cause and effect differently: for instance, positive symptoms of psychosis (delusions) are associated with increased impressions of physical causality in visual events (Tschacher and Kupper, 2006).

Whether abnormal cognitive and perceptual processing contributing to causal inferences in SZ have a common basis is not known. Some

suggest that disturbed interactions of bottom–up sensory processing and top–down attribution (of priors, or beliefs, see e.g. Corlett et al., 2009; Fletcher and Frith, 2009) might be the common basis for psychotic symptoms (Hemsley and Garety, 1986; Grossberg, 2000; Young, 2008). Particularly, impaired beliefs (e.g. delusions) and perceptions (e.g. hallucinations) about causal relations (Corlett et al., 2006; Corlett et al., 2007) could reflect disturbed integration of relevant stimulus information (Corlett et al., 2011).

The most direct cause–effect perception arises from a physical collision, also known as a launching event (Michotte, 1963). Launching stimuli are simple animations that typically show one geometric object, e.g. a billiard-like ball, moving towards and making contact with another object which then moves on. Observers have the impression of a collision, i.e. a causal relation between the objects; i.e. A caused B to move (Scholl and Tremoulet, 2000; Scholl and Nakayama, 2002).

Similarly, the impression of a social interaction can be induced by simple moving objects, which are perceived as animate (Heider and Simmel, 1944; Blos et al., 2012). This attribution of animacy is peculiar

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to social as opposed to physical causal events (Schlottmann et al., 2006). To be interacting socially, traits of living entities like intentions must be attributed to objects; a social cognitive process referred to as mentalizing (Tremoulet and Feldman, 2006).

Stimulus motion attributes in time and space are relevant to the impressions of cause and effect in both physical and social events. In physical events, spatial and temporal violations of motion contingencies lead to more non-causal judgements of launching events (Young et al., 2005; Young and Falmier, 2008). By contrast, in social events, the same violations of motion produce more causal responses (Scholl and Tremoulet, 2000; Falmier and Young, 2008; Blos et al., 2012).

Initial behavioural research suggests, that patients with delusions tend to make different judgements of causality compared to healthy subjects in both physical (Blakemore et al., 2003; Tschacher and Kupper, 2006) and social motion events (Blakemore et al., 2003). Other perceptual deficits in “Gestalt”-domains (e.g. in perceptual grouping; see Silverstein et al., 2000) are related to disorganization symptoms in psychosis (Uhlhaas and Silverstein, 2005). These altered “Gestalt”-perceptions in SZ could reflect general dysfunctions in perceptual organisation needed to integrate stimulus-attributes, i.e. motion parameters (Tschacher and Kupper, 2006). Whether SZ patients have trouble integrating spatio-temporal parameters when judging causality in physical and social motion contexts is not known.

The neural mechanisms of cause–effect inferences are still under investigation. Evidence from brain lesion studies and neuroimaging suggests a distinction between automatic causality perception and cognitive inference (Blakemore et al., 2001; Fonlupt, 2003; Fugelsang et al., 2005; Roser et al., 2005). Recently, our group conducted a set of functional magnetic resonance imaging (fMRI) studies using healthy volunteers as participants, to investigate the neural correlates of causal judgements on simple motion stimuli in physical and social contexts (Blos et al., 2012; Wende et al., 2013). Causality judgements, as compared to judgements of movement direction, engaged a fronto-parietal network (Wende et al., 2013). Similar patterns of neural activity have been associated with explicit (top–down) inferences about visual–spatial (“perceptual”) attributes during reasoning (Kranjec et al., 2012; Straube et al., 2011).

Previous psychophysiological research indicates that SZ patients may have altered experiences of launching events (Adams et al., 2012), but the neural basis of these observations remains unclear. Inference tasks used to investigate reasoning engage bilateral middle/inferior frontal cortex regions (Goel and Dolan, 2004; Goel, 2007; Rodriguez-Moreno and Hirsch, 2009; Prado et al., 2011; Watson and Chatterjee, 2012). In psychosis, frontal/prefrontal cortex dysfunction could be a common neural basis underlying inference deficits on external social (Lee et al., 2004) and visual–spatial information (Lee et al., 2008). A similar proposal comes from interactionist (“Bayesian”) models of psychosis (Fletcher and Frith, 2009) and model psychosis studies (i.e. studies, in which healthy volunteers are induced with psychotic symptoms using psychoactive drugs like ketamine to investigate underlying neural mechanisms, see e.g. Corlett et al., 2009). This line of research links the formation of altered “heuristics”, i.e. delusional beliefs, to abnormal neural responses in frontal cortices (Corlett et al., 2006). Abnormal frontal response patterns are directly related to psychotic patients’ deficits in making predictive inferences (Corlett et al., 2007).

More recent imaging work associates increased neural activity in SZ patients in inferior and middle frontal brain regions, in response to impaired social inferences in visual events (Pedersen et al., 2012). Impaired social (biological) motion perceptions might reflect similar dysfunctions in integration of external visuo–spatial motion parameters to higher–order cognitive domains (Kim et al., 2005). Indeed, recent imaging evidence indicates a reduced functional connection of the frontal lobe (central to cognitive functions) and posterior cortex regions (relevant for stimulus–information processing) in psychosis (Pettersson-Yeo et al., 2011; Straube et al., 2014). Stimulus–motion attributes (space/time) provide a crucial basis for “Gestalt”-perceptions

of causality, thus dysfunctions in the perceptual integration of those parameters could provoke altered judgement behaviour (Tschacher and Kupper, 2006). However, the specific effects on causality judgements based on spatial and temporal stimulus motion characteristics are not known. We are not aware of any imaging study that has investigated the judgements of physical and social causality in patients with SZ. In the context of deviant physical/social causal inferences in psychosis, it would be particularly interesting to assess patients’ neural correlates in causal judgements about collisions (Michotte, 1963) and comparable social motion stimuli.

In the present study, patients and control subjects were monitored in fMRI while judging causal relationships (causal/non-causal) in contrast to movement direction (left/right, control task) of abstract moving objects. Animations were configured using equally varied spatiotemporal motion parameters (angle/time delay) for physical (collisions) and social (no collisions) contexts.

We aimed to investigate the common and distinct neural correlates of causal judgements (task effect) and context (social/physical) for patients with SZ and healthy control subjects.

Behaviourally, we expected that patients’ responses would deviate from control subjects regarding the use of spatial and temporal information for their judgements, reflecting perceptual or inferential impairments of SZ patients, e.g. biases (Tschacher and Kupper, 2006).

At the neural level, we expected causality judgements to evoke common neural activity in both groups (task effect) in frontal and parietal cortex regions, a neural network confirmed to be active in tasks involving causal inferences (Kranjec et al., 2012; Watson and Chatterjee, 2012) and causality judgements (Fugelsang et al., 2005; Wende et al., 2013).

We further expected altered neural responses in the patient group located in bilateral middle/inferior frontal cortex regions associated with inferences and reasoning (Goel and Dolan, 2004; Goel, 2007; Rodriguez-Moreno and Hirsch, 2009; Prado et al., 2011; Watson and Chatterjee, 2012). Possibly, causality judgements would result in over-activation of frontal brain regions in the patient group, as recently shown for social contexts (Pedersen et al., 2012).

We additionally hypothesized reduced connections of frontal and posterior brain regions to reflect dysfunctions indicated by behavioural deviance regarding the use of motion parameters (space/time) for causal judgements in the patient group; particularly, integration of sensory information with cognitive processes (Pettersson-Yeo et al., 2011; Zalesky et al., 2011; Straube et al., 2014).

2. Methods

2.1. Subjects

Eighteen patients with schizophrenia or schizoaffective disorder and a group of eighteen control subjects (HC) matched for gender, age (SZ/HC = 35.56/34.22 years, SD = 13.48/11.09, $t = 0.32$, $p = .71$) and years of education (SZ/HC = 10.17/10.94 years, SD = 1.34/1.11, $t = -1.90$, $p = .07$), were included in the study. All patients were on stable doses of medication and none of them had acute symptoms at time of study (Andreasen et al., 2010). One patient who was diagnosed with schizotypic disorder (F21.0) was excluded from the analysis. One patient diagnosed with schizoaffective disorder (F25.2) was included as effects of interest (symptoms) are similar in both diagnoses. The exact doses of medication for two patients and the SAPS/SANS scores of one patient were missing. ICD10-diagnoses were confirmed by two independent clinical interviews with trained clinicians ($n = 16$ paranoid schizophrenia (F20.0), $n = 1$ hebephrenic schizophrenia (F20.1), and $n = 1$ schizoaffective disorder (F25.2), see Table 1). Patients were recruited at the Department of Psychiatry and Psychotherapy at the Philipps-University Marburg and SAPS and SANS ratings were used to assess their symptoms. Healthy controls were recruited via postings at the Philipps-University Marburg. All subjects had normal or corrected-

Table 1
Demographic and clinical details of the participants. Means, standard deviation and range.

| Variable | Healthy controls (HC) | | Patients with schizophrenia (SZ) | |
|---|-----------------------|-------|----------------------------------|---------------|
| | M (SD) | Range | M (SD) | Range |
| Age | 34.22 (11.09) | 20–59 | 35.56 (13.48) | 18–60 |
| Male/female ratio | 16/2 | | 16/2 | |
| Years of education | 10.94 (1.11) | 9–13 | 10.17 (1.34) | 8–13 |
| Medication (chlorpromazine equivalent dosage, mg/d) | | | 459.35 (239.48) | 131.35–801.17 |
| SAPS sum score | | | 17.05 (14.95) | 0–45 |
| SAPS global score | | | 3.18 (2.83) | 0–9 |
| SANS sum score | | | 25.82 (19.30) | 2–73 |
| SANS global score | | | 6.06 (4.67) | 0–16 |

to-normal vision, gave written informed consent and were paid 30 € for their participation. The local ethics committee had approved the study (ethic proposal No. 37/10).

2.2. Tasks, stimuli, procedure

Participants were presented videos of simple moving objects. The movements either consisted of colliding (launching) shapes introduced as “billard-balls” (physical condition) or non-colliding similar round shapes introduced as people (“Mr.Blue”/“Mrs.Red”, social condition).

Both types of videos were designed with similar stimulus-motion configurations, varying the trajectory of the affected object using different angle deviations (0, 7.5, 30, 60° with respect to the initial horizontal trajectory) and time delays (0, 33, 133, 267 ms with respect to the physical collision or potential social interaction 1 s after video-onset).

Subjects judged these videos for causality (yes/no) and movement direction (left/right; control task) by button presses on an MRI-compatible response device. Alternating blocks of conditions, each including 8 video stimuli, were presented in counterbalanced orders, using each possible video configuration for physical/social causality (PC/SC) and direction judgement (PD/SD) tasks (128 videos in total). Stimuli and procedure are depicted in Fig. 1 and further described in detail in Wende et al. (2013).

2.3. Behavioural data analysis

Causality judgements were analysed using generalized estimating equations (GEE) implemented in the SPSS 21 for Windows software package (see Straube et al., 2011). In order to account for correlations among repeated measures over time, an AR (1) working correlation

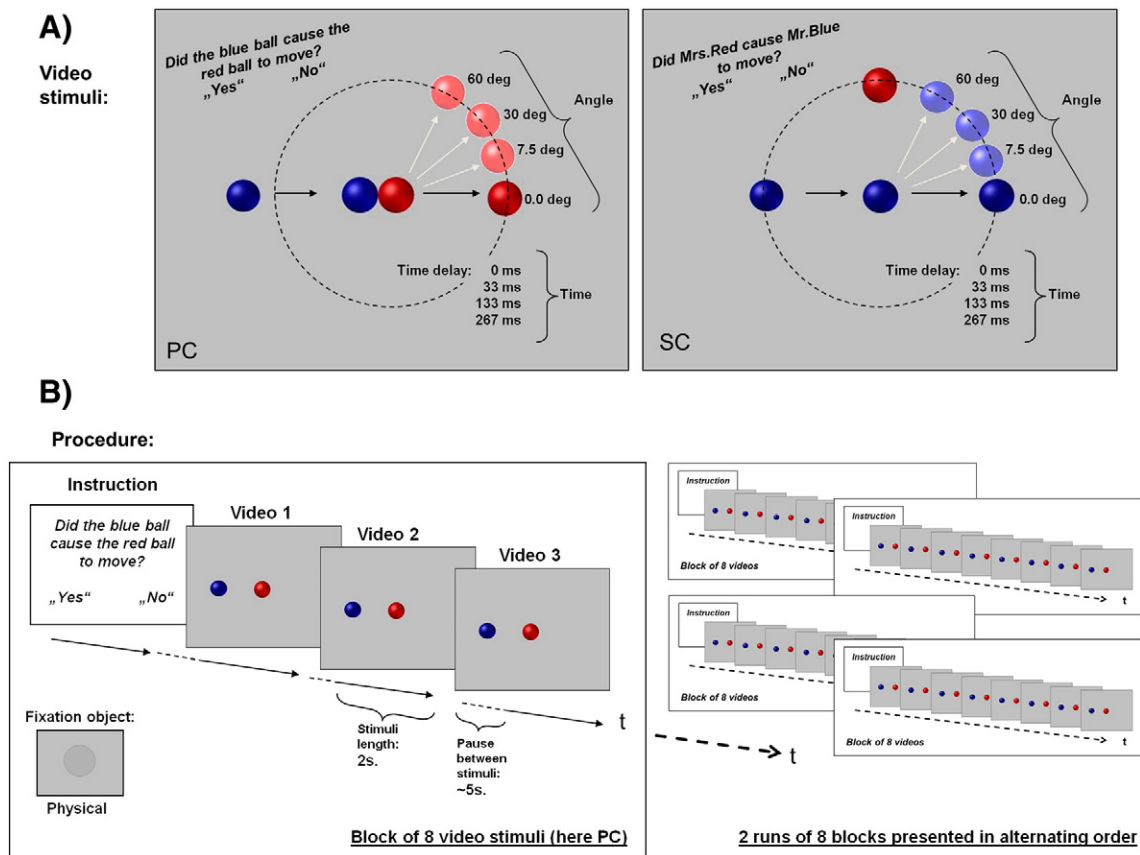


Fig. 1. Stimuli and procedure. Video animations of a blue ball launching (P: physical, left) or passing a red ball (S: social, right; in the latter, balls were referred to as persons “Mrs.Red/Mr.Blue”). Subjects judged both stimulus types for causality (experimental task; PC/SC) and movement direction (control task; PD/SD). Movement parameters (angle deviation/time delay) were varied equally in both stimulus types. Two runs of eight condition blocks (2 * PC, 2 * SC, 2 * PD, 2 * SD, presented in alternating, pseudo-randomized order) were included in the fMRI experiment. Between blocks, a pause of 10 s (# sign), was followed by the presentation of the written instruction for the next block (for 6 s). Different fixation objects were used to avoid confusion about the experimental condition.

structure and robust (sandwich) covariance estimators were used for the regression coefficients. Repetition index (trial number) was included in the model as additional predictor.

The logit link function and binomial variance function were specified for dichotomous variables (causality response: yes/no). As task-related group differences (C/D) were of interest, as well as the differential effects of angle and time on causality responses with regard to the context (SC/PC), the main coefficients of interest were the interaction effects of group * task and group * task * stimulus, as well as the interactions of group * task * stimulus * angle and group * task * stimulus * time. A sequential Bonferroni adjustment was applied to maintain the familywise error rate associated with testing multiple outcomes.

2.4. fMRI data acquisition and analysis

MRI scans were performed on a 3 T MR Magnetom Trio Tim scanner (Siemens). Imaging data were analysed using SPM8. For detailed descriptions of data acquisition and preprocessing steps see Wende et al. (2013).

2.4.1. First level analysis

For the activity analysis, each video was modelled as one event (onsets were set of 1.5 s after video onset, see Blos et al., 2012; Wende et al., 2013). BOLD-responses were measured for the four conditions of interest (PC; SC; PD; SD, each condition including 32 trials in total). Instruction blocks were modelled as a separate condition of no interest to correct for possible effects of reading. Motion parameters of each subject were implemented as regressors to correct for head motion during scanning. Baseline-contrasts (active conditions in contrast to rest: fixation cross and objects) were performed for each single condition (PC, SC, PD, SD) to assess neural responses during each condition.

2.4.2. Second level analysis

A random effects analysis (flexible factorial analysis) was conducted at the group level. The four baseline-contrast images (one per condition) from each subject (18 per group) were included, and three factors were defined (subject, group: SZ/HC and condition: PC, SC, PD, SD). In the group model, the main effect of subject was calculated, as well as the interaction of group * condition (8 regressors: PC, SC, PD, SD in SZ and HC, respectively). Mean reaction times were entered as covariate into the analysis to control for confounding effects. Medication doses (when modelled as an additional control covariate) did not affect the results. Statistical analyses were performed at a threshold of $p < 0.001$. For group differences in neural activity, all reported clusters are significant under a cluster-level FWE-threshold of $p < 0.05$.

2.4.3. Contrasts of interest

A group conjunction of task effects was performed ($SZ(PC,SC > PD,SD) \cap HC(PC,SC > PD,SD)$) to assess common neural networks for causality judgements. To assess group differences in task-related neural activity, the main interaction contrast ($SZ(PC,SC > PD,SD)$ vs. $HC(PC,SC > PD,SD)$) was performed. In addition, the interaction contrasts were performed for the social context ($SZ(SC > SD)$ vs. $HC(SC > SD)$), to reveal specific effects of the social context on neural activity in patients vs. controls.

2.4.4. Functional connectivity (PPI) analysis

An additional psychophysiological interaction (PPI) analysis was then performed to test for group differences in functional connectivity (i.e. correlational neural activity) of the inferior frontal gyrus, IFG. A region of interest (ROI) of 209 voxels in the LIFG served as the seed region for the PPI. The ROI was located in the main cluster of increased task-related activation found in the patient group (see below). For the PPI, the condition blocks (PC, SC, PD, SD; 22) were modelled at the first level. The first eigenvariate of BOLD-response within the ROI was extracted for each subject as cluster eigenvariate. It was used to calculate

the PPI-interaction terms (of which one per condition and run was calculated and entered in the first-level model, see e.g. O'Reilly et al., 2012 for a general description of the PPI procedure). At the first level, four t-contrasts were calculated on the respective PPI-terms (regressors) of each condition of interest, weighting condition (+) vs. rest (0) across sessions. These t-contrasts (one per single condition: PPI(PC), PPI(SC), PPI(PD), PPI(SD)) therefore assess condition-related changes in LIFG connectivity in each single subject.

At the group level, these four contrast images from each participant were entered in a flexible factorial model for a group t-contrast, to assess the effects of the single conditions on LIFG connectivity across subjects.

3. Results

3.1. Behavioural results

3.1.1. Causality responses

In total, 65% of trials were judged as causal by patients (controls: 61%). In the direction judgement task, both groups showed the same performance (SZ = 50%; HC = 50%). Generalized estimation equation analysis (GEE; SPSS 21, IBM Inc.) revealed a significant interaction effect of group (SZ/HC) * task(C/D) on causality response (yes/no; Wald-Chi-Square = 73.43; $df = 3$; $p < .001$).

Specifically in the physical context (PC), patients judged more trials as causal than controls (74% vs. 52%; $p < .001$), whereas in the social context; patients judged fewer trials as causal than controls (52% vs. 70%; $p < .001$). GEE analysis showed a significant interaction of group(SZ/HC) * task(C/D) * stimulus(S/P) on causality response (yes/no; Wald-Chi-Square = 79.82; $df = 4$; $p < 0.001$).

With respect to stimulus parameters (angle/time), as expected, higher aberrations were associated with increasing causal responses in social and fewer causal responses in the physical causality task in both groups. However, in the patient group, angle and time delay had less influence on causality responses (Wald-Chi-Square = 293.86; $df = 24$; $p < 0.001$ for interaction of angle * group * task * stimulus, and Wald-Chi-Square = 99.83; $df = 24$; $p < 0.001$ for interaction of time * group * task * stimulus, respectively) than in the control group, as revealed by GEE analysis (see supplements for post-hoc comparisons of all significant interactions).

At the group level, positive and negative symptom ratings did not correlate significantly with responses in the social condition, but there was a negative correlation between SANS scores and causality responses in the physical condition (Pearson's $r = -.51$, $p = .036$).

The groups did not differ in their mean reaction times (RT) in any condition or in responses to a questionnaire item assessing understanding and impression of the difficulty of the task. However, patients did rate task switches less easy to manage than controls (ratings in SZ/HC: 4.50/6.00, $p = 0.049$).

3.2. fMRI results

3.2.1. Common task effect ($SZ(PC,SC > PD,SD) \cap HC(PC,SC > PD,SD)$)

Overlaps in neural activity between patients and controls were found for causality, compared to direction judgements, predominantly in a right fronto-parietal-occipital network. Particularly, the right inferior frontal gyrus, inferior parietal lobule, as well as bilateral occipital cortical and cerebellar structures were involved in causal judgements in both groups (see Table 2).

3.2.2. Interaction of task and group ($SZ(PC,SC > PD,SD) > HC(PC,SC > PD,SD)$)

We found greater task-related (causality > direction) neural activation in patients, as compared to controls, mainly in the left inferior frontal gyrus (IFG; 488 voxels; MNI: $-42/24/20$, $T = 4.74$, $p < .05$ FWE cluster corrected). Post-hoc comparisons confirmed significant

Table 2

fMRI results. Clusters of common (group conjunction of main effects: $SZ(PC,SC > PD,SD) \cap HC(PC,SC > PD,SD)$) and differential (interaction of main effects: $SZ(PC,SC > PD,SD) > HC(PC,SC > PD,SD)$) task-related neural activity in patients with schizophrenia (SZ) and healthy controls (HC). Activation threshold $p < 0.001$. For group differences in neural activity, all reported clusters are significant under a cluster-level FWE-threshold of $p < 0.05^*$. BA = Brodman Area, H = Hemisphere, R = right, L = left, C = causality judgement, D = direction judgement, P = physical, S = social.

| Location | | Significance | | MNI coordinates | | | |
|---|---------------------------|--------------|------|-----------------|-----|-----|-----|
| H | Area (LocalMax) | BA | t | n.voxels | x | y | z |
| <i>Conjunction: SZ (C > D) \cap HC (C > D)</i> | | | | | | | |
| R | Inferior occipital gyrus/ | V3 | 4.07 | 593(*) | 30 | -86 | -12 |
| R | Lingual gyrus/ | 17 | 4.65 | | 12 | 90 | -4 |
| R | Fusiform gyrus | V4 | 3.84 | | 28 | -26 | -12 |
| L | Fusiform gyrus/ | V4 | 4.30 | 350 | -22 | -84 | -18 |
| L | Cerebellum | | 4.29 | | -14 | -80 | -30 |
| R | Inferior frontal gyrus/ | 44 | 4.22 | 336 | 50 | 12 | 22 |
| R | Middle frontal gyrus | 46 | 4.07 | | 46 | 24 | 34 |
| R | Inferior parietal lobule/ | 40 | 4.07 | 246 | 52 | 42 | 50 |
| R | Angular gyrus | 39 | 3.42 | | 56 | 50 | 38 |
| L | Middle occipital gyrus | 18 | 3.80 | 107 | -26 | -94 | 0 |
| R | Middle temporal gyrus | 21 | 4.08 | 88 | 56 | -46 | 0 |
| R | Insula | 13 | 3.78 | 61 | 32 | 24 | 4 |
| <i>Group + task interaction: SZ (PC,SC > PD,SD) > HC (PC,SC > PD,SD)</i> | | | | | | | |
| L | Inferior frontal gyrus | 44 | 4.74 | 488(*) | -42 | 24 | 20 |
| <i>Social context: group + task interaction: SZ (SC > SD) > HC (SC > SD)</i> | | | | | | | |
| L | Inferior frontal gyrus | 44 | 4.12 | 455(*) | -42 | 18 | 34 |

group differences in LIFG activation for causality judgements (see Supplementary Fig. 2). Other clusters of increased activity were found in frontal and temporal brain regions, but those were not FWE-significant at the cluster-level (see Fig. 2A). For the opposite interaction ($HC(PC,SC > PD,SD) > SZ(PC,SC > PD,SD)$), no significant activation clusters were found.

Overall, positive/negative symptom scores (SAPS/SANS sum scores) did not correlate significantly with neural activity in the left IFG. However, BOLD-response in the left IFG during causality judgements ($PC,SC > PD,SD$) did correlate positively with symptom scores for the positive formal thought disorders (FDS) subscale (Pearson's $r = .51$, $p = .032$), and negatively with symptom scores for hallucinations (Pearson's $r = -.52$, $p = .034$).

3.2.3. Social context: interaction of task and group ($SZ(SC > SD) > HC(SC > SD)$)

Only in the social context, causality judgements resulted in increased BOLD-response in the patient group in the left IFG (455 voxels; MNI: $-42/18/34$; $T = 4.12$; $p < 0.001$; $p < .05$ FWE cluster corrected, see Fig. 2B, Table 2).

Both clusters of increased neural activity for physical and social causality in the left IFG of the patient group overlapped to a significant degree (167 voxels and 132 voxels overlapping at MNI: $-36/22/50$ and MNI: $-42/24/20$, respectively). Plots of neural activity within this overlap during the respective conditions indicate that the effect of increased BOLD-response in patients for causality judgements was present in both physical and social, but was more robust in the social condition (see Fig. 2A/B and Table 2).

3.2.4. PPI results: differences in LIFG connectivity

In all conditions (PC, SC, PD, SD), and specifically during PC and SC, correlations of neural activity within the LIFG, as well as between the LIFG and bilateral occipital brain regions, were significantly stronger in controls than in patients (see Supplementary Table 1). For patients compared to controls, no brain region showed increased connectivity with the LIFG. No correlations of overall positive/negative symptoms with LIFG connectivity were found, but hallucinations correlated negatively with LIFG-intra-connectivity during causality judgement tasks ($PC,SC > PD,SD$; Pearson's $r = -.34$, $p = .031$). LIFG-connectivity

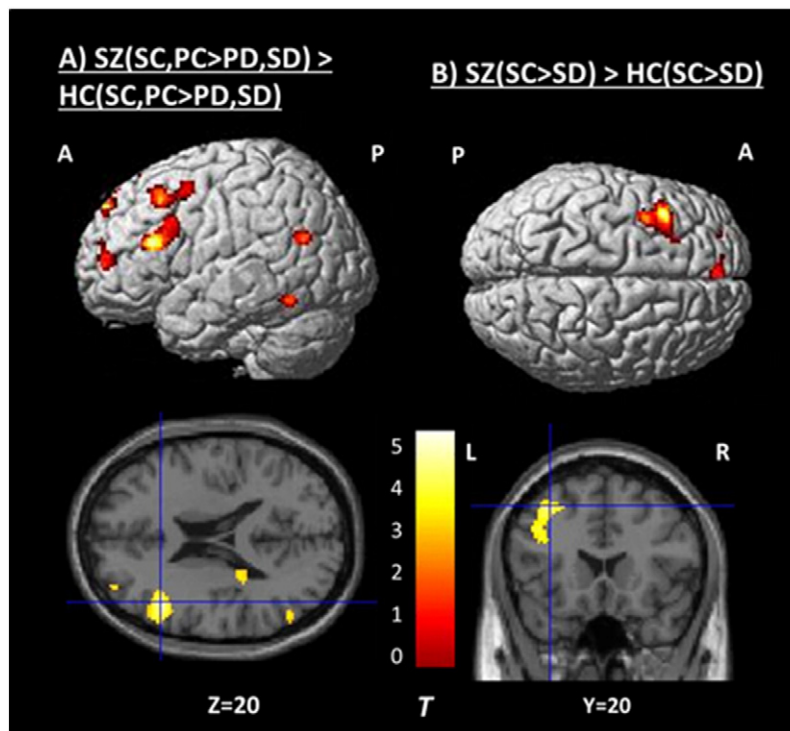


Fig. 2. Group differences (patients > controls) in task-related neural activity. A) For causality > direction judgements (interaction effect of ($SZ(PC,SC > PD,SD) > HC(PC,SC > PD,SD)$)). B) Specifically for the social causality condition (interaction effect of ($SZ(SC > SD) > HC(SC > SD)$)). Patients, compared to controls, showed increased neural activity in the left inferior frontal gyrus (LIFG). Threshold: $p < 0.001$, cluster-level FWE-corrected at $p < .05$. L = left; R = right; P = posterior; A = anterior. PC = physical causality; PD = physical direction; SC = social causality; SD = social direction. SZ = patient group; HC = healthy control group.

with left occipital areas further correlated positively with response behaviour for social judgements (Pearson's $r = .31$, $p = .008$).

4. Discussion

Inferring causal relations from visual cues is crucial for successful interactions with our physical and social environment. In this study we demonstrated the neural correlates of altered judgements of physical and social causality in patients with schizophrenia.

The findings, different behavioural response patterns and frontal hyper-activation in patients during judgements of physical and especially social causality, support the hypothesis that patients use cognitive strategies (e.g. interpretations/attributions, Crow, 2010) rather than objective stimulus motion-attributes (space/time, Tschacher and Kupper, 2006) to judge causality in visual events (Han et al., 2011; Kranjec et al., 2012). Patients' reduced sensitivity to space and time across contexts is in line with the hypothesis of a common dysfunction in integrating sensory input (stimulus motion parameters) to cognitive mechanisms (task induced) in physical and social causality judgements. Such disruptions of integration might be reflected in a general disconnection of LIFG to bilateral posterior/occipital brain regions processing visual (Blakemore et al., 2001; Fonlupt, 2003; Badler et al., 2010) and spatial event attributes (Straube and Chatterjee, 2010; Straube et al., 2011; Blos et al., 2012).

4.1. Aberrant causal judgements in patients: reduced cue relevance

Patients made more causal judgements in the physical and fewer causal judgements in the social condition, as compared to controls. These behavioural differences correspond with findings of impaired causal inferences in SZ in other cognitive domains, e.g. reasoning biases (see e.g., Kruck et al., 2011), and mental state-inferences (see e.g., Horan et al., 2009). The current results extend this body of evidence to the domain of causal judgements on motion events, indicating similar inference biases for physical/social events in SZ.

Behavioural findings further showed that patients with schizophrenia differ from controls regarding the use of perceptual cues to judge causality: stimulus characteristics contribute to patients' causal responses in the same direction as in controls, but the effect was less pronounced (i.e., patients were more liberal in judging physical causality and more conservative in judging social causality), indicating that the relevance of external parameters (space and time) for causality judgements is reduced in SZ patients in specific ways.

4.2. Frontal hyper-activation in patients during causality judgements

Both groups showed common task-related fronto-parietal/occipital activity. This observation is in line with previous fMRI studies using similar paradigms (Straube and Chatterjee, 2010; Straube et al., 2011; Wende et al., 2013) reflecting the interaction of cognitive and perceptual mechanisms when making inferences on visual stimuli (Kranjec et al., 2012; Watson and Chatterjee, 2012).

Additionally, patients show increased left inferior frontal activity during causality judgements. The frontal cortex and specifically the left IFG, play a crucial role in reasoning and inference (Prado et al., 2011; Watson and Chatterjee, 2012). Increased LIFG-response corresponds with the assumption that patients make more use of cognitive/high-level functions (e.g. interpretations/attributions) than they do of stimulus parameters when making their judgements. As in other domains of inferential reasoning, patients trended to overestimate causality in a non-social context (e.g., in jumping-to-conclusion biases, see Moritz and Woodward, 2005; McKay et al., 2007; Langdon et al., 2010; Speechley et al., 2010) and underestimate it in the social context, likely due to mentalizing/ToM deficits (Frith, 2004; Bora et al., 2009). Additional mentalizing effort prior to the inference process in the social condition could evoke the stronger increase in IFG response (Lee et al.,

2004; Pedersen et al., 2012). The role of lateralization for IFG/Broca as the defining characteristic for physical/social causality in the human brain has indeed been postulated (Crow, 2010).

LIFG-activation in patients correlated with symptoms of positive formal thought disorder (e.g. associative loosening/derailment). These symptoms are likely associated with inference deficits in psychosis, e.g. in the form of excessive attributions of causality, as suggested by "Bayesian" accounts to psychotic symptomatology (Grossberg, 2000; Corlett et al., 2009). Interestingly, hallucinations had an opposite effect. Hallucinations in these patients might be associated with differential sensitivity to perceptual cues or differences in their processing (Corlett et al., 2009; Fletcher and Frith, 2009). This could also relate to explanations of hallucinations as a consequence of excessive top-down inferences (Grossberg, 2000; Corlett et al., 2009).

4.3. Disconnectivity in patients: dysfunctional perceptual organisation?

Reduced LIFG-connectivity to bilateral occipital cortex was found in the patient group, as compared to controls. This result corresponds with other findings of occipital-frontal disconnectivity and the claim of reduced connection between perceptual and inferential processes in SZ (Pettersson-Yeo et al., 2011; Zalesky et al., 2011; Straube et al., 2014). LIFG-connectivity was reduced across conditions in the patient group (main effect), which is in line with the explanation for the inference deficits in psychotic patients (Corlett et al., 2007) as a manifestation of general dysfunction in integrating bottom-up and top-down processing (Corlett et al., 2006). In "Gestalt"-domains, disconnection likely influences perceptual organisation, and notably it could disrupt the integration of the stimulus information. Impaired organisation of stimulus motion attributes (space/time) might lead to altered "Gestalt"-perceptions of causality (Uhlhaas and Silverstein, 2005; Tschacher and Kupper, 2006). Integration dysfunctions during motion perception in psychosis have previously been suggested for both social (abstract) motion attributes (Kim et al., 2005; Kim et al., 2011) and physical parameters, e.g. time (Volz et al., 2001; Papageorgiou et al., 2013). Visual-spatial motion characteristics are processed by the visual system in the occipital lobe (Blakemore et al., 2001; Fonlupt, 2003; Badler et al., 2010) and further integrated by posterior (occipito-parietal) regions (Straube and Chatterjee, 2010; Straube et al., 2011; Blos et al., 2012). Especially in the social judgement task, LIFG-connectivity directly correlated with patients' causality judgements. Therefore, frontal-posterior disconnection and related deficits in stimulus-integration might result in behavioural alterations in which motion-parameters (space/time) are less relevant for causal judgements, as observed in the patient group.

5. Limitations and future objectives

As discussed, increased IFG response in patients likely reflects cognitive mechanisms to judge causality. However, distinct effects of e.g. biases/over-attributions or compensational mechanisms on altered responses in patients could not be assessed in the current experimental design. Investigating these mechanisms in detail is an objective for future research.

As the paradigm was focused on comparability of both stimulus types; the social context was set up by our instructions and not directly perceived from the stimulus, which are inherently artificial in nature. Therefore, the generalizability of the paradigm to real world social inferences is limited. Difficulties of patients to imagine this social interaction likely contributed to fewer causal responses, but this symptom spectrum was also of interest in the study. On the other hand, with regard to the particular influence of e.g. phase/severity of illness, the small sample size limits the power of the study.

Lastly, group differences in task demand might also produce increased frontal activity. However, RTs did not significantly differ between groups, and did not correlate with IFG-activity; it is therefore unlikely that mere demand differences evoked the IFG-hyperactivity in patients.

6. Conclusion

In this study we found altered judgements of physical and social causality in patients with schizophrenia.

The patient group made fewer social causal judgements and more physical causality judgements than control subjects and their responses were more disconnected from the influence of stimulus motion attributes (space and time). Task-related frontal hyper-activation in patients, especially associated with positive FDS symptoms, suggests deviant cognitive strategies used in cause–effect judgements in SZ (e.g., excessive attributions). In both physical and social motion contexts, impaired integration of stimulus-parameters (space and time) in perceptual inferences of SZ patients could be an underlying mechanism, possibly due to general disconnection between occipital and frontal brain regions.

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Contributors

Authors KCW, BS, TK, AC and AN designed the study. Authors KCW and MS were responsible for recruitment of participants and data acquisition. KCW and BS conducted the statistical analyses and wrote the manuscript. All authors contributed to and have approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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