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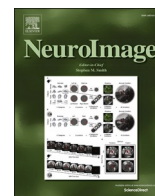
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Functional connectivity and glutamate levels of the medial prefrontal cortex in schizotypy are related to sensory amplification in a probabilistic reasoning task

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ABSTRACT

The *circular inference* (CI) computational model assumes a corruption of sensory data by prior information and vice versa, leading at the extremes to 'see what we expect' (through prior amplification) and/or to 'expect what we see' (through sensory amplification). Although a CI mechanism has been reported in a schizophrenia population, it has not been investigated in individuals experiencing psychosis-like experiences, such as people with high schizotypy traits. Furthermore, the neurobiological basis of CI, such as the link between hierarchical amplifications, excitatory neurotransmission, and resting state functional connectivity (RSFC), remains untested.

The participants included in the present study consisted of a subsample of those recruited in a study previously published by our group, [Kozuharova et al. \(2021b\)](#). We included 36 participants with High (n=18) and Low (n=18) levels of schizotypy who completed a probabilistic reasoning task (the Fisher task) for which individual confidence levels were obtained and fitted to the CI model. Participants also underwent a 1H-Magnetic Resonance Spectroscopy (MRS) scan to measure medial prefrontal cortex (mPFC) glutamate metabolite levels, and a functional Magnetic Resonance Imaging (fMRI) scan to measure RSFC of the medial prefrontal cortex (mPFC).

People with high levels of schizotypy exhibited changes in CI parameters, altered cortical excitatory neurotransmission and RSFC that were all associated with sensory amplification. Our findings capture a multimodal signature of CI that is observable in people early in the psychosis spectrum.

1. Introduction

Impairments observed along the psychosis spectrum might be understood within the framework of Bayesian inference and predictive coding ([Denève & Jardri, 2016](#)). In this framework, neural processing is interpreted as a propagation of bottom-up sensory information and top-down prior knowledge, which are optimally combined using Bayes principles. When reverberations of these messages occur in an uncontrolled fashion (i.e., prior beliefs are misinterpreted as sensory information, and vice et versa), rigid and unshakable beliefs can emerge in the network, a phenomenon called "Circular Inference" (CI). More

precisely, ascending loops make us '*expect what we see*' translating in over-relying on sensory evidence, while descending loops cause us to '*sense what to expect*', with prior beliefs being overcounted ([Jardri & Denève, 2013](#)). As a result of reverberation, inputs are counted multiple times, explaining the emergence of erroneous percepts.

Previous studies examining CI in schizophrenia samples ([Jardri et al., 2017](#); [Simonsen et al., 2021](#)) reported stronger ascending loops in schizophrenia patients than controls, while this amount of sensory amplification was shown to be associated with the severity of hallucinations and delusions ([Jardri et al., 2017](#)). Interestingly, CI was also evidenced to a smaller extent in healthy subjects, suggesting that a

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tendency to misinterpret top-down predictions as if they were external sensory signals ('perceive what we expect') is present in the general population (Leptourgos et al., 2017, 2020).

From a mechanistic point of view, CI assumes a link between messages propagation in the cortical hierarchy and a tight control of the neural excitatory/inhibitory (E/I) balance (Jardri & Denève, 2013; Leptourgos et al., 2017, 2022). If neural inhibition appears insufficient, uncontrolled recurrent excitation occur, leading to a reverberation of externally triggered sensory evidence and/or internally generated prior expectations. We already know that alterations of the excitatory neurotransmission (Kehrer et al., 2008; Lewis, 2014; Lisman et al., 2008) plays a major role in neural information processing (Hensch & Fagiolini, 2004; Okun & Lampl, 2008) and may sustain the processes of prior and sensory integration in schizophrenia (Jardri & Denève, 2013). Notably, dysregulation of glutamatergic circuitry in the medial prefrontal cortex (mPFC) has been implicated in schizophrenia (Bauer et al., 2008; Oni-Orisan et al., 2008; Woo et al., 2008; Zmarowski et al., 2009).

Alteration of glutamatergic neurotransmission has also been observed in schizotypy, a latent personality organization reflecting an underlying vulnerability to developing schizophrenia (Barrantes-Vidal et al., 2015). Individuals with higher schizotypy traits exhibited reduced levels of glutamate metabolites in the mPFC when compared to individuals with lower schizotypy traits (Kozhuharova et al., 2021). Furthermore, functional and structural changes in the mPFC have been evidenced in high schizotypy populations (Wang et al., 2015). Investigating schizotypal traits in non-clinical populations has also the advantage of providing information about the neurobiological alterations underlying psychosis-like symptoms, without the effect of confounding factors like hospitalisation or medication (Ettinger et al., 2014). However, CI has yet to be investigated in people with high schizotypy traits.

In the present study, we sought to replicate findings of aberrant sensory amplifications observed in patients with schizophrenia (Jardri et al., 2017; Simonsen et al., 2021), in a high schizotypy sample (HS) thought to be at elevated risk for psychotic-like experiences. We thus quantified how participants with high and low levels of schizotypy derive confidence from sensory evidence and prior information, using a probabilistic reasoning task that can be fitted with CI. Second, we examined if mPFC levels of glutamate in high and low schizotypy participants were associated with the CI parameters showing significant group differences. Lastly, we predicted that changes in mPFC resting state functional connectivity (RSFC) would be seen in a HS group (vs. LS group) and would be associated with sensory amplifications.

2. Methods

2.1. Participants

The participants in the present study were a subsample of those recruited to the Kozhuharova et al. (2021) study previously published by

our group (see Table 1). More information about recruitment and exclusion criteria for recruitment are available in the Kozhuharova et al. (2021) study and are also reported in the Supplementary Material (c.f. 1. Methods: Recruitment and exclusion criteria). In brief, the bottom and top deciles (10%) of the Schizotypal Personality Questionnaire (SPQ) distribution (individuals scoring below 12 and above 41 on the SPQ), and in which 1H-MRS, Fisher task, and RSFC data were also available, were retained for the present study.

As such, data from 17 participants reported in Kozhuharova et al. (2021) were excluded from the present analysis as 1H-MRS, Fisher Task, and/or RSFC data were missing. The final sample comprised 36 participants (HS: n=18, mean age(sd)=19.3(1.03), n(females)=11; LS: n=18, mean age(sd)=20.0(1.33), n(females)=13).

Ethical approval for the study was obtained from the University of Roehampton's Ethics Committee and written informed consent was provided by all participants. Research participants were compensated for their time.

2.2. Study measures and statistical analyses

2.2.1. Clinical and cognitive assessments

Intellectual functioning was measured with a validated short version of the Wechsler abbreviated scale of intelligence (WASI II; (McCrimmon & Smith, 2013) and working memory was assessed using the digit span backward task (Dobbs & Rule, 1989). These measures were used to ensure that High and Low schizotypy groups were matched for estimated IQ and working memory function. Notably to ensure that all participants were able to correctly understand and perform the Fisher task.

The Schizotypal Personality Questionnaire (SPQ) provides a self-reported measure of individual differences in schizotypal personality traits and includes three latent dimensions: positive, negative, and disorganised. These dimensions mimic the 3-factors structure of schizophrenia and clinical high-risk states. The SPQ consists of 74 Yes/No items (Raine, 1991).

The Beck Depression Inventory short form (BDI-SF, Beck, 1961) was used to measure depression, scores higher than 10 are associated with moderate and severe depressive symptoms. As expected, BDI scores differed between HS and LS participants, and were later included in our statistical models as a covariate of no interest since we wanted to focus on psychotic beliefs (see below).

Descriptive statistics and statistical comparisons between High and Low schizotypy groups on all demographic data and questionnaire's variables are presented in Table 1.

2.2.2. Circular inference: the fisher task

Participants completed a version of the Fisher task introduced by Jardri and colleagues (Jardri et al., 2017) that comprised 8 blocks of 20 trials each for a total of 160 trials per participants (experiment files can be downloaded at: https://github.com/RenaudJA/Fisher_Task_Exp). The prior was represented by a first screen showing two fish baskets (left

Table 1
Descriptive statistics of clinical and cognitive measures and participants' demographics.

| Variables | High schizotypy | Low schizotypy | Statistic (t) | p-value | Effect size (Cohen's d) |
|------------------|-------------------------------------|-------------------------------------|----------------|---------|-------------------------|
| n | 18 | 18 | | | |
| Age | 19.3 (1.03) | 20.0(1.33) | -1.68 | 0.101 | -0.561 |
| Sex | Male: n=7, Female: n=11 | Male: n=7, Female: n=13 | $\chi^2=0.500$ | 0.480 | Odd ratio=0.604 |
| Ethnicity | Asian:2, Idian:1, Mixed:1, White:14 | Asian:0, Idian:0, Mixed:1, White:15 | $\chi^2=2.01$ | 0.734 | Cramer's V=0.239 |
| IQ | 92.7(9.07) | 95.3(9.95) | -0.823 | 0.416 | -0.274 |
| Digit span | 4.17(0.924) | 4.56(1.15) | -1.12 | 0.271 | -0.373 |
| SPQ Total | 47.5(5.36) | 8(2.99) | 27.3 | <0.001 | 9.10 |
| SPQ Positive | 21.6(5.16) | 2.72(2.14) | 14.3 | <0.001 | 4.77 |
| SPQ Negative | 20.4(4.31) | 3.83(2.38) | 14.3 | <0.001 | 4.77 |
| SPQ Disorganized | 11.1(2.75) | 2.17(2.48) | 10.2 | <0.001 | 3.39 |
| BDI-SF | 12.1(4.77) | 4.06(3.73) | 5.60 | <0.001 | 1.87 |

Note. Age is presented as Mean(SD); SPQ corresponds Schizotypal Personality Questionnaire; IQ for Intelligence Quotient; BDI for Beck Depression Inventory.

and right) presented for 1000 ms. Participants were instructed to interpret the size of the basket as the degree of preference that the fisher has for the right or left lake. Then, this information was removed. After a delay of 50 ms, the likelihoods were presented at the same location where the basket were previously showed. The likelihood represents the proportion of black and red fish found within both lakes (right and left). The number of fish present in each lake was fixed, and the value associated to the prior and sensory evidence ratios of the two lakes were symmetrical.

Participants were instructed to report their confidence that a red fish originated from one of the two lakes. Their responses were recorded using a semi-circular scale, ranging from 100% confidence that the fish originated from the left lake to a 100% confidence it originated from the right lake. Reaction times (RT) were recorded. There was a 200 ms delay before the onset of the next trial. The prior and likelihood information were manipulated and presented in a pseudo-random manner for each trial and could take different values: 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 for the prior, and from 0 until 1 for the likelihood.

Two distinct variables were manipulated in the Fisher task. i) The size of the baskets reflected the prior probability for each lake. ii) The proportion of fish in each lake reflected the sensory evidence (i.e., the likelihood that the fish originated from the right or left lake). Participant's responses were calculated as the normalized position on the confidence scale and were considered a proxy of the posterior probability, see [Jardri et al \(2017\)](#) for full details. These responses ranged between 100% confident that the fish came from the left lake to 100% confident that the fish came from the right lake. This position was secondarily rescaled to range between 0.00001 et 0.99999 (i.e., participant's confidence). Sensory evidence varied between 0 (proportions of fish in the two lakes is equal, no sensory evidence) and 1 (all the red fish are in one lake, completely unambiguous). Prior congruency varied between -1 (the prior contradicted the sensory evidence the most) to 1 (the prior confirmed the sensory evidence the most). RTs were used to exclude the potential confounding effect of speed or accuracy between the two groups. These variables were firstly used in the *model free analyses*.

The CI model implements a variant of the *Belief propagation* algorithm, which considers that recurrent information is not totally controlled and cancelled when propagated in the hierarchy. See [Jardri et al \(2017\)](#) for a detailed explanation of the model estimation, equations, and parameters calculations. Briefly, CI assumes that sensory evidence and prior can reverberate, rather than being just considered once and added as in the weighted Bayes model. This model has four free parameters that will be used in the model-based analyses. Firstly, the sensory weight w_s and the prior weight w_p , representing a fixed degree of trust for the sensory information (fish proportion), or the prior information (basket size). And secondly, two amplification factors, representing the number of times the sensory evidence (α_s) or the prior information (α_p) is taken into account redundantly before the network can reach a decision. Each time the sensory evidence is reverberated into the recurrent network, it will be interpreted as new additional evidence. In other words, at each reverberation, the likelihood is multiplied by itself, representing a redundant contribution ($\alpha_s L_s$). Regarding reverberation of the prior, redundant contribution translates in ($\alpha_p L_p$). Because participants do not trust completely either source of information, the effective contributions of over-counting information can be summarized as $F(\alpha_s L_s, w_s)$ and $F(\alpha_p L_p, w_p)$. Furthermore, over-counted information will equally corrupt the top-down and bottom-up components of inference because these are the results of multiple reverberations up and down in the hierarchy. The simplified equation of the CI model is thus as follows:

$$Lc = F(L_s + F(\alpha_p L_p, w_p) + F(\alpha_s L_s, w_s), w_s) \\ + F(L_p + F(\alpha_s L_s, w_s) + F(\alpha_p L_p, w_p), w_p)$$

For model comparisons, we referred to a 'simple Bayes' model,

integrating priors and likelihoods with the same initial trust to generate posterior beliefs ((see Supplementary material Fig. 2).

Model-free analyses: Group comparisons were conducted using general linear mixed models, that modelled the parametric effect of sensory evidence, prior congruency, and their interaction as fixed-effects, while participants were treated as a random factor. The same set of analyses were conducted on the RTs to reject the hypothesis of a potential confounding effect of speed/accuracy trade-off between groups.

Circular inference model-based analyses: To assess the different factors that might affect group differences in the model parameters, we compared the four parameters' values between HS and LS: α_s , α_p , w_s and w_p using a MANCOVA, with depression (BDI) scores as covariate of no interest. Furthermore, we computed correlation(s) to assess the relationship between model parameters that showed significant differences between LS and HS groups, and mPFC glutamate metabolite concentrations using the same covariate of no interest than in the previous analysis.

For both 1H-MRS and RSFC analyses, MRI scans were acquired with a 3T Siemens Magnetom TIM trio scanner with a 32-channel head coil at the Combined Universities Brain Imaging Centre.

2.2.3. 1H-Magnetic resonance spectroscopy

The 1H-MRS procedure was described by Kozuharova and colleagues ([Kozuharova et al., 2021](#)). Data were extracted and pre-processed using LCModel 6.3-1 N and the basis set was simulated using FID-A for TE=8.5 ms, magnetic field strength=3T and assuming ideal RF pulses. amongst the 19 simulated basis spectra, glutamate (GLU) metabolite concentrations were computed as indices of excitatory neurotransmission. Briefly, 1H-MRS in vivo spectra were acquired using spin echo full intensity-acquired localized spectroscopy (SPECIAL: [Mlynárik et al., 2006](#)) from a $20 \times 20 \times 20$ mm voxel located in the bilateral medial PFC during rest (see Kozuharova et al. for control measures, correction, and processing). Voxel placement is shown for a single participant in the Supplementary material Fig. 1. Medial PFC GLU levels were corrected for voxel grey matter, white matter and CSF values as reported in [Kozuharova et al. \(2021\)](#). We excluded two participants for the MRS analyses, as Glu-spectra with Cramer-Rao lower bounds (CRLB) exceeded 20%. CRBL-GLU did not differ between groups (HS (n=16), Mean:5.13, sd:1.45 vs LS (n=18), Mean:5.33, sd:1.91; t (32)=-0.354, p=0.725). To test for group effects between LS and HS groups, MANCOVA with corrected GLU metabolite levels as dependant variables were performed, with depression (BDI) as covariate of no interest because glutamate excitotoxicity has been reported to be associated with depressive states ([Marsden, 2011](#); [McCarthy et al., 2012](#)).

2.3. Resting-state fMRI data acquisition and functional connectivity analyses

A 10-minute resting-state echo-planar imaging (EPI) scan (32 axial sections collected with multiband interleaved ascending acquisition; voxel size=3 mm x 3 mm x 4.5 mm; TE=30 ms; TR=2000 ms; flip angle=70°; matrix=64 x 64; FOV=192 mm; 300 vol) was acquired for each participant. Participants were instructed to lie still with their eyes closed and to remain awake during the scan. High resolution five minutes T1-weighted anatomical images were also acquired (TR=1900 ms; voxel size= 1 mm x 1 mm x 1 mm; plane resolution= 256 x 256 x 176 slices).

The data were pre-processed using SPM12 (The Wellcome Department of Cognitive Neurology, London, UK, <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). All functional images were slice-timing corrected and realigned to the first volume using a 6-parameter rigid body transformation. The mean image generated was spatially normalized into standard stereotaxic space, using the Montreal Neurological Institute (MNI) echo planar imaging (EPI) template. Computed transformation parameters were applied to all functional images, interpolated to isotropic voxels of 2 mm^3 and the resulting images were

smoothed using an 8-mm full-width half-maximum (FWHM) Gaussian kernel.

Functional connectivity analyses were carried out using the CONN-fMRI Functional Connectivity toolbox (www.nitrc.org/projects/conn, Whitfield-Gabrieli & Nieto-Castanon, 2012). Using the default preprocessing parameters, the potential confounding effects of head motion artifacts, white matter and CSF BOLD signal were defined and regressed out. Denoising and band pass filtering was performed with a frequency window of 0.01 to 0.1 Hz.

Seed-to-voxel whole-brain functional connectivity maps were created for each participant. Bivariate-correlation analyses were used to determine the association of the BOLD time series between the seed region and all other voxels in the brain. The predefined seed region was based on the spectroscopy placement of the mPFC, which is the most used MRS voxel placement for psychosis-populations (Egerton et al., 2017; Kozhuharova et al., 2021; Modinos et al., 2017; Stone et al., 2001). The seed was placed in the Frontal Medial Cortex (7796 voxels, mm^3), defined by the CONN atlas cortical ROIs (Harvard-Oxford, Desikan et al., 2006).

Second level analyses were performed to create seed-to-voxel connectivity maps and LS and HS groups as a between groups factor. We were interested in the effect of the main variables of interest defined by previous analyses - Glutamate metabolite concentrations (GLU) and Ascending loop (α_s) as the circular inference parameter of interest, on resting state functional connectivity between HS and LS groups. Thus, we included participants' GLU concentrations, and α_s scores in two separate analyses as principal regressors. Due to the significant difference in depression scores between groups, BDI scores were included as covariates of no interest. A peak voxel threshold of $p(\text{unc}) < 0.005$ and a cluster extent threshold of $p(\text{FWE}) < 0.05$ were set for bidirectional explorations of connectivity (i.e., positive, and negative associations). Results were considered significant if clusters survived FWE correction of $p < 0.05$.

3. Results

3.1. Participants characteristics

Participant demographic and clinical data are presented in Table 1. Overall, HS and LS groups were matched for age, sex, ethnicity, estimated intellectual functioning, and working memory. By design HS group presented significantly higher schizotypal total and subscales scores, relative to the LS group. Of note, results of the demographic and clinical data between groups in the original sample (P. Kozhuharova, Diaconescu, et al., 2021) remain significant for the reduced sample included here.

3.2. Circular inference: the fisher task

3.2.1. HS participants were overall more confident in their responses

Across all participants, mean confidence increased with sensory evidence (main effect of sensory evidence: $F=24.686$, $t=4.968$, $p < 0.001$), and the effect of sensory evidence was modulated by prior congruency (interaction sensory evidence x prior congruency: $F=4.936$, $t=2.220$, $p=0.027$, Table 2 & Fig. 1A), confirming that all participants performed the task properly and used both types of information to make a decision. Participants in the HS group were overall more confident in their responses than those in the LS group (Table 2, $F=5.554$, $t(\text{low-high}) = -2.356$, $p=0.019$). However, the two-way interaction between group and sensory evidence, or relative prior on the mean confidence was non-significant (Table 2), as was the three-way interaction group x sensory evidence x prior congruency.

To check for potential effect of speed/accuracy trade-offs we examined task reaction times. Similar reaction times were observed for both groups ($F=2.402$, $t(\text{low-high}) = 1.550$, $p=0.122$). Across all participants, mean RT decreased with prior congruency ($F=33.135$, $t=-5.755$, $p < 0.001$), and the effect of prior congruency was modulated by the type of sensory evidence (prior congruency x sensory evidence, $F=8.504$, $t=-2.915$, $p=0.004$). The two-way interactions between group and either sensory evidence or prior congruency were non-significant (Table 3 & Fig. 1.B).

3.2.2. HS participants overcounted sensory evidence and underweighted priors

MANCOVA showed significant differences for the model parameters (α_s , W_s and W_p) between HS and LS groups (Table 4 and Fig. 2). After controlling for depression, we observed that HS participants over-weighted the sensory evidence (W_s ; $F=7.258$, $p=0.011$) and over-counted their inputs as shown by increased number of ascending loops (α_s ; $F=10.572$, $p=0.003$), and underweighted their priors (W_p ; $F=5.035$, $p=0.032$). However, groups did not differ with regard to the extent to which the priors were over-counted, as evaluated by the amount of descending loops (α_p ; $F=1.505$, $p=0.229$).

3.3. HS participants showed a decrease in excitatory neurotransmission (glutamate metabolite levels)

The significant results regarding the glutamate levels comparison between group in Kozhuharova et al. (2021) remained significant in the sub sample reported here. MANCOVA showed that the HS group ($M=5.28$, $SD=2.57$) showed significantly reduced mPFC GLU metabolite levels relative to the LS group ($M=6.97$, $SD=2.20$), $F=6.74$, $p=0.014$, $\eta^2=0.165$.

Moreover, partial correlation analyses between the CI model parameter presenting between-group differences and mPFC metabolites levels revealed a significant negative correlation between α_s (i.e. sensory amplification) and GLU metabolite levels across all subjects (Pearson's

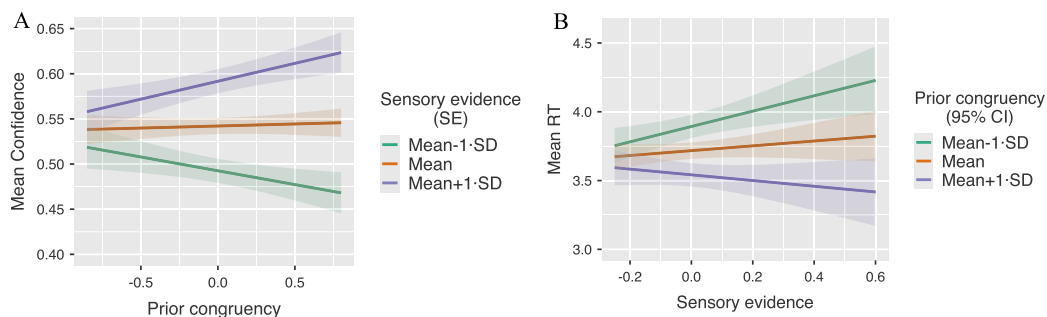


Fig. 1. A. Effect of the interaction between sensory evidence * prior congruency on mean confidence. B. Effect of the interaction between prior congruency * sensory evidence on mean reaction time (Mean RT). Note. Coloured lines represent + or - 1 standard deviation from the mean. Shades represent confidence intervals (95%).

Table 2
Model free analyses of participants' mean confidence.

| Names | Effect | Estimate | SE | 95% Confidence Interval | | df | t | p |
|---|--|----------|---------|-------------------------|----------|--------|---------|--------|
| | | | | Lower | Upper | | | |
| (Intercept) | (Intercept) | 0.54212 | 0.00892 | 0.5246 | 0.55960 | 1834.6 | 60.7954 | < .001 |
| Group | Low - High | -0.04202 | 0.01783 | -0.0770 | -0.00706 | 1834.6 | -2.3560 | 0.019 |
| Sensory Evidence | Sensory Evidence | 0.21812 | 0.04391 | 0.1321 | 0.30418 | 53.7 | 4.9678 | < .001 |
| Prior Congruency | Prior Congruency | 0.00454 | 0.01621 | -0.0272 | 0.03630 | 1832.2 | 0.2799 | 0.780 |
| Sensory Evidence * Prior Congruency | Sensory Evidence * Prior Congruency | 0.15449 | 0.06958 | 0.0181 | 0.29087 | 1832.1 | 2.2202 | 0.027 |
| Group * Sensory Evidence | Low - High * Sensory Evidence | -0.05400 | 0.08782 | -0.2261 | 0.11811 | 53.7 | -0.6150 | 0.541 |
| Group * Prior Congruency | Low - High * Prior Congruency | 0.01877 | 0.03242 | -0.0448 | 0.08230 | 1832.2 | 0.5789 | 0.563 |
| Group * Sensory Evidence * Prior Congruency | Low - High * Sensory Evidence * Prior Congruency | -0.00212 | 0.13916 | -0.2749 | 0.27064 | 1832.1 | -0.0152 | 0.988 |

Note. SE stands for Standard Error.

Table 3
Model free analyses of participants' mean reaction times.

| Names | Effect | Estimate | SE | 95% Confidence Interval | | df | t | p |
|---|--|----------|--------|-------------------------|--------|--------|---------|--------|
| | | | | Lower | Upper | | | |
| (Intercept) | (Intercept) | 3.7174 | 0.0305 | 3.6576 | 3.777 | 1841.9 | 121.828 | < .001 |
| Group | Low - High | 0.0945 | 0.0610 | -0.0251 | 0.214 | 1841.9 | 1.549 | 0.122 |
| Sensory Evidence | Sensory Evidence | 0.1754 | 0.1461 | -0.1110 | 0.462 | 46.3 | 1.200 | 0.236 |
| Prior Congruency | Prior congruency | -0.3190 | 0.0554 | -0.4276 | -0.210 | 1838.6 | -5.755 | < .001 |
| Sensory Evidence * Prior congruency | Sensory Evidence * Prior congruency | -0.6956 | 0.2386 | -1.1634 | -0.228 | 1838.6 | -2.915 | 0.004 |
| Group * Sensory Evidence | Low - High * Sensory Evidence | -0.1878 | 0.2923 | -0.7607 | 0.385 | 46.3 | -0.643 | 0.524 |
| Group * Prior congruency | Low - High * Prior congruency | -0.0336 | 0.1109 | -0.2509 | 0.184 | 1838.6 | -0.303 | 0.762 |
| Group * Sensory Evidence * Prior congruency | Low - High * Sensory Evidence * Prior congruency | 0.3050 | 0.4773 | -0.6304 | 1.241 | 1838.6 | 0.639 | 0.523 |

Note. Significant effects are presented in italic. SE stands for Standard Error.

Table 4
Comparison of CI model parameters between HS and LS groups controlling for the effect of BDI.

| MODEL COMPARISON | | VALUE | F | DF1 | DF2 | P |
|---|-------------------|----------------|-------|--------------|--------|-------|
| MODEL 1 | Hotelling's Trace | 0.0990 | 0.743 | 4 | 30 | 0.570 |
| MODEL 2 | Hotelling's Trace | 0.5612 | 4.209 | 4 | 30 | 0.008 |
| COMPARISON CI MODEL PARAMETERS (HS VS LS) | | Sum of squares | df | Mean squares | F | p |
| MODEL 1 | α_p | 8.39e-4 | 1 | 8.39e-4 | 0.111 | 0.741 |
| | α_s | 0.00300 | 1 | 0.00300 | 0.506 | 0.482 |
| | W_s | 0.03660 | 1 | 0.03660 | 1.394 | 0.246 |
| | W_p | 0.04257 | 1 | 0.04257 | 0.934 | 0.341 |
| MODEL 2 | α_p | 0.01138 | 1 | 0.01138 | 1.505 | 0.229 |
| | α_s | 0.06275 | 1 | 0.06275 | 10.572 | 0.003 |
| | W_s | 0.19052 | 1 | 0.19052 | 7.258 | 0.011 |
| | W_p | 0.22955 | 1 | 0.22955 | 5.035 | 0.032 |

Note. The four circular inference (CI) parameters are defined as follow: α_p stands for descending loops, α_s for ascending loops, W_s for weight of likelihood (weight put in sensory evidence), W_p for weight of prior. BDI stands for Beck Depression Inventory. HS stands for High Schizotypy group, LS for Low schizotypy group. Model 1 represents the MANCOVA comparing model parameters between groups (HS vs LS) without controlling for BDI. Model 2 represents the MANCOVA comparing model parameters between groups (HS vs LS) with BDI included as a covariate of no interest.

$r = -0.426, p = 0.029$). This correlation was driven by the HS group in which Pearson's $r = -0.518, p = 0.021$, while in the LS group, Pearson's $r = -0.170, p = 0.513$ (See Supplementary material Fig. 3).

3.4. Neural bases of sensory amplification in high vs low schizotypy

3.4.1. High vs low schizotypy

Seed based (mPFC) analysis between HS and LS groups did not reveal any significant RSFC group effect. Results remained the same with and without the inclusion of BDI scores as a covariate of no interest.

3.4.2. Interaction effects of glutamate and α_s with high vs low schizotypy

There was no significant supra-threshold effect of mPFC glutamate levels when added as regressor of interest to the RSFC group model. Results remained the same with and without the inclusion of BDI scores as a covariate of no interest.

However, when controlling for the effect of depression, a significant interaction effect between the ascending loop parameter (α_s) and group ($HS^* \alpha_s < LS^* \alpha_s$) was observed in Cluster A (Table 5 and Fig. 3A, $T(32) = -5.05; p(FWE) < 0.000$), Cluster B (Table 5 and Fig. 3B, $T(32) = 5.28; p(FWE) < 0.000$) and Cluster C (Table 5 and Fig. 3B, $T(32) = 4.40; p(FWE) < 0.000$). In Cluster A, the HS group showed a positive RSFC between mPFC and regions within the Cluster, whereas in the LS group, RSFC between mPFC and regions within the Cluster was negative. Cluster A included the right anterior supramarginal gyrus (x-y-z=60 -34 40; Z-peak=4.41; $p(unc) < 0.000$) and right posterior supramarginal gyrus (x-y-z=56 -32 56; Z-peak=3.98; $p(unc) < 0.000$).

In Clusters B and C, the HS group exhibited significantly reduced RSFC between mPFC and regions within Clusters B and C when compared to the LS group. Cluster B included the following regions: right medial frontal gyrus (BA10: x-y-z=2 64 20; Z-peak=4.77; $p(unc) < 0.000$; BA9: x-y-z=12 44 22; Z-peak=3.59; $p(unc) < 0.000$) and left anterior cingulate (x-y-z=-6 40 12; Z-peak=4.09; $p(unc) < 0.000$). Cluster C included: right superior frontal gyrus (x-y-z=4 50 -24; Z-peak=4.18; $p(unc) < 0.000$), right anterior cingulate (x-y-z=2 36 -6; Z-peak=3.92; $p(unc) < 0.000$) and left medial frontal gyrus (x-y-z=-2 30 -20; Z-peak=3.7; $p(unc) < 0.000$).

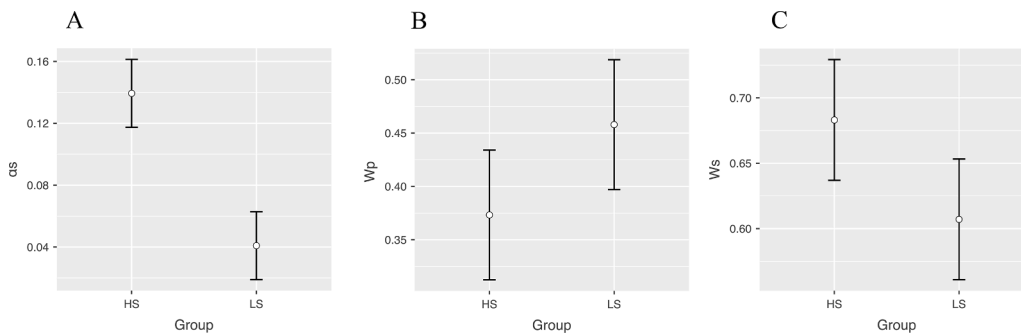


Fig. 2. Comparison of CI model parameters between HS and LS groups controlling for the effect of BDI. **A.** Comparison between groups on the Ascending loop parameter (α_s). **B.** Comparison between groups on the Weight of likelihood (W_s). **C.** Comparison between groups of the Weight of prior (W_p). *Note.* α_s for ascending loops, W_s for weight of likelihood (weight put in sensory evidence), W_p for weight of prior. Error bars represent standard error. HS stands for High schizotypy group, LS for low schizotypy group.

Table 5
Seed (mPFC) to voxels analyses - resting-state functional connectivity.

| | Cluster maxima | | | voxels per cluster | cluster p (FWE-corr) | cluster p (FDR-corr) | cluster p (unc) | Brain region | T | Z | peak p (FWE-corr) | peak p (FDR-corr) | peak p (unc) |
|--|----------------|-----|-----|--------------------|----------------------|----------------------|-----------------|---|------|------|-------------------|-------------------|--------------|
| | X | Y | Z | | | | | | | | | | |
| HS* $\alpha_s > LS^*\alpha_s$ | | | | | | | | | | | | | |
| Cluster A | 60 | -34 | 40 | 486 | 0.000 | 0.001 | 0.000 | Right-Supramarginal gyrus (Anterior division), BA 40 | 5.23 | 4.41 | 0.227 | 0.503 | 0.000 |
| | 56 | -32 | 56 | | | | | Right-Supramarginal gyrus (posterior division), BA 40 | 4.58 | 3.98 | 0.683 | 0.503 | 0.000 |
| HS* $\alpha_s < LS^*\alpha_s$ | | | | | | | | | | | | | |
| Cluster B | 2 | 64 | 20 | 929 | 0.000 | 0.000 | 0.000 | Right-Medial Frontal gyrus, BA 10 | 5.82 | 4.77 | 0.06 | 0.322 | 0.000 |
| | -6 | 40 | 12 | | | | | Left-Anterior Cingulate, BA 32 | 4.73 | 4.09 | 0.559 | 0.674 | 0.000 |
| | 12 | 44 | 22 | | | | | Right-Medial frontal gyrus, BA9 | 4.02 | 3.59 | 0.979 | 0.745 | 0.000 |
| Cluster C | 4 | 50 | -24 | 825 | 0.000 | 0.000 | 0.000 | Right-Superior frontal gyrus, BA 11 | 4.87 | 4.18 | 0.443 | 0.674 | 0.000 |
| | 2 | 36 | -6 | | | | | Right-Anterior cingulate, BA 32 | 4.48 | 3.92 | 0.76 | 0.674 | 0.000 |
| | -2 | 30 | -20 | | | | | Left-Medial frontal gyrus, BA 11 | 4.17 | 3.7 | 0.94 | 0.745 | 0.000 |

Note. Seed-to-voxels connectivity maps were compared in relation to the effect of ascending loops (α_s) between groups with BDI scores as a covariate of no interest. HS stands for High schizotypy, LS for Low schizotypy. Results were retained when clusters survived correction of $p(FWE) < 0.05$. Results yielded three main significant clusters: cluster A for the contrast HS > LS, and B and C for the contrast HS < LS, both including several brain regions. BA stands for Brodman Area.

4. Discussion

We explored probabilistic reasoning in participants with high and low levels of schizotypy using the Fisher task paradigm. Behavioural data were fitted with the *Circular Inference* (CI) model, which was found to robustly capture the variability in the behavioural data compared with a more conventional Bayesian approach (see Supplementary material Fig. 2). Participants in the HS group were more confident in their responses than those in the LS group, and HS and LS groups differed in terms of CI model parameters, suggesting that CI mechanisms may underlie schizotypal traits.

Using the Fisher task, we were able to compare the degree of confidence that both HS and LS groups derived from combining prior information and sensory evidence. As expected, across all participants, mean confidence levels increased with the amount of sensory evidence. However, individuals in the HS group were overall more confident than the LS group. This level of overconfidence has previously been shown in schizophrenia patients relative to healthy controls (Glöckner & Moritz, 2008; Jardri et al., 2017; Moritz et al., 2006). Our findings confirm that people with psychosis-like experiences are prone to make overconfident decisions (i.e., overconfidence for the same level of information). Behaviourally, this might mean that whilst low schizotypes tend to be cautious when presented with ambiguous inputs - modulating their behaviour to seek more information and withhold strong actions - people with high levels of schizotypy, closer to what is observed in schizophrenia (Jardri et al., 2017), tend to over interpret the predictive

value of the available information. Thus, an overconfidence bias seems to be observable across the psychosis spectrum, reinforcing the idea of shared behaviours observable between high schizotypy and full-blown psychosis.

Importantly, when controlling for subclinical depression levels, HS and LS groups differed on CI estimated parameters, suggesting that schizotypal traits are specifically associated with the inference mechanism. The large overcounting of sensory evidence and under weighting of priors in HS when compared to LS are in line with findings in schizophrenia patients who exhibited similar behaviours when compared to a control group (Jardri et al., 2017). This difference between HS and LS participants could also be explained in terms of a larger number of ascending loops (α_s) in the HS group, similarly to schizophrenia patients. However, these findings contrast with Karvelis and colleagues' study (Karvelis et al., 2018), who did not find any measurable effect of schizotypal traits on perceptual biases. Such difference may reside in the different selection criteria applied in the two studies, since the schizotypy scores reported in Karvelis et al. experiment ranged between 4 and 59 (mean 26.4). These participants, not selected for the top decile, might have been less representative of higher schizotypy. In support of this interpretation, the 2017 paper from (Jardri et al., 2017) reported a correlation between the severity of positive symptoms in schizophrenia patients, the overcounting of sensory evidence and the under-weighting prior expectations.

Other computational studies focused on prior misuse instead of the imbalance between priors and likelihood. amongst studies that

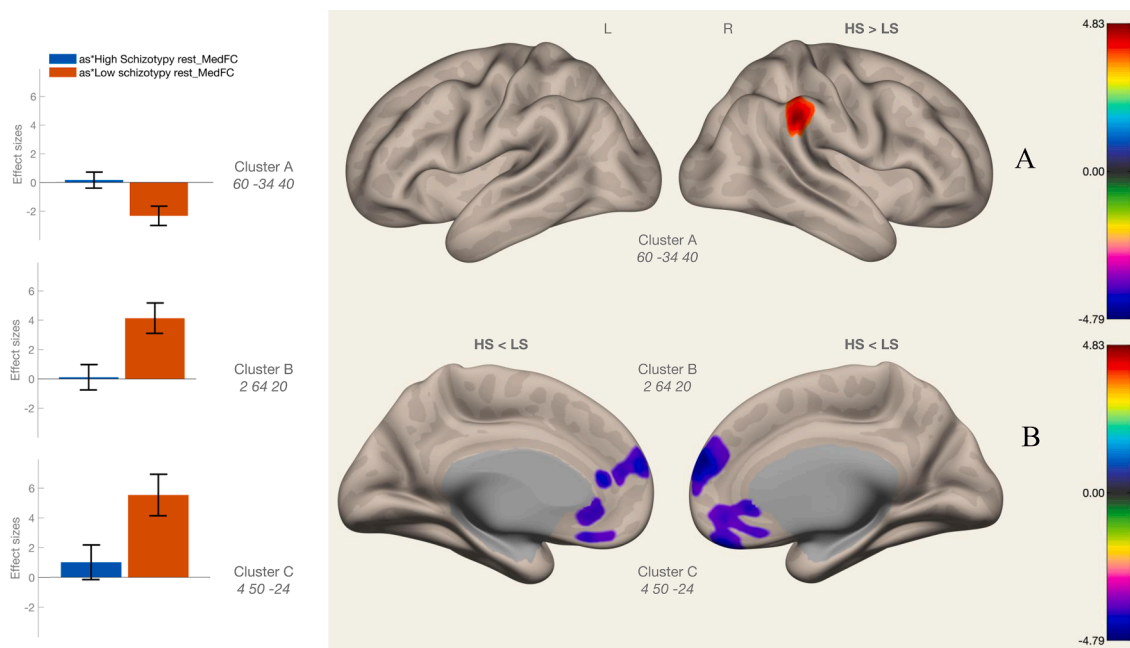


Fig. 3. Results of the resting state connectivity analyses - mPFC (seed) to voxels.

Note. Graphs: Bar charts illustrate rs-functional connectivity (mPFC- cluster A, mPFC- cluster B and mPFC- cluster C) in the High schizotypy group relative to the Low schizotypy group. Brain figures: **A.** Significant effect of ascending loop (α_s) on resting state connectivity between groups: HS > LS (with BDI scores as a covariate of no interest): Cluster A. **B.** Significant effect of ascending loop (α_s) on resting state connectivity between groups: HS < LS (with BDI scores as a covariate of no interest): Clusters B and C.

investigated the general population samples, Powell and colleagues (Powell et al., 2016) reported that the overweighting of perceptual priors was associated with hallucination proneness. Also, Teufel and colleagues (Teufel et al., 2015), showed a stronger influence of prior knowledge was linked with hallucinatory but not to delusion propensities. Results from these studies reinforce the hypothesis that experiential states of schizotypy might also be associated with false inference, even if the direction of this difference is assumed to be different. Interestingly, different CI profiles can lead to aberrant beliefs or percepts, while they can be associated to different clinical dimensions in the same disorder (Jardri & Denève, 2013, Jardri et al., 2017). In our sample, correlations in the HS group between schizotypy subdimensions and CI model parameters did not yield significant results, maybe due to the limited sample size. Further research is needed to replicate and/or investigate the precise relationship between schizotypy subclinical dimensions and CI parameters in larger samples.

Crucially, our interpretation was reinforced by complementary imaging findings. First, by testing the relationship between CI parameters and in-vivo excitatory neurotransmission (in terms of glutamate metabolite concentrations). In line with (Kozhuharova et al., 2021), we observed reduced mPFC glutamate metabolite in the HS relative to the LS group, albeit in a slightly smaller sample of participants. This appears fully in line with our interpretation of an altered excitatory neurotransmission in the HS group. Of note, Kozhuharova et al. (2021) also found lower GABA levels in the HS group. However, we chose not to include these data in the current study due to the reduced number of participants with linked GABA, RSFC and CI data. Nevertheless, we could also observe even in a smaller sample ($n=26$) lower levels of GABA in the HS group ($F=-4.42$, $p=0.043$). By showing a negative association between mPFC glutamate metabolite levels and the ascending loop CI parameter (α_s , obtained from parameter recovery after fitting the CI model to the Fisher task data), we provide the first experimental support to the link proposed between altered excitatory neurotransmission and sensory amplification (Jardri & Denève, 2013; Leptourgos et al., 2017).

Changes in cortical inhibitory and/or excitatory signalling may lead

to asynchronous cortical activity (Lewis et al., 2012), and underlie the behavioural alterations seen in schizophrenia (Jardri et al., 2017). The present findings extend this assumption to people with high schizotypy; showing that HS individuals exhibited lower levels of glutamate, which were associated with an elevated number of ascending loops. In other words, the over-reliance on sensory evidence measured experimentally in HS individuals was associated with reduced excitatory signalling at the top of the cortical hierarchy. One would have expected increased sensory amplification to be related to disinhibition rather than decrease in excitatory signalling. Glutamate was found to direct expression on GABA terminals and therefore regulates GABA inhibition via dual retrograde signal. Acting as a feedback mechanism, excitatory sensory activity drives GABAergic inhibition to maintain circuit homeostasis (Mende et al., 2016). Here, we hypothesise that the excitatory imbalance evidenced remains consistent with the model predictions, although this will need to be further confirmed with more direct measures of E/I imbalance (i.e., measurement of concomitant GABA metabolites, using functional MRS while doing the Fisher task, as well as more invasive measures in animal models).

We also augmented the initial behavioural findings by adding RSFC analysis which showed that HS and LS groups have opposite and differential patterns of mPFC connectivity associated with the sensory amplification (α_s parameter). Precisely, with regions in the posterior fronto-parietal control network (FCPN) (supramarginal gyri) and regions including the bilateral anterior cingulate and the medial frontal cortex (both major nodes of the default mode network (DMN)). Yang and colleagues (Yang et al., 2016) also showed a preferential vulnerability of association networks to E/I imbalance, while Bouttier et al. confirmed an inhomogeneous distribution of overconfidence/overactivation in large-scale networks, affecting more connector hubs with high degree (Bouttier et al., 2022). Typically, resting state networks gather higher-order association regions, including the fronto-parietal control network (FCPN, Yang et al., 2014) and the default mode network (DMN, Baker et al., 2014). Our results appear to corroborate both Yang and Bouttier assumptions. Yang and colleagues showed an increased FCPN connectivity in schizophrenia patients, which echoes our finding that HS

participants exhibited higher RSFC between mPFC and parts of FCPN (supramarginal gyri). The medial frontal cortex represents one of the major connector hub of the DMN, and compared with healthy controls, patients with schizophrenia and their siblings have been reported to exhibit increased RS activity of this region (Guo et al., 2017). In the present study, we found slightly different results within the HS group, who showed decreased RSFC between the mPFC and anterior cingulate relative to the LS group. Moreover, the ACC has been associated with both hypo and hyper activation relative to task performance in schizophrenia (Adams & David, 2007), as well as with ACC cortico-prefrontal hyperconnectivity and ACC medial prefrontal hypoconnectivity (Cui et al., 2015). Taken together, interactions between ACC and PFC nodes have been regularly implicated in the neurobiology of schizophrenia, which seem to align with our results.

5. Limitations

First, the sample size is relatively small, which may limit the generalizability of the results. Although it can be logistically difficult to acquire multimodal data of this type, future work is needed to test these interactions in larger sample, as well as in patients' population. Secondly, the SPQ-total score was used to define the HS/LS groups and further studies should aim at delineating CI, MRS and RSFC correlates of the specific dimension's profiles. However, our approach was led by the concept of schizotypy as a constellation of interpersonal, cognitive-perceptual, and disorganised symptoms. Future studies could also consider different measures than the SPQ, such as interview-driven assessments. Regarding spectroscopy methodology, an inherent limitation of 1H-MRS is that total glutamate concentration is measured in a relatively large voxel, which is determined a priori and cannot discriminate metabolites levels between the extracellular milieu and different cell type. Finally, we choose the mPFC as a seed for the resting state functional connectivity analyses as it was the spectroscopy placement of mPFC, thus using any other regions as seeds might yield different results.

6. Conclusion

In addition to group-differences in the circular inference model parameters, HS individuals exhibited altered mPFC glutamatergic neurotransmission and functional connectivity at rest. Both of these neurobiological measures were associated with sensory amplification in the probabilistic reasoning task. This multimodal study posits that aberrant glutamatergic function in the mPFC, a region believed to be high in the cortical hierarchy (Riga et al., 2014), might locally disrupt the excitatory balance and distally impact the mPFC RSFC, both found associated with sensory amplification in people with high levels of schizotypal traits. Future work, notably testing longitudinally at-risk individuals who convert or not to psychosis should help testing this new hypothesis.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was also approved by the ethical committee of the University of Roehampton.

Credit author statement

Author Mélodie Derome managed the literature search, statistical analyses and wrote the manuscript. Author Paul Allen initiated and secured funding for the project. Author Renaud Jardri provided the Fisher Task, supervised the preparation of data and statistical analyses. Author Petya Kozuharova participated in the recruitment and evaluation of participants. Author Andrea Diaconescu, Sophie Denève, Renaud

Jardri and Paul Allen contributed to the interpretation of the data and proofread the manuscript. All authors critically revised the manuscript and approved its final version for publication.

Declaration of Competing Interest

PA has received enterprise funding from Opitebionix Ltd UK, for work unrelated to the study reported here. RJ has been invited to expert boards by Lundbeck, Janssen, Rovi, and Otsuka. None of these links of interest are related to the present work. The other authors have no conflicts of interest to declare.

Data availability

Analyses codes are available in the supplementary material section of the previously published paper from Jardri and colleagues: [10.1038/ncomms14218](https://doi.org/10.1038/ncomms14218). The Fisher task is available to download at https://github.com/RenaudJA/Fisher_Task_Exp.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2023.120280](https://doi.org/10.1016/j.neuroimage.2023.120280).

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