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Functional brain networks underlying probabilistic reasoning and delusions in schizophrenia

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ABSTRACT

Delusions in schizophrenia are false beliefs that are assigned certainty and not afforded the scrutiny that normally gives rise to doubt, even under conditions of weak evidence. The goal of the current functional magnetic resonance imaging (fMRI) study is to identify the brain network(s) involved in gathering information under conditions of weak evidence, in people with schizophrenia experiencing delusions. fMRI activity during probabilistic reasoning in people with schizophrenia experiencing delusions (n = 29) compared to people with schizophrenia not experiencing delusions (n = 41) and healthy controls (n = 41) was observed when participants made judgments based on evidence that weakly or strongly matched (or mismatched) with the focal hypothesis. A brain network involved in visual attention was strongly elicited for conditions of weak evidence for healthy controls and patients not experiencing delusions, but this increase was absent for patients experiencing delusions. This suggests that the state associated with delusions manifests in fMRI as reduced activity in an early visual attentional process whereby weak evidence is incorrectly stamped as conclusive, manifestating as a feeling of fluency and misplaced certainty, short-circuiting the search for evidence, and providing a candidate neural process for 'seeding' delusions.

1. Introduction

Delusions are fixed false beliefs that are maintained despite contradictory evidence, and are one of the primary symptoms of schizophrenia (American Psychological Association, 2013). Investigations into the cognitive underpinnings of delusions have demonstrated that, relative to other schizophrenia patients and healthy controls, those patients experiencing delusions make firm decisions based on little evidence. This manifests as premature termination of data collection during decision making, commonly referred to as the jumping to conclusions (JTC) bias (Dudley et al., 2016; Fine et al., 2007; Garety et al., 1991; Huq et al., 1988; McLean et al., 2017; Menon et al., 2008, 2006; Moritz and Woodward, 2005; van Dael et al., 2006; Woodward et al., 2009). JTC is typically measured using probabilistic reasoning paradigms for which the participant is presented two jars/lakes holding coloured beads/fish in different proportions. Beads/fish are drawn, one at a time, from one jar/lake only, and after each draw, the participants are asked to state from which jar/lake this bead/fish had been drawn/caught, and JTC is defined as deciding after very few beads/fish in a series.

In addition to JTC, a number of other cognitive biases have been put

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forward as underpinning delusions; for example, liberal acceptance (LA), hypersalience of evidence-hypothesis matches (EVH matches), bias against disconfirmatory evidence (BADE), overconfidence in errors, and prediction error disruption (for summaries see Balzan and Moritz, 2017; Broyd et al., 2017; McLean et al., 2017). All these accounts provide different candidate pathways for understanding why delusions "feel" true, are assigned certainty, are fluently processed, and do not elicit the type of scrutiny that would normally give rise to doubt, even under conditions of weak evidence (Broyd et al., 2017). The goal of the current functional magnetic resonance imaging (fMRI) study is to identify activity in the brain network(s) involved in gathering information under conditions of weak evidence in people with schizophrenia experiencing delusions, providing a candidate biomarker.

A number of previous studies have employed fish/beads/boxes paradigms to investigate probabilistic reasoning using fMRI (Andreou et al., 2018b; Esslinger et al., 2013; Krug et al., 2014a, 2014b). In these studies, sequences of fish/beads/boxes were presented, and participants provided a binary yes/no decision only once they felt they had sufficient information to reach a decision about the origin/majority colour of the fish/beads/boxes. Due to the nature of the task designs, there were relatively few event trials, because the events/blocks of interest could only be determined once decisions had been made after a series of trials involving weighing evidence, an acknowledged limitation of such tasks, negatively affecting their reliability and utility for repeated-measures trials (McLean et al., 2018). To counter this, our group has developed single-trial probabilistic reasoning tasks that do not require a series of evidence-weighing trials, but instead combine the evidence weighing and moment of decision-making into a single trial. This single-trial probabilistic reasoning work has demonstrated, over a series of studies, that there is a greater self-selection bias (Whitman and Woodward, 2012) among schizophrenia patients experiencing delusions (Whitman et al., 2013a), that evidence accumulating gradually affects hypothesis judgments more than evidence presented simultaneously (Whitman and Woodward, 2011), and that a frontoparietal network and beta-band power decreases in neural activity is involved in a decision to accept a hypothesis using fMRI (Whitman et al., 2013b), and magnetoencephalography (MEG) (Whitman et al., 2016).

These single-trial probabilistic reasoning studies also used a continuous rating scale, such that participants responded with a variable number of button-presses to indicate the probability that the coloured fish originated from lake A and not lake B. For the current fMRI study, we continued with the single-trial probabilistic reasoning paradigm, but introduced a novel addition: the use of a single-press yes/no response as opposed to the multiple-press continuous rating scale used previously. Relative to previous fMRI probabilistic reasoning studies using the fish/lakes/boxes paradigms (Andreou et al., 2018b; Esslinger et al., 2013; Krug et al., 2014a, 2014b), this design sharply delineates trial onset and offset times in an event-related fashion, thereby allowing an accurate estimation of the task-related hemodynamic response (HDR), as well as substantially increasing the number of decision trials per run. This single-trial design was used to determine the brain networks involved in decisions based on strong versus weak evidence; however, it does not provide the traditional draws-to-decision or JTC measures most commonly associated with probabilistic reasoning studies of delusions (Dudley et al., 2016; Fine et al., 2007; Garety et al., 1991; Huq et al., 1988; McLean et al., 2017; Menon et al., 2008, 2006; Moritz and Woodward, 2005; van Dael et al., 2006; Woodward et al., 2009).

Derivation of task-based brain networks during probabilistic reasoning was achieved using group constrained principal component analysis for fMRI (group fMRI-CPCA), which derives estimated HDR shapes for task-based brain networks that can be compared between patients experiencing and not experiencing delusions, and healthy controls (Lavigne et al., 2020b; Metzak et al., 2011; Sanford et al., 2020a). Brain network(s) involved in gathering information under conditions of uncertainty would be expected to be more active during presentation of weak relative to strong evidence. Since patients with delusions show increased certainty (Broyd et al., 2017; McLean et al., 2017), patients experiencing delusions should not show increased responses in visual attention networks under conditions of weak evidence, providing a candidate brain network for a biological underpinning for delusions.

2. Methods and materials

2.1. Participants

Healthy controls were recruited through physical and electronic bulletin boards and word of mouth in Greater Vancouver, British Columbia, Canada. Participants with psychosis were recruited through Vancouver Coastal Health mental health teams, psychiatric hospitals, and community health agencies. The sample consisted of 41 participants in the healthy control group and 70 participants in the schizophrenia group. Participants were excluded if they were unable to read or write in English, not between 19 and 64 years of age, reported any neurological conditions (e.g., stroke, aneurism, Parkinson's, seizure disorder, multiple sclerosis, encephalitis, meningitis), electroconvulsive therapy in the past 6 months, brain injury resulting in loss of consciousness for greater than 30 min., severe current substance dependence (excluding alcohol), surgery within the last 6 weeks, any surgery to the brain, heart or eyes, colour blindness, IQ below 80, or level of thought disorder higher than 3 on the SSPI (as well as exclusion criteria for MRI scans such as pregnancy or metal fragments in eyes). Controls were additionally excluded if they reported previously being diagnosed with a psychiatric disorder.

The Mini International Neuropsychiatric Interview (MINI) was used to validate the patients' diagnosis of schizophrenia in accordance with the Diagnostic and Statistical Manual (DSM)-IV-TR. The patient group was separated into those with marked delusions ($n = 29$) and mild-to-absent delusions ($n = 41$) based on the Signs and Symptoms of Psychotic Illness (SSPI) rating scale (Liddle et al., 2002). The SSPI is a 20-item rating scale that assesses the severity of the major symptoms in psychotic illness on a range from 0 to 4 (with 0 = absent, 4 = severe). Item 7 from the SSPI was used to quantify the presence/absence of delusions. A rating of 3 (definite delusions, but the delusional beliefs do not have a pervasive influence on thinking or behaviour) or 4 (definite delusions which have a pervasive influence on thinking and/or influence observable behaviour) warranted classification into the delusions group. The study procedure was approved by the Clinical Research Ethics Board at the University of British Columbia, Canada, and all participants provided informed consent before partaking in the study.

Demographic and symptom information for participants is reported in Table 1. The groups did not differ in age, $F(2, 108) = 2.47, p = 0.09$, or sex, $\chi^2(2) = 2.93$, $p = .23$, and the patient groups did not differ on medication dosage converted to chlorpromazine equivalent units, $t(63) = 0.84$, $p = 0.34$. There was a significant difference between groups in years of education, $F(2, 108) = 9.97$, $p < 0.001$, with controls having a significantly higher number of years of education compared to the patients experiencing delusions ($p < 0.005$) and those not experiencing delusions ($p < 0.001$), with no significant difference between the patient groups ($p > 0.40$). A significant difference among groups was also found for WAIS-IV Full Scale IQ (Wechsler, 2011), $F(2, 108) = 14.58$, $p < 0.001$, with controls having a significantly higher IQ compared to patients experiencing delusions ($p < 0.001$) and those not experiencing delusions ($p < 0.001$), with no significant difference between the patient groups ($p > 0.50$). With respect to patient group differences in symptom ratings (using $p < 0.01$ as a cut-off for significance as a compromise between Type I and Type II errors), patients with and without delusions differed in severity of delusions ($p < 0.001$), hallucinations ($p < 0.01$), and impaired insight ($p < 0.001$).

2.2. Task

The timing of the probabilistic reasoning task is presented in Fig. 1.

Table 1
Signs and Symptoms of Psychotic Illness (SSPI) and demographic information. Means are reported with standard deviations (in brackets).

	Healthy (n = 41)	Schiz. no delusions (n = 41)	Schiz. delusions (n = 29)
Age	35.46 (12.57)	31.95 (8.93)	37.72 (11.34)
Age Range	20–60	19–50	20–59
Sex (female:male)	21:20	19:22	9:20
Years of Education	16.74 (2.78)	14.23 (2.75)***	14.72 (2.36)**
Full Scale IQ (FSIQ-4)	110.83 (13.55)	99.63 (9.92)***	98.10 (8.99)***
Handedness, right:left	39:2	39:2	27:2
Chlorpromazine equ.	N/A	827 (1990)	447 (829)
1. Anxiety	N/A	0.76 (1.07)	1.07 (1.19)
2. Depression	N/A	1.29 (0.93)	1.66 (1.29)
3. Anhedonia	N/A	1.51 (1.25)	1.62 (1.45)
4. Elated Mood	N/A	0.07 (0.35)	0.07 (0.26)
5. Insomnia	N/A	0.18 (0.50)	0.14 (0.58)
6. Somatic Complaints	N/A	0.20 (0.51)	0.45 (0.87)
7. Delusions	N/A	0.88 (0.95)	3.52 (0.51) †††
8. Hallucinations	N/A	0.85 (1.42)	2.14 (1.81) ††
9. Attentional Impairment	N/A	1.02 (1.15)	1.38 (1.18)
10. Disorientation	N/A	0.12 (0.46)	0.07 (0.26)
11. Overactivity	N/A	0.24 (0.66)	0.45 (0.95)
12. Underactivity	N/A	1.15 (1.24)	1.14 (1.3)
13. Flattened Affect	N/A	1.32 (1.27)	1 (1.07)
14. Inappropriate Affect	N/A	0.15 (0.57)	0.62 (1.21)
15. Pressure of Speech	N/A	0.27 (0.71)	0.76 (0.99)
16. Poverty of Speech	N/A	0.71 (1.08)	0.21 (0.77)
17. Disordered Form of Thought	N/A	0.39 (0.89)	0.86 (1.06)
18. Peculiar Behaviour	N/A	0.12 (0.4)	0.52 (0.83)
19. Irritability/Hostility	N/A	0.27 (0.67)	0.14 (0.44)
20. Impaired Insight	N/A	0.78 (1.06)	2.59 (1.3) †††

** =control vs no-delusions or delusions, $p < 0.01$.
*** =control vs no-delusions or delusions, $p < 0.001$.
†† =no-delusions vs. delusions, $p < 0.01$.
††† =no-delusions vs. delusions, $p < 0.001$.

On each trial, participants were presented with two lakes, one with green water and the other with blue water, each containing 30 fish in different proportions of black to white fish. On each trial, a single fish, either black or white in colour, was presented centrally between the two lakes and always pointed toward the green lake. In each trial, participants were asked, "Do you think that the fish in the middle came from the green lake rather than the blue lake?", after which they responded with a button press indicating a 'Yes' or 'No' response. Both response boxes were displayed with gray fill at trial onset, and the selected box switched to white once a response was recorded. Participants had 4 s to respond, and the screen display remained visible after the response was recorded. Participants responded with their right hand, with the index finger indicating 'Yes' and middle finger 'No', and responses were recorded using a LUMItouch fiber-optic response device. If participants made multiple responses within the 4 s period, the last response was retained and RT recorded. Participants completed a total of 112 trials across two different runs (56 trials per run). The inter-trial intervals (ITIs) were 2, 4, 6, or 8 s, with occurrences 24, 16, 8, and 8 times within a run, respectively. The temporal location of these ITI lengths was randomly distributed within each run. Therefore, total stimulus time = (4s × 56) = 224 s, total ITI time = (2 × 24) + (4 × 16) + (6 × 8) + (8 × 8) = 224 s, and total length of run = (224 + 224) = 448 s = 7 min 28 s. A series of practice trials were administered outside the fMRI scanner prior to entry into the scanning suite.

2.3. Conditions

The proportion of black to white fish in the lakes was manipulated to provide either strong or weak evidence for or against the focal hypothesis that the central fish came from the green-water lake rather than the blue-water lake. Four different conditions were created based on the colour of the central fish and the ratio of black to white fish in the two lakes: (1) strong evidence matching the focal hypothesis (Match/Strong), (2) weak evidence matching the focal hypothesis (Match/Weak), (3) strong evidence against the focal hypothesis (Non-match/Strong) and (4) weak evidence against the focal hypothesis (Non-match/Weak). The four conditions had the following proportions of coloured fish in each lake: Match/Strong (80% of central coloured fish in green-water lake and 10% in blue-water lake), Match/Weak (20% of central coloured fish in green-water lake and 10% in blue-water lake), Non-match/Strong (20% of central coloured fish in green-water lake and 90% in blue-water lake), and Non-match/Weak (80% of central coloured fish in green-water lake and 90% in blue-water lake). The location of central coloured fish in each lake was randomized across trials such that any two trials containing the same ratio of black to white fish would not be identical in appearance. The location of the green-water lake (left or right) and order conditions (Match/Non-match/Weak/Strong) were also randomized for each participant separately.

2.4. Behavioural data analysis

A 2 × 2 × 3 mixed-model analysis of variance (ANOVA) was conducted to examine effects of condition and Group on participants' response time (RT) and accuracy. Within-subject factors were Match Status (Match/'Yes' vs. Non-match/'No') and Strength of Evidence (Strong vs. Weak), and the between-subject factor was participant Group (Control vs. Non-delusions vs. Delusions).

2.5. fMRI data analysis

Imaging data were collected using the Philips Achieva 3.0 Tesla MRI scanner at the University of British Columbia MRI Research Centre. fMRI data were analyzed via fMRI-CPCA with orthogonal rotation (Metzak et al., 2011; Sanford et al., 2020b; Woodward et al., 2006). Specific details regarding the theoretical principles behind applications of CPCA as a psychometric method, which combines multivariate multiple regression analysis and principal component analysis into a unified framework, are found in previous work (Takane and Hunter, 2001; Takane and Shibayama, 1991). In fMRI-CPCA, multivariate multiple regression is used to constrain the variability in blood oxygenation level dependent (BOLD) signal to that predictable from the task-timing model, which is a finite impulse response (FIR) model. This allows an estimated HDR shape to be obtained for each combination of component, subject, and task condition.

In the current study, all trials were analyzed whether or not the yes/no response was correct. In order to estimate the BOLD signal over 20 s, the FIR model contained 10 time points (due to the repetition time [TR] of 2 s). Principal component analysis (PCA) was then applied to the variability in BOLD signal predictable from task timing, producing components that contained information about brain networks and their associated HDR shapes. These networks were depicted spatially through component loadings, which identified dominant dimensions of inter-correlated voxel activity, and temporally through component scores, which provided a value indexing activity of every brain network for every full-brain scan (TR). Component scores were regressed onto the FIR model matrix to obtain predictor weights for each participant, group, and condition in each component, and predictor weights were plotted to produce an estimated HDR. Thus, fMRI-CPCA allowed us to identify functionally connected brain regions that increased or decreased in activation in synchrony, and the effects of experimental conditions on this activity. For imaging and preprocessing, fMRI-CPCA matrix equations, and analysis details, see Supplementary Material.

2.6. Predictor weights (HDR)

Repeated measures ANOVA was used to test the reliability of the

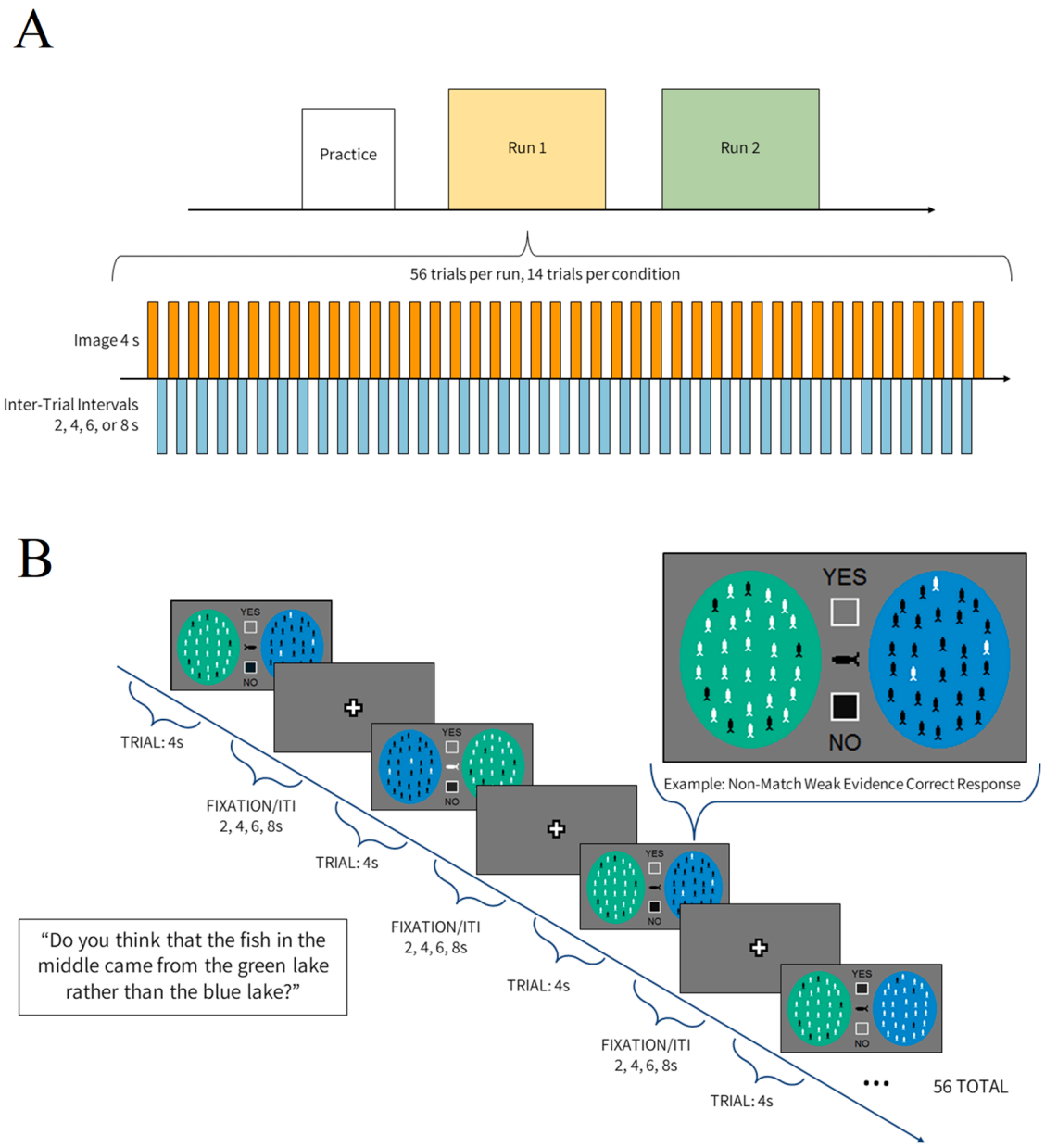

Fig. 1. A (top): Overview of fish task trial and run organization. After a practice run, participants completed 2 separate runs consisting of 56 trials each run, which included 4 different condition combinations of Match/Non-match ('Yes' vs 'No') and Strong/Weak evidence, creating 4 conditions: Match/Strong, Match/Weak, Non-match/Strong, Non-match/Weak. Each run lasted 7 min 28 s. B (bottom): Timeline of stimulus presentations: 4 s of stimulus presentation was followed by 2-, 4-, 6- or 8-seconds inter-trial interval (ITI). Participants responded to the question, "Do you think that the fish in the middle came from the green lake rather than the blue lake?". Both response boxes were displayed filled with gray at trial onset, and the selected box switched to white once a response was recorded. The stimulus display remained visible for the full 4 s.

HDR associated with each component, and differences in brain activity between groups, conditions, and over post-stimulus time for each identified functional brain network. For this purpose, a 2 × 2 × 10 × 3 repeated measures ANOVA was conducted on the subject- and condition-specific predictor weights (HDRs), with "repeated" contrasts of adjacent factor levels used to interpret interactions. Within-subject factors were Match Status (Match/Non-match), Strength of Evidence (Strong/Weak), and Time (10 time bins). The between-subject factor was Group (Control/No Delusions/Delusions). Unadjusted degrees of freedom are reported, but only for effects that were also significant when the degrees of freedom were adjusted used using the Greenhouse–Geisser correction for violation of sphericity.

3. Results

3.1. Behavioural results

Mean RT and accuracy for each group are reported in Table 2. For RT, there was a significant Match Status effect, $F(1, 108) = 38.46$, $p < 0.001$, $\eta^2_p = 0.26$, as participants across the groups had a faster RT in the Match compared to Non-match conditions ($M = 1957$ ms vs. 2064 ms, respectively). There was also a significant Strength of Evidence effect, $F(1, 108) = 446.48$, $p < 0.001$, $\eta^2_p = 0.81$, as participants had a faster RT in the Strong condition compared to the Weak condition ($M = 1846$ ms vs. 2175 ms, respectively). Additionally, there was a significant Match Status × Strength of Evidence interaction, $F(1, 108) = 6.18$, $p < 0.05$, $\eta^2_p = 0.05$, whereby the faster RT for Match relative to Non-match was,

Table 2
Mean response time (RT) in ms and accuracy (ACC) for controls, schizophrenia patients with delusions, and schizophrenia patients experiencing and not experiencing delusions.

Condition	RT (ms) (SD) Controls	No delusions	Delusions	ACC (%) (SD) Controls	No delusions	Delusions
Match Strong	1651 (376)	1857 (424)	1919 (396)	95 (11)	90 (13)	90 (13)
Match Weak	1974 (413)	2150 (505)	2192 (399)	92 (13)	85 (16)	88 (12)
Non-Match Strong	1791 (398)	1893 (427)	1968 (451)	94 (11)	91 (13)	91 (12)
Non-Match Weak	2168 (392)	2225 (479)	2339 (541)	87 (16)	84 (18)	85 (18)

as expected, smaller in the Strong condition ($M = 1809$ ms vs. 1884 ms, Strong Match vs. Strong Non-match respectively, difference = 75 ms) than the Weak condition ($M = 2105$ ms vs. 2244 ms, Weak Match vs. Weak Non-match respectively, difference = 139 ms). The main effect of Group was not significant ($p > 0.05$), but there was a significant Group × Match Status interaction, $F(2, 108) = 4.01$, $p < 0.05$, $\eta^2_p = 0.07$, whereby the difference between Match and Non-match was greater for healthy controls (mean difference = 167 ms) relative to patients experiencing and not experiencing delusions (mean difference = 98 and 56 ms, respectively), and there was no significant difference between the patient groups ($p > 0.30$). This single trial method does not allow quantification of the traditional draws-to-decision or JTC measures for comparison between groups.

For accuracy, effects involving Group differences were not significant (all $ps > 0.15$). There were significant effects of Match Status, $F(1, 108) = 4.39$, $p < 0.05$, $\eta^2_p = 0.04$, Strength of Evidence, $F(1, 108) = 43.67$, $p < 0.001$, $\eta^2_p = 0.29$, and a significant Match Status × Strength of Evidence interaction, $F(1, 108) = 8.15$, $p < 0.01$, $\eta^2_p = 0.07$. In accordance with the RT effects, the accuracy was higher for Match relative to Non-match conditions in the Weak condition ($M = 88\%$ vs. 85%, respectively), which was not the case in the Strong condition ($M = 92\%$ for both Strong Match and Strong Non-match).

3.2. Neuroimaging

The scree plot (Cattell, 1966, 1977) of singular values suggested that a four-component solution should be extracted. Only Component 4 showed significant differences between schizophrenia patients experiencing delusions and those not experiencing delusions; therefore, only the results for Component 4 are reported here, and the results for Components 1–3 are presented in the Supplementary Material.

3.2.1. Component 4: visual attention/default mode network (DMN)

The brain regions associated with Component 4 are displayed in Fig. 2A, Fig. S8, and Fig. S12, and the estimated HDR shape is displayed in Fig. 2B. This network showed activation in the Middle Frontal Gyrus (BA 6), Precentral Gyrus (BA 44), Occipital Fusiform Gyrus (BA 18), Cingulate Gyrus (BA 32), and bilateral Insular Cortices, and decreased

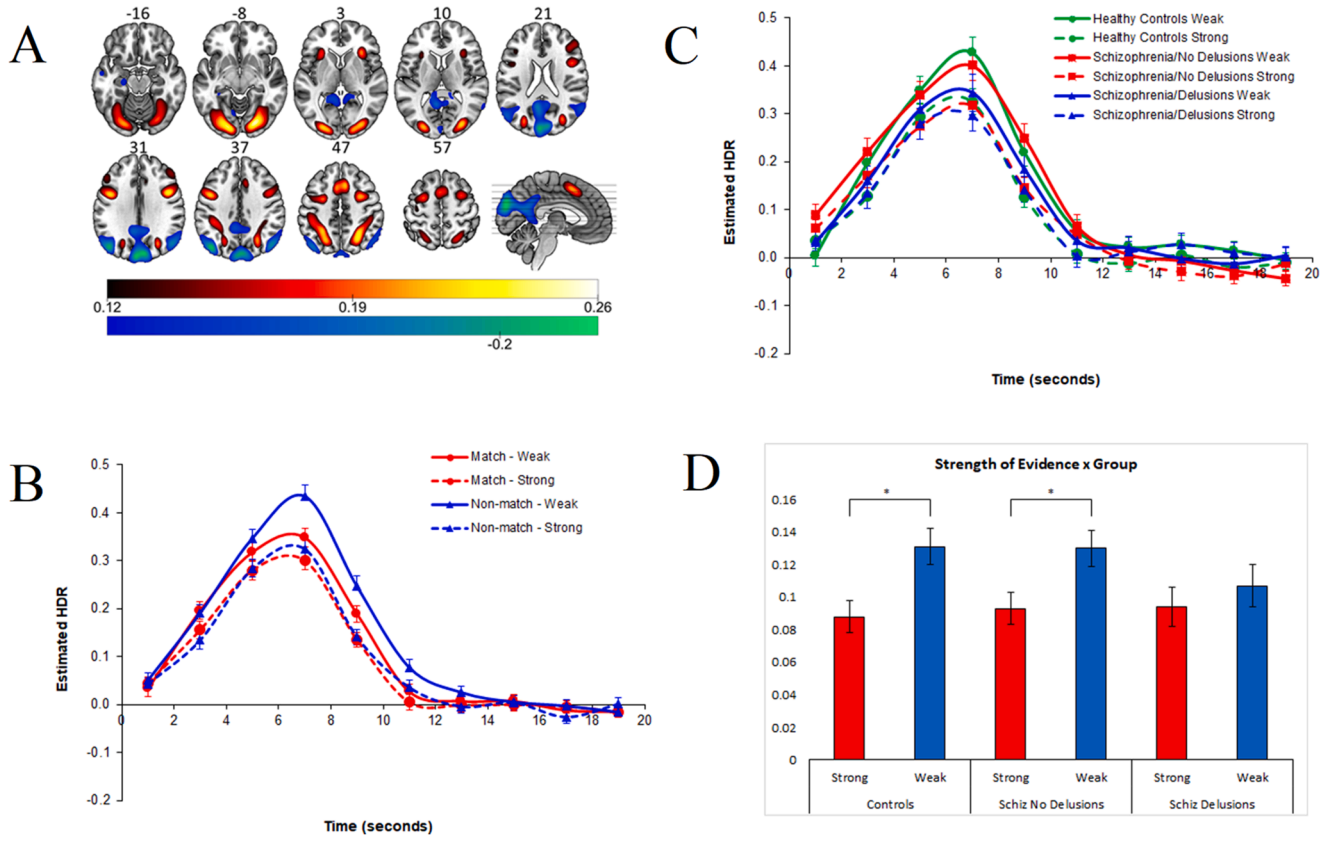

Fig. 2. A: Dominant 10% of component loadings for Component 4 (Visual Attention/Default Mode Network; DMN). Red/yellow indicates positive loadings (positive threshold = 0.12, max = 0.26). Blue/green areas indicate negative loadings (negative threshold = −0.12, min = −0.22). MNI z-axis coordinates are listed above axial slices. B: Mean FIR-based predictor weights plotted as a function of post-stimulus time (TR = 2000 ms) for Match Status and Strength of Evidence. C: Mean FIR-based predictor weights plotted as a function of post-stimulus time (TR = 2000 ms), Strength of Evidence and Group. D: Mean HDRs averaged over all time bins and presented as a function of Group and Strength of Evidence.

activity in Cingulate Gyrus (BA 27), Precuneus Cortex (BA 23) and Cuneal Cortex (BA 18). Table S4 includes the complete anatomical description of regions involved in the functional network. Fig. S8 shows how this network overlaps with resting state networks (Buckner et al., 2011; Choi et al., 2012; Yeo et al., 2011), and Fig. S12 shows how it overlaps with task-based networks (Percival et al., 2020).

The HDR shape for Component 4 peaked at 6–7 s, and displayed increased activity early in the trial, 3 s after stimulus onset. This suggests a type of early visual attention that activates on contact with the stimulus. For Component 4, repeated measures ANOVAs revealed significant main effects of Time, $F(9, 972) = 133.80$, $p < .001$, $\eta^2_p = 0.55$, Strength of Evidence, $F(1, 108) = 42.96$, $p < 0.001$, $\eta^2_p = 0.29$, and Match Status, $F(1, 108) = 9.00$, $p < 0.05$, $\eta^2_p = 0.08$. Significant two-way interactions were observed for Match Status × Time, $F(9, 972) = 3.94$, $p < 0.001$, $\eta^2_p = 0.04$, and Strength of Evidence × Time, $F(9, 972) = 8.36$, $p < .001$, $\eta^2_p = 0.07$, but the three-way interaction was not significant ($p > 0.25$). The Match Status × Time interaction was dominated by increases from time bins 3 and 4, $F(1, 108) = 5.68$, $p < 0.05$, $\eta^2_p = 0.05$, and 6 and 7, $F(1, 108) = 6.40$, $p < 0.05$, $\eta^2_p = 0.06$, caused by a higher peak and slower return to baseline for Non-match relative to Match (averaged over Strength of Evidence; see Fig. 2B). The Strength of Evidence × Time interaction was dominated by the increases from time bins 1 and 2, $F(1, 108) = 7.40$, $p < 0.01$, $\eta^2_p = 0.06$, and decrease from times 5 and 6, $F(1, 108) = 7.40$, $p < 0.01$, $\eta^2_p = 0.06$, caused by a higher peak and slower return to baseline for Weak relative to Strong conditions when averaged over match status (see Fig. 2B).

With respect to the Group factor, a significant Strength of Evidence × Group interaction was present, $F(2, 108) = 3.36$, $p < 0.05$, $\eta^2_p = 0.06$, and no other main effects or interactions involving Group were significant (all $ps > 0.30$). The interaction was significant when only the two patient groups were included in the analysis, $F(1, 68) = 4.27$, $p < 0.05$, $\eta^2_p = 0.06$, and not when only the control and patient group without delusions were included, $F(1, 80) = 0.40$, $p = 0.53$. This interaction was due to the Weak > Strong contrast being much stronger for the healthy controls, $F(1, 40) = 27.09$, $p < 0.001$, and patient group not experiencing delusions, $F(1, 40) = 29.36$, $p < 0.001$, compared to the patients experiencing delusions, $F(1, 28) = 1.93$, $p = 0.18$ (see Fig. 2D, or compare dotted lines and solid lines, within colours, in Fig. 2C).

4. Discussion

In the current fMRI study, we identified activity in a brain network involved in gathering information under conditions of weak versus strong evidence to observe impairment in delusions in schizophrenia. The spatiotemporal features suggested involvement in early visual attention, and activation showed no difference between weak- and strong-match conditions for patients experiencing delusions. These results suggest that activity in this brain network, which is normally strongly elicited under conditions of weak evidence, is reduced for people with schizophrenia experiencing delusions. This provides a candidate mechanism for how certainty in delusional thought can be present even under conditions of weak evidence, and suggests involvement in the absence of scrutiny in delusions that would normally give rise to doubt under conditions of weak evidence.

This set of results cannot be directly compared to previous fMRI studies that employed the fish/lakes/boxes paradigm to investigate probabilistic reasoning, because in all past studies, only the brain images for contrasts of task conditions were reported in detail, as opposed to the current dimensional approach to characterizing networks and displaying their associated HDRs for all conditions. However, the probabilistic reasoning > control contrast in past studies showed activity in similar fronto-parietal regions as reported in the current study's Fig. 2 (Andreou et al., 2018a Fig. 1A; Esslinger et al., 2013 Fig. 4A; Krug et al., 2014b, Fig. 2). The interpretation of the cognitive function associated with this network is visual attention (Tomasi et al., 2007; Wager et al., 2004); therefore, from this it can be concluded that the basis of the contrast images from the previous fMRI studies (probabilistic reasoning > control) are grounded in the brain networks presented here, which underpin visual attentional processes. This is also in accordance with the commonly reported finding of impairment in prefrontal regions in schizophrenia (Coltheart et al., 2007; Corlett et al., 2007; Ford et al., 2002; MacDonald et al., 2005).

The cognitive process(es) underpinning delusions have been variously described as hypersalience of EVH matches (Speechley et al., 2010), a reduced threshold for accepting evidence (LA) (Moritz et al., 2017), overconfidence (Balzan, 2016), increased certainty (Broyd et al., 2017) or heightened salience due to prediction-error disruption (Corlett et al., 2010). These accounts (among others) provide different theories for how delusions "feel" true, are assigned certainty, and are fluently processed such that they do not elicit the type of scrutiny that would normally give rise to doubt (Broyd et al., 2017; Fazio, 2020; Unkelbach and Greifeneder, 2013). The present set of results suggests that during conditions of weak evidence, the fMRI network measures an early, basic visual attentional process that is reduced in patients experiencing delusions relative to those without, and the resulting misplaced certainty could be the result of, and/or enhanced by, increased cognitive biases underlying delusions (Balzan and Moritz, 2017; McLean et al., 2017; So et al., 2016). Patient-group differences were present only on this visual attentional network and not the other three (see Supplementary Material), which accounts for the intact behavioural measures, as the brain networks are largely intact. This network has strong anatomical representation of the salience network relative to the other networks (discussed in Supplementary material, and directly compared with Component 1 in Fig. S4). The aberrant salience account of delusions holds that salience of external and internal representations are mediated by dopamine, with a hyperdopaminergic state leading to aberrant assignment of salience to the patient experience (Gray, 1998; Kapur, 2003; Miyata, 2019). The current set of results suggest that this hyperdopaminergic state manifests in fMRI as reduced activity in an early, basic visual attentional process when confronted with weak evidence, incorrectly leading to manifestation of a feeling of fluency and misplaced certainty. This may lead to premature termination of data collection in probabilistic reasoning (Dudley et al., 2016; Fine et al., 2007; Garety et al., 1991; Huq et al., 1988; McLean et al., 2017; Menon et al., 2008, 2006; Moritz and Woodward, 2005; Woodward et al., 2009), and also accords with reports of reduced mismatch negativity in schizophrenia, an electroencephalogram index that is elicited in response to stimuli that deviate from a predictable sequence (Javitt, 2009). When weak evidence does not elicit the attentional processing that normally leads to doubt and searching for more evidence, this is a candidate neural process for 'seeding' delusions.

Limitations of this study include group differences in education, IQ levels, medication between controls and patients, and baseline levels of BOLD activity in schizophrenia (Pinkham et al., 2015); however, these variables presumably did not differ between groups of schizophrenia patients experiencing and not experiencing delusions, and would apply equally to all components despite only Component 4 showing differences between patients with and without delusions, so would not affect the main findings. The SSPI items "Hallucinations" and "Impaired Insight" also differed between the groups of patients experiencing delusions and those not experiencing delusions. Although these could have played a confounding role in group differences found in functional network activation, reduced insight is to some extent redundant to delusions, and delusion severity is known to correlate with hallucination severity (e.g., Liddle et al., 1989; Woodward et al., 2003).

This was the first study to examine task-based functional network activity in patients with schizophrenia experiencing and not experiencing delusions during a single-trial probabilistic reasoning task. Among the four networks identified, a visual attention network appears to play an important role in delusions; whereas the healthy control group and the group with schizophrenia not experiencing delusions exhibited greater activity when evaluating weak evidence (in

comparison to strong evidence), the patients experiencing delusions did not, possibly reflecting the experience of fluency when evidence is weak, leading to misplaced certainty, possibly to early termination of data collection and JTC. The latter bias was not measured in the current study due to the single-trial design, and a direction for future research is to demonstrate correlations between activity in brain networks and cognitive biases on behavioural tests (e.g. Lavigne et al., 2020a). Brain networks associated with delusions/certainty/doubt are candidate targets for non-invasive neuromodulation/neurostimulation treatments such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). If such an approach is to be effective in the future, it should be combined with medication and treatments that target cognitive biases, such as metacognitive training (MCT; Eichner and Berna, 2016; Moritz and Woodward, 2007) or cognitive behavioural therapy (CBT; Garety, 2008; Mehl et al., 2015; Wykes et al., 2008), adding to the increasing options for treatments for people with schizophrenia.

Declaration of Competing Interest

None of the authors have financial disclosures or conflicts to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2022.111472.

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