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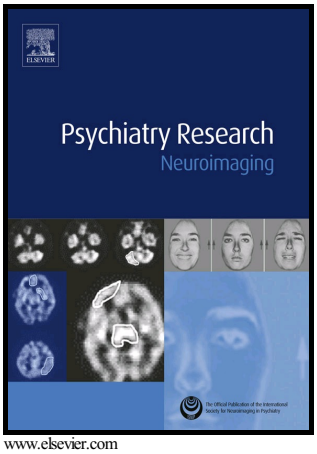

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Impaired frontal processing during agency inferences in schizophrenia

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Abstract

People generally experience themselves as the cause of outcomes following from their own actions. Such agency inferences occur fluently and are essential to social interaction. However, schizophrenia patients often experience difficulties in distinguishing their own actions from those of others. Building on recent research into the neural substrates underlying agency inferences in healthy individuals, the present study investigates how these inferences are represented on a neural level in patients with schizophrenia. Thirty-one schizophrenia patients and 31 healthy controls performed an agency inference task while functional magnetic resonance images were obtained. Participants were presented with a task wherein the relationship between their actions and the subsequent outcomes was ambiguous. They received instructions to cause specific outcomes to occur by pressing a key, but the task was designed to match or mismatch

the color outcome with the participants' goal. Both groups experienced stronger agency when their goal matched (vs. mismatched) the outcome. However, region of interest analyses revealed that only controls showed the expected involvement of the medial prefrontal cortex and superior frontal gyrus, whereas in patients the agency experience was not related to brain activation. These findings are discussed in light of a hypofrontality model of schizophrenia.

Keywords: fMRI; authorship; priming; medial prefrontal cortex; goals

1. Introduction

The feeling that we are in control of our actions and their consequences is central to self-awareness and social interaction. Whether one makes someone smile with a funny remark, or raises one's hand to stop a bus, we generally experience ourselves as the author of the consequences of these actions. Whereas the experience of agency appears quite natural to many individuals, these experiences are impaired in psychiatric illnesses such as schizophrenia. Patients with schizophrenia often exhibit difficulties in experiencing or establishing agency, which may lead to delusions of control, ideas of reference, or hallucination as well as maladaptive social interactions (Schneider, 1957; Blakemore and Frith, 2003).

People experience agency when there is a match between their intended goal and the outcome. Often, these experiences derive from motor cue processes that involve internally-generated (efference) copies that fully predict outcome sensations of one's action (Frith, Blakemore, and Wolpert, 2000; Wolpert and Flanagan, 2001). However, there are many situations in which the relationship between actions and outcomes is less clear, such that individuals cannot easily rely on motor cue processes. The experience of agency, then, relies on non-motor predictions and may result from a cognitive inference process. Such agency

inferences are prevalent and may occur when one's own action can produce multiple outcomes or when there are multiple agents who are potentially responsible for an outcome (Wegner, 2002; Moore et al., 2009; Dogge et al., 2012; van der Weiden et al., 2013a). The present study focuses on the neural underpinnings of such agency inferences.

A previous study showed that inferring agency over intended outcomes recruits frontal and parietal regions, specifically the medial prefrontal cortex, bilateral superior frontal gyrus and inferior parietal lobule (Renes et al., 2014). These frontal regions may be part of a broader inferential network that enables us to make inferences about goals and beliefs that underlie another agent's behavior (Van Overwalle and Baetens, 2009), and allows processing of self-relevant information (Amodio and Frith, 2006; Northoff et al., 2006; Mason et al., 2007; Van Buuren et al., 2010). Furthermore, the parietal region has often been implicated in multisensory integration of information, and is a likely candidate for comparing goals with related action outcomes (O'Connor et al., 2010; Seghier, 2013).

To date, little is known about the mechanisms underlying (abnormal) agency inferences in schizophrenia. In one study, it was shown that in the context of high predictability of an action outcome, patients were not able to use this information to establish agency. However, when the task allowed them to compensate this by using retrospective inference to establish a sense of agency over outcomes, they were able to do so (Voss et al., 2010). This finding suggests that patients' inherent self-awareness difficulties might be overcome by a cognitive mechanism. Indeed, a study specifically testing agency inferences showed that although patients showed a generally lower sense of agency during an agency inference task, they displayed an increased experience of agency when action outcomes matched their intended outcomes – thereby showing a similar pattern as healthy individuals (Renes et al., 2013). The present study aims to investigate

whether the same neural substrates are underlying these agency experiences in patients with schizophrenia as compared with controls, i.e. medial prefrontal cortex, bilateral superior frontal gyrus and inferior parietal lobule.

For this purpose, we used an agency inference task that showed robust and reliable effects in previous research in healthy individuals (Dogge et al., 2014; Renes et al., 2015a). In this task, participants are presented with two rapidly alternating color words (blue and red) in the middle of a computer screen. They are instructed to cause either one of the two colors to stop by pressing a key at a specific moment in time, and hence, the act of pressing a key is followed by the color word red or blue presented on the computer screen Thus, participants received the goal to produce a specific outcome by performing an action. The outcome either matched or mismatched the goal that was given to them before the action was performed. The actual color word presented on the screen is determined by the computer, and accordingly, the task is ambiguous in terms of the relation between the participants' action and the resultant outcome.

We have shown robust behavioral effects for this task in that experienced agency was significantly more pronounced when the goal matched rather than mismatched the outcome (Dogge et al., 2014; Renes et al., 2015a), and a recent electroencephalography (EEG) study using this paradigm showed fronto-parietal connectivity related to agency experiences (Dogge et al., 2014). Accordingly, based on the EEG data and our previous fMRI study (Renes et al 2014), we expect to conceptually replicate the involvement of fronto-parietal regions in agency experiences in healthy controls. For patients with schizophrenia, our expectations are less clear-cut. Because patients, like healthy controls, have shown increased agency experiences over matches (vs. mismatches) between goal and outcome, one might expect similar brain activation as in healthy controls. However, since accumulating evidence suggests that self-awareness processes in

schizophrenia are disturbed at the neural level in the medial prefrontal cortex (e.g., Lee et al., 2006; Vinogradov et al., 2008), and because our task does not measure performance but self-awareness experiences pertaining to agency, it might be possible that the underlying process and the accompanying neural substrates leading to these experiences are different from those in healthy controls. The present study will test these competing possibilities.

2. Methods

2.1. Participants

Thirty-one patients with schizophrenia and 31 healthy controls participated in the study. The sample reported here engaged in a larger study with different tasks (see Renes et al., 2015b). Symptom levels were assessed with the *Positive and Negative Syndrome Scale* (PANSS; Kay et al., 1987) by trained raters, and their diagnosis was confirmed by the *Comprehensive Assessment of Symptoms and History* (CASH; Andreasen et al., 1992). Participants did not have any drug abuse/dependence during the last six months prior to inclusion. Furthermore, neither controls nor their first-degree relatives had a psychiatric disorder. Patients were recruited from the psychiatry departments of the University Medical Centre Utrecht (UMCU) and Amsterdam Medical Centre. The UMCU's Humans Ethics Commission approved the study. See Table 1 for participant characteristics.

2.2. Agency inference task and procedure

The agency inference task (Figure 1) was taken from previous studies designed to gain high experimental control of timing and presentation parameters (Dogge et al., 2014; Renes et al., 2015a). Participants completed two versions of the task; first, they did a prime-based agency

inference task which will be discussed in section 2.3; the goal-based task, which participants completed after the prime-based task, is the focus of this study and shall therefore be presented first. Before starting the experiment, participants were told that the task was designed to assess how experiences of agency come and go, and were asked to indicate how these experiences vary during the task. Similar to playing a slot machine, this task required participants to stop a sequence of rapidly presented information to produce a particular outcome (i.e., the color word red or blue[1]) on the computer screen. Specifically, participants pressed a button on an MRI-compatible fiber-optic response box in response to a cue while viewing alternating letter strings. Upon pressing this button, the stream of letter strings stopped and the color word 'red' or 'blue' was presented. This outcome could either match or mismatch with prior knowledge regarding the action-effect (i.e., goals). In addition, participants learned that the computer could have caused the presented outcome as well. In other words, the cause of the observed effect was ambiguous. After viewing the effect following their button press, participants reported their feelings of agency over causing the outcome.

Each trial consisted of five different phases: an exposure phase, a filler phase, an action phase, an outcome phase and a rating phase (see Figure 1). Each trial started with the exposure phase, where participants were exposed to a series of 18 letter strings followed by a color word that was clearly presented on the screen for 200 milliseconds. This sequence was repeated twice, such that participants were exposed twice to the goal within a 1600 milliseconds period. Participants were instructed to produce the color word that appeared within the series of letter strings (goal setting). During the filler phase, participants attended to rapidly alternating letter strings consisting of 4 or 5 random consonants. This interval served as a delay between exposure

[1] Note that throughout the task, text was presented in a white font color with a dark gray background.

to pre-activated information (goal) and the action. Such a delay was also present in previous work on agency inferences (e.g., van der Weiden et al., 2013b). In the action phase, participants responded to a circle (the action-cue) that was presented above or below the letter strings throughout the action phase by pressing a key on the response box with their right thumb. The response could be given within an 800 millisecond interval. The strings continued to alternate until the end of the response interval, regardless of when participants pressed the button. In case they pressed too late, an error message occurred and the trial was processed as missing (6.7% of the trials for controls, 7.2% for patients).

Following the action phase, the color word 'red' or 'blue' (counterbalanced between trials) was shown for 1500 milliseconds. A 100 milliseconds delay was added between the action and outcome phase to make these two phases more distinguishable. To ensure that participants maintained looking at the letter strings, participants were told that pressing the key during the presentation of a string containing the letter R (e.g., MTFR) would cause the word 'red' to appear, whereas a key press during the presentation of a string containing the letter 'B' (e.g., NXBCZ) was followed by the word 'blue'. Letter strings were presented for 2 cycles on a 60 Hz MRI compatible LCD screen (thus, presentation time was ±33 ms). Importantly, no letter strings containing both B and R were present. Furthermore, this proposed mechanism did not actually cause these colors to occur. In reality, the computer always randomly determined the outcomes, and participants did not have actual control. Thus action and outcome were independent, ruling out the potential contribution of motor-prediction cues.

After each trial, experienced agency was assessed during a rating phase by asking participants to what extent they felt their key press caused the presented color word to occur. They could respond by moving a square on an 8-point analogue scale ranging from '*not me*' (1)

to '*me*' (8). The square was positioned in the middle of the scale and participants had to provide their response by moving the square to the left (not me) or the right (me) of the scale. Before starting the next trial, a small white square was shown, functioning as a fixation point during the intertrial interval, which lasted for three seconds minus the response time to the rating phase.

Prior to the fMRI session, participants practiced the task both outside and inside the scanner. The goal trials consisted of 64 trials in a single pseudo-random counterbalanced order. In half of the trials, pre-activated color words corresponded with the actual outcome, whereas in the other half of the trials they did not correspond with this outcome. The ratio of the color words red and blue was always 50/50. Furthermore, the goal trials were divided into 4 parts of 16 trials – each with eight matching and eight mismatching trials – interleaved with 30s rest periods.

2.3. Prime-based agency inferences

The agency task described above assesses the individual's ability to experience agency as a result of goal-based inferences, that is, agency experiences over outcomes that ensue from the explicit goal to produce the outcomes by performing an action. However, building on the role of implicit processes in agency inferences, previous research showed that agency experiences are also enhanced when the mere activation (or priming) of outcome information matches (vs. mismatches) with inferences on the actual outcome, and these effects do not seem to mediated by explicit goal-based processes (Renes et al., 2015a). Thus, agency experiences can result from goal-based and primed-based inferences that can be empirically isolated in agency inferences tasks. Accordingly, the present fMRI study also included an agency task to examine the neural substrates of prime-based inferences in healthy controls and patients with schizophrenia. This

prime-based inference task was presented to all participants prior to the goal-based inference task described above[2].

In the prime-based agency inference task (also consisting of 64 trials), participants were presented with subtle presentations (i.e., primes) of a color-word, which subsequently matched or mismatched with the actual outcome. Specifically, participants were exposed to a series of 5 letter strings followed by a briefly presented color word (±33 ms). This sequence of events was repeated eight times, resulting in a total of eight primes within a 1600 milliseconds period (see Figure 1). Note that the duration of the exposure phase was identical for both types of pre-activation (i.e., goals and primes). Importantly, participants were not instructed to formulate a goal in the prime trials, but were asked to simply respond to the action cue, after which they should trust their feeling to ascertain self-causation. As in the goal-based inference task, key-presses outside the time-window of 800 milliseconds were rare (5.1% of all trials). Crucially, previous studies indicate that patients with schizophrenia are able to process pre-activated information about the outcome of an action but, unlike healthy controls, they do not show the higher levels of experienced agency in the presence of a match relative to a mismatch (Renes et al., 2013; 2015b).

2.4. Image acquisition

The experiment was performed on a 3.0 T Philips Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) at the University Medical Center Utrecht. Head motion was restricted using a vacuum cushion and foam wedges. Images were acquired using an eight-channel sensitivity-encoding (SENSE) parallel-imaging head coil. Whole-brain T2*-weighted

[2] Order effects do not play a statistically significant role in this agency inference task, an observation that has also been reported in a previous publication of this task (Renes et al., 2015a).

echo planar images (EPI) with blood-oxygen level dependent (BOLD) contrast (410 volumes per task; 30 slices per volume; interleaved acquisition; repetition time, 1600 ms; echo time, 23.5 ms; field of view: 256×208 mm; flip angle = 72.5°; 64×51 matrix; 4×4 mm in-plane resolution; 4 mm slice thickness; SENSE-factor, 2.4 (anterior-posterior)) oriented in a transverse plane tilted 20° over the left-right axis were acquired in a single run. The sequence started with six dummy scans to allow for T1 equilibration effects. A whole-brain three-dimensional fast field echo T1-weighted scan (150 slices; repetition time = 8.4 ms; echo time = 3.8 ms; flip angle = 8°; field of view, 288×252×185 mm; voxel size: 1 mm isotropic) was acquired for within-subject registration purposes.

2.5. Imaging data pre-processing

Image preprocessing and analyses were carried out with SPM 5 (http://www.fil.ion.ucl.ac.uk/spm/). After realignment, the structural scan was co-registered to the mean functional scan. Next, using unified segmentation, the structural scan was segmented and normalization parameters were estimated. Subsequently, all scans were registered to an MNI T1-standard brain using these normalization parameters, and a 3D Gaussian filter (8 mm full width at half maximum) was applied to all functional images.

2.6. Data analysis

For each subject, a model was generated describing event-related changes time-locked to the start of the trial (the exposure, filler, and action phase), the outcome phase and the rating phase (no self-agency experience: ratings 1-4; self-agency experience: ratings 5-8). Agency experience-related activation was modeled as activation during the presentation of the actual

outcome, based on whether this outcome matched or mismatched the pre-activated information and the subsequent agency experience. This resulted in four conditions: outcome match and agency experience, outcome match and no agency experience, outcome mismatch and agency experience, outcome mismatch and no agency experience.

To correct for head motion, the six realignment parameters were included in the design matrix as regressors of no interest. Two participants were excluded from further analysis due to excessive head movement (>4 mm) during the acquisition of fMRI scans (van Dijk et al., 2012). To correct for drifts in the signal, a high-pass filter (discrete cosine transform basis functions) was applied to the data with a cutoff frequency of 0.0039 Hz. For each individual subject, brain activation related to agency experience was calculated by contrasting match-agency trials with mismatch-no-agency trials (henceforth referred to as the Agency > No-Self-agency contrast). The resulting individual statistical maps were subjected to a region of interest (ROI) analysis. For this analysis, a mask (see Figure 2) was created from the results of the previous study (Renes et al. 2014). This mask contains four regions: left superior medial frontal gyrus (lSFG), right superior medial frontal gyrus (rSFG), medial prefrontal cortex (mPFC) and left inferior parietal lobule (IPL). Furthermore, to examine further brain activations outside of the mask, group-wise whole-brain analyses were performed. Maps resulting from this analysis were tested for significance using cluster-level inference (cluster-defining threshold, $p < 0.001$; critical cluster size: 21 voxels, cluster probability of $p < 0.05$, family-wise error corrected for multiple comparisons). These parameters were determined using SPM and a script (CorrClusTh.m, http://www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/scripts/spm), which uses estimated smoothness (estimated full width at half maximum: 3.56 x 3.65 x 3.46 voxels) and random field theory to find these corrected thresholds.

3. Results

3.1. Behavioral data:

3.1.1. Agency ratings

Mean agency experiences were calculated for matches and mismatches (see Figure 3). A Group (2 levels: Schizophrenia vs. Control) by Matching (2 levels: match vs. mismatch) repeated-measures ANOVA yielded a main effect for Matching ($F(1,60)=18.8$, $p<0.001$, $n_p^2=0.24$), indicating that when a goal matched the actual outcome, more agency was experienced than when it mismatched the actual outcome. No effect of Group was found for mean agency experiences ($F(1,60)=0.06$, $p=0.803$, $n_p^2<0.01$), nor was there an interaction of Group by Matching ($F(1,60)=0.02$, $p=0.900$, $n_p^2<0.01$), indicating that goal-driven agency inferences operated equally well in both groups. Follow-up analyses confirmed this, as both controls ($F(1,30)=7.14$, $p=0.012$, $n_p^2=0.19$) and patients with schizophrenia ($F(1,30)=13.1$, $p=0.001$, $n_p^2=0.31$) showed a significant effect of Matching.

3.1.2. Response times to the action-cue

To check whether response time might influence the agency inference effects, we compared response times for the action cues in the match and mismatch condition as a function of group. Importantly, no main effect of Group was found ($F(1,60)=0.28$, $p=0.595$, $n_p^2<0.01$), as both groups were equally able to respond to the action cue (controls: M=351ms, SD=67ms; patients: M=359ms, SD=56ms). Furthermore, neither the effect of Matching ($F(1,60)=0.40$, $p=0.528$, $n_p^2<0.01$), nor its interaction with Group was significant ($F(1,60)=1.00$, $p=0.321$, $n_p^2=0.02$).

3.2. fMRI

After excluding 4 outliers per group, i.e., participants with activation levels ± 2 SD from the mean activation per ROI, we performed a Group (2 levels: Schizophrenia vs. Control) by ROI (4 levels: lSFG vs. rSFG vs. mPFC vs. IPL) repeated measures ANOVA on the resulting activations in the Agency > No self-agency contrast (Figure 4; for sample characteristics, see Supplemental Table 13). There was a main effect of Group, $F(1,52)=4.30$, $p=0.043$, $n_p^2=0.08$, showing more brain activation in controls than in patients. No main effect of ROI was found, $F(3,156)=0.33$, $p=0.804$, $n_p^2=0.01$, nor was there an interaction effect between Group and ROI, $F(3,156)=1.62$, $p=0.187$, $n_p^2=0.03$. Follow-up analyses with t-tests (see Table 2) showed that for controls, all ROI's except the IPL were activated, whereas for patients no significant activations were found in the ROIs. The two-sample t-tests revealed that there was a significant difference between the groups for the lSFG and the MPFC, showing more activation in controls than in patients. Note that none of the findings of the t-tests would survive stringent bonferroni correction.

Whole brain analyses were performed to check for any activations outside of these regions of interest, both within each group and comparing group differences. However, no significant activations were found in the Agency > No self-agency contrast, nor in the reverse No self-agency > Agency contrast. Removing extend thresholds did not reveal any exploratory differences in these contrasts.

3.3. Prime-based agency inferences

For the prime-based agency inference task, there were no significant findings. Matching failed to show a significant behavioral effect, $F(1,60)=2.86$, $p=0.096$, $n_p^2=0.05$, yielding no stronger agency experiences when primes matched the actual outcome as compared to when they mismatched it. Furthermore, no effect of Group was found, $F(1,60)=1.10$, $p=0.299$, $n_p^2=0.02$, nor

an interaction of Group and matching, $F(1,60)=1.39$, $p=0.243$, $n_p^2=0.02$, indicating that there was no difference in the effect of Matching between the groups. Follow-up analyses confirmed this. Whereas the means are in the expected direction, for the controls there was no significant matching effect (M=4.86, SD=0.69 for match trials; M=4.59, SD=0.75 for mismatch trials; $F(1,30)=2.35$, $p=0.136$, $n_p^2=0.07$). For patients with schizophrenia the matching effect was completely absent (M=4.90, SD=0.66 for match trials; M=4.85, SD=0.59 for mismatch trials; $F(1,30)=0.53$, $p=0.473$, $n_p^2=0.02$). As a result, we did not perform fMRI analyses on prime-based agency inferences.

4. Discussion

The present study investigated the neural basis of agency inferences in patients with schizophrenia and healthy controls. We obtained functional MRI brain activation measures from brain regions previously found to be associated with agency processing in healthy individuals (Renes et al., 2014). Both groups reported stronger experiences of agency when action outcomes matched intended goals, replicating earlier work (Renes et al., 2013). Healthy controls activated regions previously associated with agency inferences, being bilateral superior frontal gyrus and the medial prefrontal cortex, although this would not reach significance after correction for multiple comparisons. In contrast, our findings constitute suggestive evidence that the left superior frontal gyrus and the medial prefrontal cortex were not engaged in agency inferences within patients.

Our findings suggest that goal-based agency inferences are associated with reduced frontal activation in schizophrenia patients, implicating inadequate neural processing underlying these agency inferences. As both groups exhibited similar behavioral effects on agency ratings,

our findings are not confounded by poor task performance. These findings add to a broader understanding of agency processes and perturbed frontal processing in schizophrenia. Our finding of reduced frontal activations during agency inferences is consistent with the general observation of frontal dysfunction in schizophrenia (Andreasen et al., 1992b; Buchsbaum et al., 1992; Weinberger et al., 1992; Yurgelun-Todd et al., 1996; Ragland et al., 1998; Karlsgodt et al., 2007; van Veelen et al., 2010; 2011), specifically that of hypoactivation in the superior frontal gyrus and medial prefrontal cortex (Koch et al., 2008; Vinogradov et al., 2008; Holt et al., 2011; Bedford et al., 2012).

These results suggest that the neural process underlying agency inferences is impaired in schizophrenia. Impairments in the regions involved in this process may be related to broader self-disturbances in schizophrenia. Indeed, hypoactivations in these frontal regions are associated with deficits in self-awareness (Lee et al., 2006), theory of mind (e.g., Russel et al., 2000; Brunet et al., 2003; Walter et al., 2009), and self-referential processing (Vinogradov et al., 2006; Holt et al., 2011; van Buuren et al., 2012). Despite these widespread deficiencies, patients still display the ability to process agency inferences in the context of our task. Interestingly, we did not detect group differences outside the regions of interest. One would expect to find such differences, as it is not unlikely that patients utilized a compensatory mechanism to overcome their frontal abnormalities.

A potential explanation is that the task, although well-validated, may have been relatively easy. Indeed, when patients with schizophrenia are faced with a more difficult agency inference task where outcome information is implicitly pre-activated (i.e., primed) instead of presented as an explicit goal, patients are no longer able to experience more agency when this pre-activated information is matched by the actual outcome (Renes et al., 2013; 2015b). This suggests that,

despite abnormal frontal activation, patients might apply a compensatory mechanism enabling them to report agency in an easy context where the experience is informed by explicit goal-directed behavior. It might be that hypofrontality makes them vulnerable for misjudgments of agency in more complex (real-life) situations, where patients often experience difficulties in social functioning and communication.

For healthy controls, our finding of increased bilateral superior frontal gyrus and medial prefrontal cortex activation during agency inferences is consistent with previous findings testing a different type of agency inference task (Renes et al., 2014). The medial prefrontal regions have also been associated with thinking about agency judgments (Miele et al., 2011), self-referential processing (Kelley et al., 2002; van Buuren et al., 2010), making trait or social inferences (van Overwalle and Baetens, 2009; Ma et al., 2011), whereas the more lateral regions are related to self-referential processing and other higher-order processing of self-awareness (Northoff et al., 2006).

In contrast to our hypothesis and earlier findings (Renes et al., 2014), we did not find significant inferior parietal lobule activation during agency experiences in healthy controls. This discrepancy could be due to the difference between the tasks. In the previous study, subjects had to follow rotating squares across a rectangular field, and were instructed to stop them at a specific location by a button press (i.e., goal-directed processing; Aarts et al., 2005; Renes et al., 2014). In contrast, the present task used semantic information which was centrally presented on the screen to prevent biases related to eye movement deficiencies typically observed in patients (e.g., Raemaekers et al., 2006).

Yet, the absence of involvement of the inferior parietal lobule was not expected, given recent findings of parietal lobe involvement during a similar semantic version of the task using

EEG (Dogge et al., 2014). Also, a recent review describing the functions of this region suggested that the angular gyrus (a subregion of the IPL) is involved in both spatial attention and semantic processing, among many other functions (Seghier, 2013). Specifically, this area plays a major role in the integration of multisensory information and interpretation of the sensory information at a conceptual level. Therefore, it is not unlikely that the IPL is indeed involved in both tasks, as both semantic and special information is processed and integrated here. Hence, the absence of the expected inferior parietal lobe activation in the current study might be due to low statistical power.

In line with previous studies (Renes et al., 2013; 2015b), patients did not rely on pre-activated information about the outcome (i.e., primes) to guide experiences of agency. However, in contrast to earlier findings (Aarts et al., 2005; Linser and Goschke, 2007; Sato, 2009), no prime-based agency inferences were found in healthy controls either. Whereas we currently do not know the cause of the absence of the primed-based inferences in healthy controls, one possibility might be that the task environment (administering the prime-based agency inference task in the MRI scanner) increased stress and distraction in our participants (e.g., Tessner et al., 2006), such that the otherwise subtle effects of primed-based agency inferences vanished. Whatever the exact reason for the absence of a clear primed-based agency inference effect in healthy controls, we deemed further interpretation of the primed-based agency inference data uninformative.

We wish to stress that the present findings need to be interpreted in light of a few limitations. First, there is the potentially confounding factor of antipsychotic medication. Future studies could eliminate this factor by testing medication-naïve patients with schizophrenia. However, it is unlikely that medication actually confounds these findings, as hypoactivation in

the frontal cortex has also been shown in medication-naive patients (e.g., Snitz et al., 2005; Lee et al., 2006; van Veelen et al., 2010; 2011). Additionally, it is important to note that the patients in the current study are relatively high functioning; they have mild symptoms, and education levels are similar to controls. Finally, the present study aimed to capture the strength of conscious experiences of agency, which may be more difficult to assess than, for example, simple motor performance, due to the inherent noisiness and complexity of measuring individual differences in, and reporting of conscious experiences (Frith et al., 1999; Rees et al., 2002; Block, 2005). In the context of our task this means that the attribution of a self-agency experience over an outcome of patients may differ from that of the healthy controls. One of the disadvantages of measuring conscious experiences is that it remains unclear whether patients and controls interpret and apply the agency rating scale in the same way, i.e., whether the experience of agency is qualitatively the same for healthy controls and schizophrenia patients.

4.1. Summary and conclusion

The present study employed an agency inference task to investigate the neural correlates of agency inference processing in patients with schizophrenia. This is the first study showing that agency inferences are associated with frontal hypofunction in patients with schizophrenia, contributing to a rapidly growing body of research showing disturbances in self-processing in schizophrenia. Future studies might investigate how agency deficiencies develop over time in a high-risk population to help understand how such experiences develop during transition to psychosis and how they relate to agency related symptoms and social functioning.

Contributors

Author Renes aided in study design, data collection, conducted statistical analyses, interpreted results, and wrote the first draft of the manuscript. Author Vink conducted statistical analyses, interpreted results and edited the manuscript. Authors Kahn and van der Weiden aided in directing data collection and editing the manuscript. Authors Prikken and Koevoets aided in data collection and editing the manuscript. Author Aarts aided in designing the study, directed data collection, provided conceptualization and theory used to integrate the findings, interpreted results, and edited the manuscript. Author van Haren aided in study design, obtained grant funding, directed data collection, interpreted results, and edited the manuscript. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Finally, all authors declare that they have no conflicts of interest.

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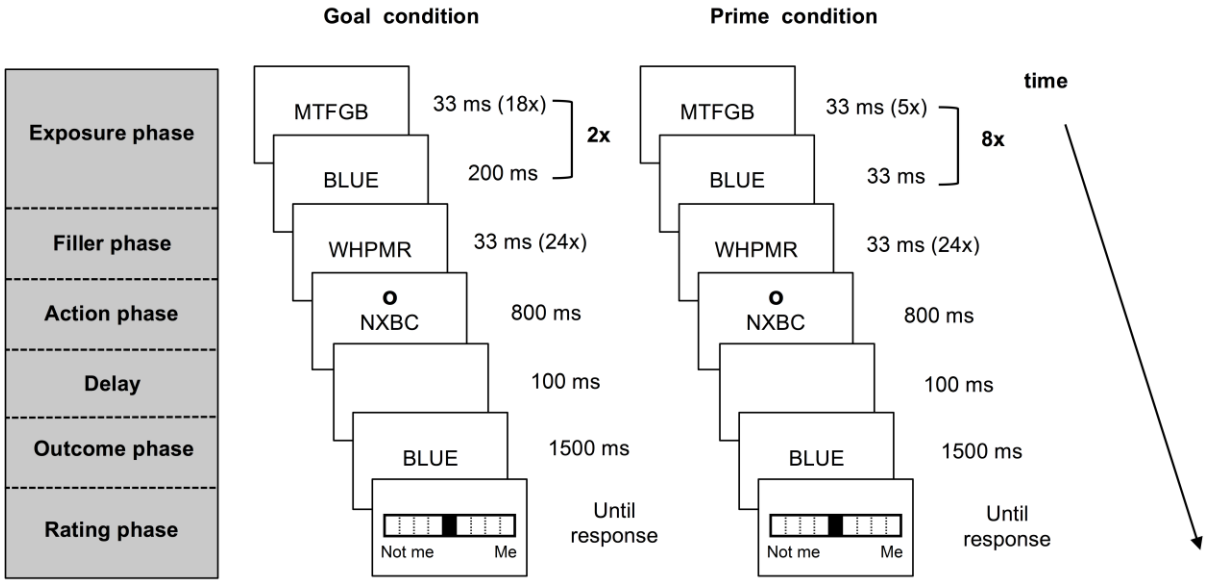
Figure Legends

Figure 1: Schematic presentation of a match trial in the agency inference task for the goal condition and the prime condition. Presentation times are rounded based on a 60 Hz monitor (e.g., 33ms equals 2 cycles).

Figure 2: Mask of areas related to inferences of self-agency based on Renes et al (2014). Legend: 1 = left superior frontal gyrus (lSFG); 2 = right superior frontal gyrus (rSFG); 3 = medial prefrontal cortex (mPFC); 4 = inferior parietal lobule (IPL).

Figure 3: Goal based self-agency experiences as a function of Group (control/schizophrenia) and Matching (match/mismatch). Error bars represent standard errors of the mean.

Figure 4: Level of activation in predefined regions of interest in patients and controls. lSFG = left Superior Medial Frontal Gyrus, rSFG = right Superior Medial Frontal Gyrus, mPFC = medial Prefrontal cortex, IPL = Inferior Parietal Lobule.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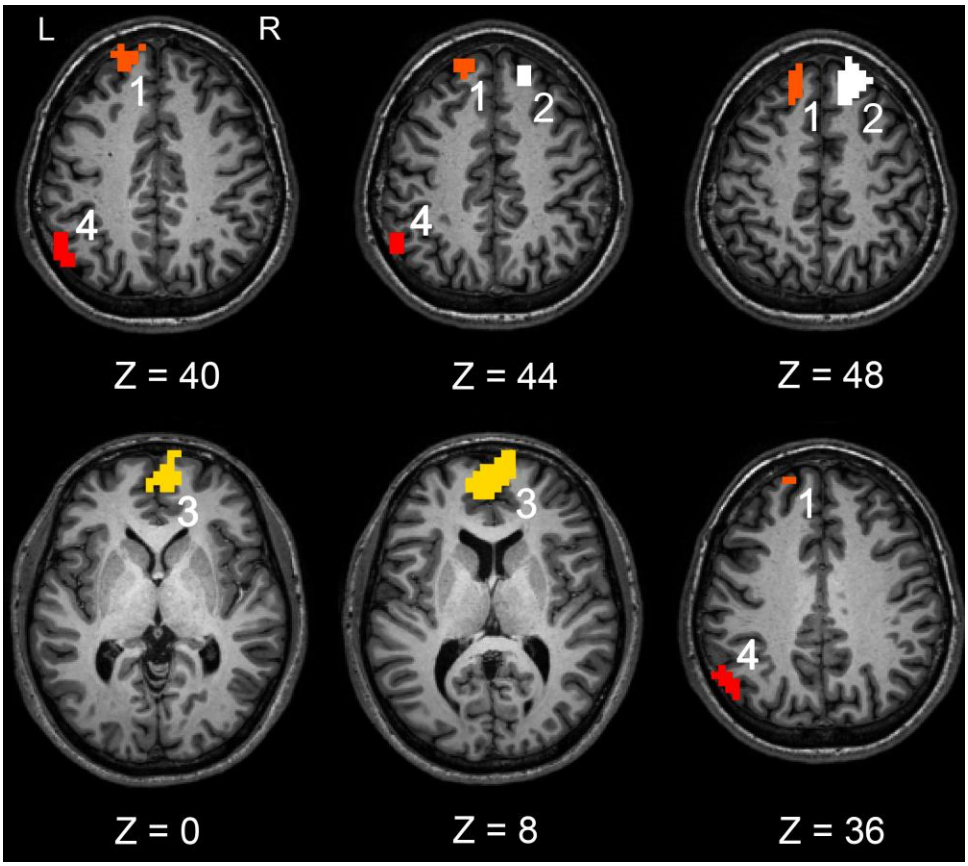
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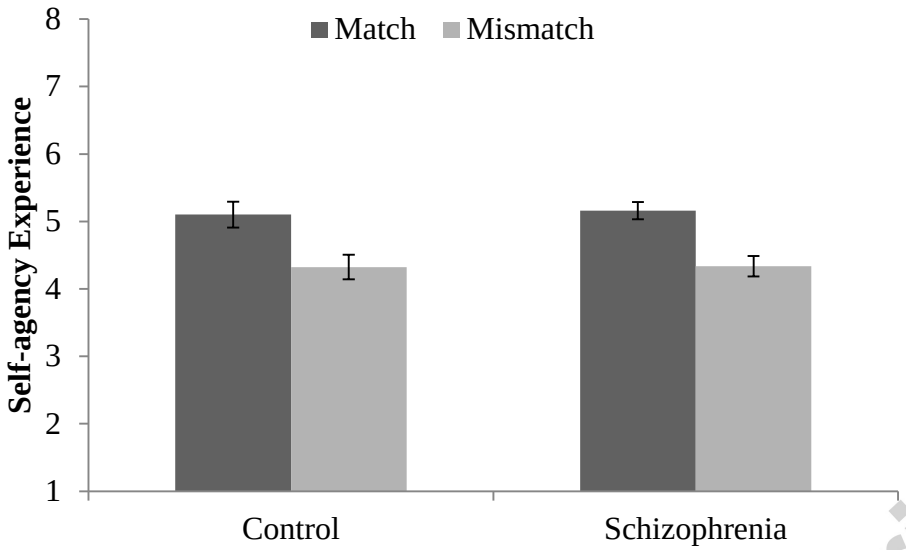

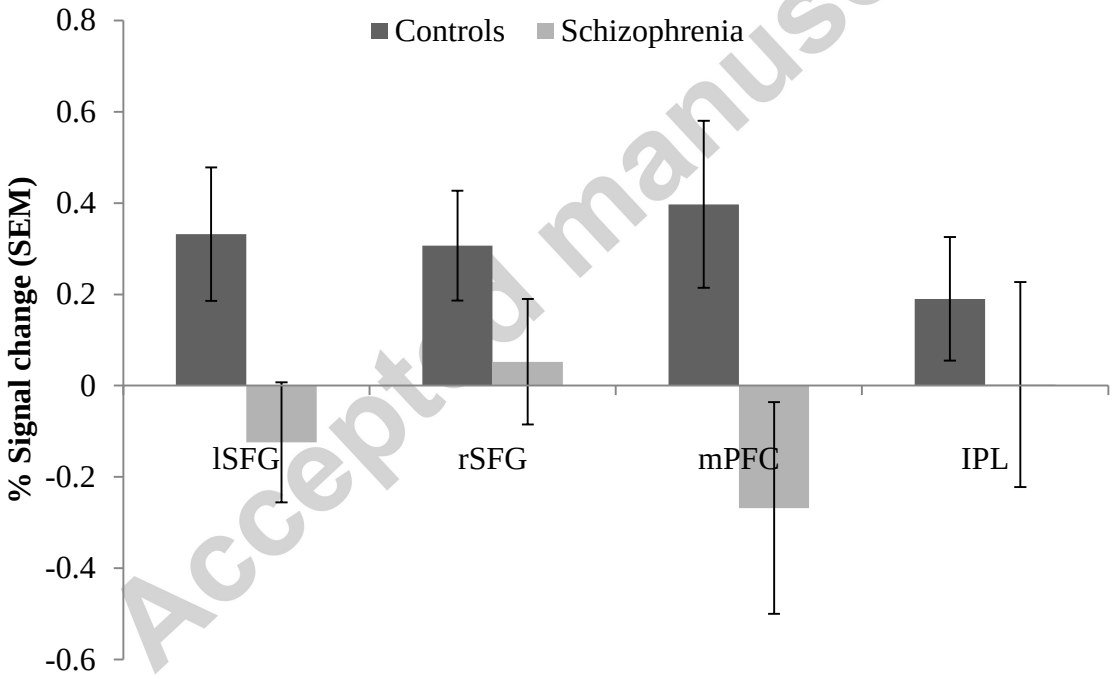

Table 1

Characteristics of patients with schizophrenia and control subjects (standard deviations in parentheses).

	Schizophrenia Patients (N = 31)	Healthy Controls (N = 31)
Age	29.4 (7.1)	31.3 (6.5)
Male / Female	28 / 3	28 / 3
Years of education[a]	13.1 (1.8)	13.2 (3.9)
Parental years of education	14.1 (3.1)	14.7 (2.6)
Premorbid intelligence[b]	102.1 (8.0)	107.7 (6.7)
Illness duration (years)[c]	9.2 (7.9)	–
PANSS Positive score	10.1 (2.7)	–
PANSS Negative score	11.8 (4.2)	–
PANSS General score	21.7 (3.4)	–
Typical / Atypical medication	3 / 25	–

Patients and controls did not statistically differ on any of the characteristics, except for premorbid intelligence ($t(60)=3.04$, $p=0.004$).

[a] Education information was estimated as part of the *Comprehensive Assessment of Symptoms and History* (CASH; Andreasen et al., 1992).

[b] Premorbid intelligence was estimated with the Dutch Adult Reading Test (Schmand et al., 1992).

[c] Time between onset of psychotic symptoms and inclusion in the study.

Table 2. Analyses and statistics for the regions of interest.

	One sample t-tests (df=26)				Two sample t-tests (df=52)	
	Control		Schizophrenia			
Region of interest	t	Sig.	t	Sig.	t	Sig.
lSFG	2.27	0.032	-0.94	0.355	2.32	0.025
rSFG	2.55	0.017	0.38	0.706	1.39	0.170
mPFC	2.17	0.039	-1.16	0.258	2.25	0.029
IPL	1.41	0.172	0.01	0.991	0.72	0.478

lSFG = left Superior Medial Frontal Gyrus, rSFG = right Superior Medial Frontal Gyrus, mPFC = medial Prefrontal cortex, IPL = Inferior Parietal Lobule.

- We examine goal-based agency inferences in controls and patients with schizophrenia
- Both groups show similar agency experiences, but differ on a neural level.
- The findings corroborate a hypofrontality model of schizophrenia.