Atypical spatial frequency dependence of visual metacognition among schizophrenia patients

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Abstract

Although a potential link between altered metacognition and schizophrenia has been speculated, studies have yielded inconsistent results. This may be partly because such findings would depend on the stimulus properties. Here we tested the hypothesis that metacognitive performance may be atypically modulated by spatial-frequency of visual stimuli among individuals with schizophrenia, given their altered magnocellular function. In Experiment 1, we used the signal detection theoretic measure meta-d' to quantify metacognitive performance of healthy participants in a visual detection task with confidence ratings. We then compared metacognitive performance between patients and controls with high and low spatial-frequency (HSF/LSF) stimuli outside and inside of an fMRI scanner (Experiment 2 and 3). Experiment 1 revealed that metacognitive performance is typically better after yes- (stimulus-presence) rather than after no- (stimulus-absence) responses. Experiment 2 revealed that control subjects showed such 'yes-response advantage' with HSF stimuli but not with LSF stimuli, while such spatial-frequency dependency was absent among the patients. Experiment 3 showed that the patients and controls differ in the functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and visual or parietal cortices as well as in the multivoxel decoding accuracy of perceptual confidence in DLPFC, in a spatial-frequency-dependent manner. While individuals without schizophrenia may flexibly adapt differential metacognitive computations across spatial-frequency range, patients may employ a different mechanism that is not dependent on spatial-frequency. Because visual stimuli of low spatial-frequency have been linked to top-down processing in predictive coding, this may reflect atypical functioning in these processes in schizophrenia.

Introduction

Schizophrenia is a neurodevelopmental psychopathology which is found in about 1% of the population [1, 2]. One of the positive symptoms is hallucination [3]. Many studies have shown atypical early sensory processing in patients with schizophrenia [3]. However, higher-order processing may also contribute to their symptomatology [3].

In particular, patients with schizophrenia may show altered metacognitive ability to discern between true and false percept [4], which would limit their ability to discern and disregard false perception of external events. Although recent studies have systematically examined perceptual metacognition among people with schizophrenia, the results appear mixed and non-conclusive [5-7].

For example, patients showed lowered metacognitive sensitivity (meta-d') relative to controls [5], on some conditions where patients also showed lowered perceptual sensitivity (d'). Thus, there remains a possibility that lowered metacognitive sensitivity was merely due to lowered perceptual sensitivity because they generally covary [8, 9]. In line with this, Powers et al. [6] reported that metacognitive sensitivity (meta-d') was unrelated with psychosis and/or hallucination when perceptual sensitivity (d') was taken into account (i.e., meta-d'/d' showed no difference). Similarly, Rouault [7] showed that self-reported schizotypy had little contribution to metacognitive performance. One reason for these mixed results could be that one critical atypicality among patients with schizophrenia resides not in their general metacognitive performance but in how their metacognitive performance is modulated by some perceptual conditions. Such atypicality may result in a group-by-condition interaction, leading to a notable group difference in metacognitive performance under some specific conditions [5], but not others.

Here, we tested the hypothesis that individuals with and without schizophrenia may differ in how their metacognitive performance is modulated by spatial-frequency levels of visual stimuli. Previous studies demonstrated that individuals with schizophrenia show altered visual processing as a function of spatial-frequency [10, 11], potentially due to altered magnocellular function among patients [10-12]. For example, patients make perceptual decisions with more weight on low spatial-frequency input, while control subjects generally rely more on high spatial-frequency input [10, 11, 13]. We hypothesized that metacognition, which is a higher-order function relative to first-order perceptual judgements [14], may also be susceptible to a similar interaction between the group and spatial-frequency levels. That is, while metacognition among individuals without schizophrenia may rely more on higher than lower spatial-frequency inputs, metacognition among patients may be differently modulated by spatial-frequency, e.g., with relatively more reliance on sensory input in a lower spatial-frequency range. We examined this potential group by spatial-frequency interaction at the level of metacognition, while equating the perceptual-level performance between the groups through stimulus calibration.

We first conducted Experiment 1 with only healthy participants in order to quantify their typical metacognitive performance during a visual detection task in a signal detection theoretic framework. The results of Experiment 1 revealed generally higher metacognitive performance with yes (stimulus-present) and no (stimulus-absent) responses (i.e., yes-response advantage). We then compared the response-specific metacognitive performance between patients with schizophrenia and control subjects enrolled in two detection tasks with either higher or lower spatial-frequency (HSF or LSF) target. We compared their performance in a behavioral study as well as in an fMRI study (Experiment 2 and 3, respectively).

Experiment 1

Methods and Materials

Participants

Fifteen students from Columbia University were enrolled. They had either normal or corrected-to-normal vision, and were free from clinical conditions. All participants gave written informed consent prior to their participation and received $10/h. The study was approved by the Columbia

University's Committee for the Protection of Human Subjects. The estimated age range is from 18 to 23. Further details of their demographic information are missing due to research site relocations.

Procedure

The task consisted of a detection task block (720 trials, performed in eight subblocks of 90 trials each), which followed two practice blocks (28 trials each) and one calibration block (120 trials). On each trial of the main blocks (Figure 1A), a fixation cross was presented on the center of the screen for 1 s, replaced by a background patch (4° in visual angle) containing dynamic white noise refreshed at 60 Hz (similar to TV static) presented for 1 s. On half of the trials, a horizontal grating (2.6 cycle per degree, cpd) briefly emerged within a background noise patch for 250 ms. On the other half of trials, a background patch remained for another 250 ms without a grating. For both trial types, the noise patch alone continued to be presented for a final 250 ms. Subsequently, participants were asked to indicate whether there was a grating (yes-response) or not (no-response) by pressing either "1" or "2" key. The key-assignment was counterbalanced across participants and was fixed across the blocks for each participant. They were further asked to rate their confidence in perceptual response on a four-point scale, by pressing one of the aligned 7-8-9-0 keys on a keyboard. The assignment for confidence rating was fixed across participants to minimize task load (i.e., assigning higher confidence to smaller number, rather than to larger number, would unwantedly increase task load). For both perceptual response and confidence rating, response-to-key assignments were presented on the lower screen as reminders, and participants made response within 5 s. The next trial began after participants responded or 5 s elapsed from the onset of reminder for confidence rating. The trial sequence of the calibration blocks was identical to that of the main blocks, except that a horizontal grating appeared on all the trials.

During the calibration block, Michelson contrast of grating was titrated with QUEST threshold estimation procedure [15]. Three independent sequences of 40 trials were interleaved during the calibration block to yield three estimates of contrast level to achieve hit rate of 50%. The median of three estimates was multiplied by 0.7, 1.0, 1.3 to serve as three levels of difficulty (high/mid/low) in the detection task block. There were equal numbers of trials with high, mid, and low task difficulty levels. The order of trials was randomized within each block.

The background of the screen remained gray throughout the blocks, and the viewing distance was fixed at 60 cm. The stimuli were generated and presented with the Psychophysics Toolbox [16] in MATLAB (Mathworks) implemented in iMac (21.5 inch).

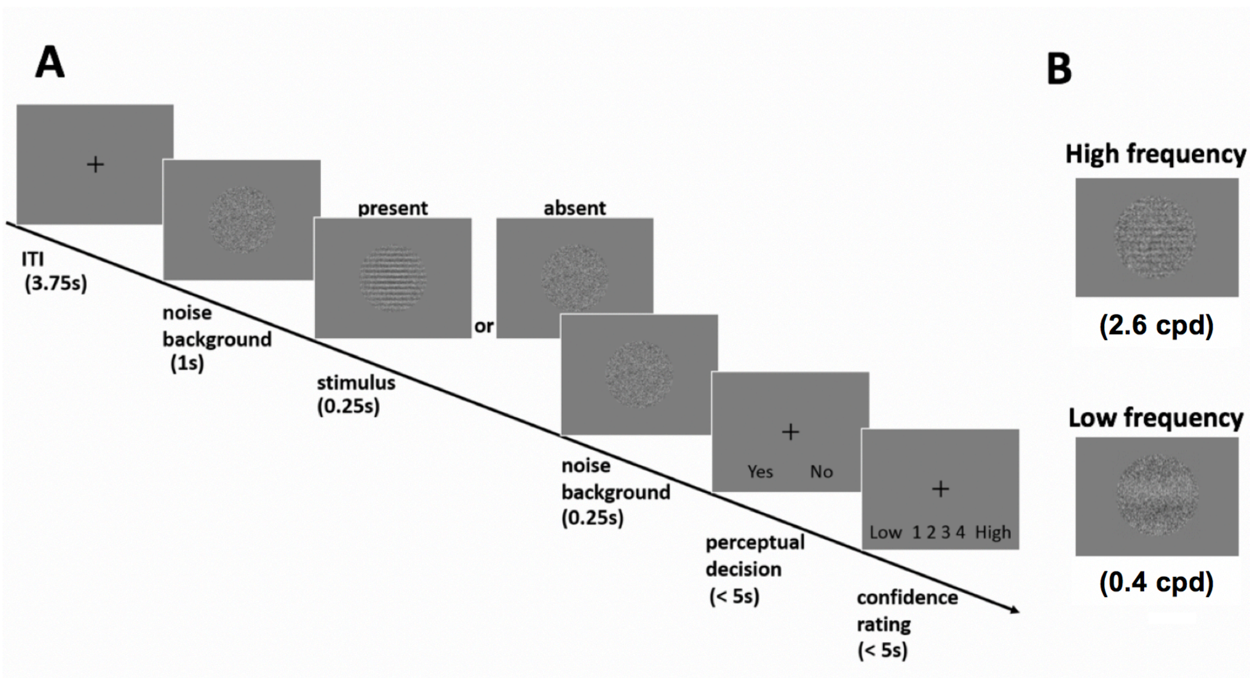

Figure 1. Schematics of the detection task. **A.** A trial sequence of the task. On half of the trials, a grating target briefly emerged and faded within a background patch containing dynamic white noise refreshed at 60 Hz (similar to TV static). Participants were asked to make a perceptual response indicating whether a grating was present ("yes" response) or absent ("no" response), and then to rate their confidence in their perceptual response with a four-responses scale. **B.** Two levels of spatial-frequency of a grating target. Only a grating with a high spatial-frequency

level (2.6 cycle per degree, cpd) was used in Experiment 1, whereas a grating with both high and low spatial-frequency (0.4 cpd) levels were used as a target in two separate sessions of Experiment 2. A phase of grating was randomized across trials. ITI: inter-trial-interval. cpd: cycle per degree (in visual angle).

Analyses

Detection sensitivity was calculated as d' for each of the three levels of task difficulty with standard signal detection theory (SDT) methods [17]. Metacognitive sensitivity for yes- and no-responses was separately calculated as response-specific meta-d' (rs-meta-d'; http://www.columbia.edu/~bsm2105/type2sdt/fit_rs_meta_d_MLE.m) [9], separately for each of the three levels of task difficulty. We estimated rs-meta-d' with the assumption of equal variance between signal (i.e., target presence) and noise (i.e., absence) (i.e., z-transformed receiver operating characteristic (zROC) slope, s = 1) (see related technical issues in properly correcting for potential unequal variance in detection tasks [9]). The ratio of meta-d' to d' (meta-d'/d') was then calculated for each difficulty level, to quantify metacognitive efficiency i.e., how much sensory signal remained available for metacognitive judgement given how much was originally accessible for perceptual judgement [8, 9]. Across-participant means for d', meta-d', and meta-d'/d' were analyzed with Analysis of Variance (ANOVA) in SPSS version 25 (IBM). One caveat of the ANOVAs here was that the same set of target absent trials were resampled to estimate d' and meta-d' across different task difficulty levels. However, we considered this as only a minor issue as it did not bias certain experimental condition over others. For the subsequent analyses, an ANOVA with two within-participant factors of Response-type (yes/no) and Task-difficulty (high/mid/low) were conducted.

Results and discussion

Means of response-specific meta-d'/d', response-specific meta-d', and detection d' are shown in Figure 2 for each level of task difficulty. As shown in Figure 2A, meta-d'/d' was generally higher for yes-responses than no-responses, although the main effect of Response-type was not significant ($F(1, 14) = 3.71$, $p = .075$). This yes-response advantage (i.e., a main effect of response-type) significantly interacted with Task-difficulty ($F(2, 13) = 4.27$, $p =.038$, partial $\eta 2 = .396$). This interaction was due to yes-response advantage being significant only with low difficulty level (i.e., highest contrast) ($p = .008$, Bonferroni-corrected) but not with mid and high difficulty levels ($p = .138$, $p = .217$, respectively).

As expected, detection d' (Figure 2B) monotonically increased as the task difficulty level decreased (a main effect of Task-difficulty: $F(2,13) = 162.32$, $p < .001$, partial $\eta 2 = .961$). That is, low difficulty level yielded significantly higher detection d' than mid difficulty level ($p < .001$), and mid difficulty level yielded significantly higher detection d' than high difficulty level ($p < .001$).

The analysis of meta-d' (Figure 2C) was qualitatively similar to that of meta-d'/d', revealing a significant main effect of Response-type ($F(1, 14) = 4.76$, $p = .047$, partial $\eta 2 = .254$) which significantly interacted with Task-difficulty ($F(1, 13) = 6.72$, $p = .01$, partial $\eta 2 = .508$). Similar to the aforementioned results of meta-d'/d', this interaction was due to the fact that yes-response advantage was significant only with low task difficulty level ($p = .006$, Bonferroni-corrected) but not with mid or high task difficulty levels ($p = 225$, $p = .276$, respectively).

Taken together, the results suggest that yes-response advantage in metacognition is robust enough to be qualitatively retained across different levels of task difficulty (i.e., stimulus contrast), although it was only significantly observed with the easiest task difficulty (i.e., highest contrast), potentially due to lowered metacognitive performance even for yes-response with increased task difficulty. Such yes-response advantage is in line with previous studies [18, 19], suggesting that response-specific meta-d' used here has sensitivity to capture the difference in metacognitive sensitivity between yes- and no-responses.

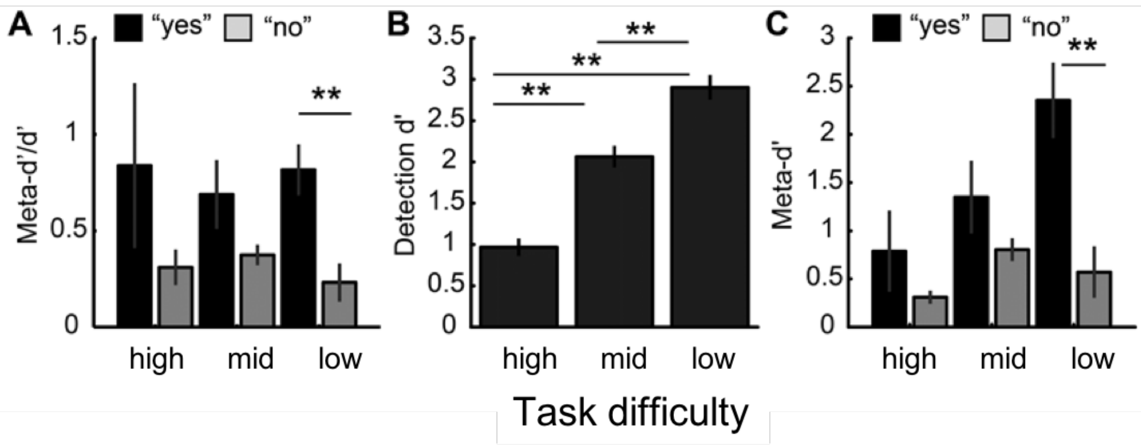

Figure 2. Metacognitive and perceptual sensitivity as a function of task-difficulty level among healthy participants in Experiment 1. **A.** Metacognitive performance is quantified as Meta-d’/d’ to depict metacognitive sensitivity (Meta-d’) in relation to perceptual sensitivity (d’). Meta-d’/d’ was numerically higher following “yes” than “no” responses in general, although a main effect of Response-type was not significant (F(1, 14) = 3.707, p =. 075). There was a significant interaction between Response-type and Task-difficulty (F(2, 13) = 4.268, p =.038), which was due to that there was a significant difference between response types only with low task difficulty level (p = .008) but not with mid and high difficulty levels (p = .138, p = .217, respectively). **B.** Across participant mean of Detection *d’* showing perceptual sensitivity during the detection task, which monotonically decreased with task difficulty. **C.** Across participant mean of response-specific Meta-d’. Similarly to Meta-d’/d’ shown in A, there was a significant interaction between Response-type and Task-difficulty (F(2, 13) = 6.716, p =.01). This interaction was due to that yes-response advantage was significant only with low task-difficulty level (i.e., highest contrast) (p = .006) but not with mid and high difficulty levels (p = .225, p = .276, respectively). Error bar indicates standard error of mean. ** *p*<.01.

Experiment 2

With the rs-meta-d' measurement from Experiment 1, we examined the response-specific metacognitive performance among patients with schizophrenia and the age matched control subjects. Both groups performed a detection task with a grating with high and low spatial-frequency. We here chose such simple visual stimuli over other more complex stimuli, such as faces and words, in order to avoid potential confounding variables due to other visual dysfunctions in processing these complex stimuli [20, 21]. Perceptual sensitivity (d') was prepared to be similar across groups and conditions by calibrating the grating contrast level prior to the detection task, which allowed us to selectively examine the potential differences in metacognitive performance.

Methods and Materials

Participants

Twenty patients with schizophrenia diagnosed with DSM-IV Axis I Disorders Patients Edition, Version 2.0 (SCID-P) (9 males, mean age = 42.3 ± 11.9) and eighteen healthy control subjects (12 males, mean age = 40.2 ± 11.6) were enrolled in this study. The data from three female patients were excluded from the analyses because they had apparent difficulty in comprehending the task (i.e., persisting to respond with only one particular key or in making two successive responses for detection and confidence rating), leaving the data from remaining seventeen patients for the analyses (9 males, mean age = 40.5 ± 11.9). Those patients were medicated with antipsychotics (atypical N = 15; typical + atypical N = 2). The patients and control subjects did not statistically differ in their age ($t(33) = .19$, $p = .850$) and gender ratio ($\chi2 = .69$, $p = .407$). However, consistent with previous studies and the nature of schizophrenia [22], patients showed significantly lower estimated IQ (M = 108.2 ± 7.8) than control subjects (M = 112.5 ± 5.0) ($t(33) = 4.08$, $p < .001$), when measured with a standardized Japanese Adult Reading Test (JART-25) to estimate full scale intelligence quotient (FSIQ) [23, 24]. Other demographic information is summarized in Supplementary Table 1. See Supplementary material for the details on participant recruitment.

Procedure

Procedure of Experiment 2 was similar to that of Experiment 1, except for the following changes. In Experiment 2, two levels of grating spatial-frequency (High spatial-frequency, HSF = 2.6 cpd; Low spatial-frequency, LSF = 0.4 cpd) were embedded in a noise patch (diameter = 3.9° in visual angle). These two levels of spatial-frequency were expected to evoke differential neural activity between patients with schizophrenia and control subjects [12]. The spatial-frequency of HSF grating was identical to that in Experiment 1. During the calibration block, Michelson contrast of grating was continuously adjusted with the QUEST threshold estimation procedure [15]. Two sets of 40 trials were randomly interleaved to estimate the two levels of contrast to achieve hit rate of 55% and 65%. Calibration was conducted separately for each spatial frequency level.

The response keys for confidence rating were changed to 1-2-3-4 (from 7-8-9-0 in Experiment 1) to enable the participants to make both perceptual and metacognitive responses with only one hand, avoiding potential difficulty in coordinating two hands among patients. The stimuli were generated and presented with the Psychophysics Toolbox [16] in MATLAB implemented in MacBook Pro (13 inch). See Supplementary material for further details on procedure and analyses.

Results and discussion

First, Meta-d'/d' was analyzed with a Group x Response-type x Spatial-frequency ANOVA, which revealed a main effect of Response-type ($F(1, 33) = 25.99$, $p < .001$, partial $\eta 2 = .441$) (Figure 3). This main effect was due to higher Meta-d'/d' following yes- than no-responses, which is consistent with Experiment 1 and previous studies [18, 19]. Interestingly, such yes-response advantage was modulated by Group and Spatial-frequency (a three-way interaction: $F(1, 33) = 4.60$, $p = .039$, partial $\eta 2 = .122$). Post-hoc t-tests revealed that Controls showed significantly higher Meta-d'/d' following yes- than no-responses (i.e., yes-response advantage) only when detecting a HSF grating target ($p < .001$) but not LSF grating target ($p = .169$). By comparison, Patients showed significant yes-response advantage irrespective of target spatial-frequency (HSF: $p = .013$; LSF: $p = .001$). There was no significant main effect of Group ($F(1, 33) = .77$, $p = .386$), suggesting that Patients did not show any generic reduction of metacognitive performance relative to Controls. The magnitude of yes-response advantage (i.e., the difference in meta-d'/d' between yes- and no-responses, Figure 3B) was significantly larger with HSF than LSF targets among Controls ($t(17) = 2.22$, $p = .040$) but not among Patients ($t(16) = -.63$, $p = .540$). The degree to which confidence rating captured the accuracy of perceptual response qualitatively mirrored the results of Meta-d'/d' (Supplementary Figure 1).

For the detection sensitivity d' (Supplementary Figure 2), there was neither a significant main effect of Group ($F(1, 33) = .16$, $p = .694$) nor a significant interaction between Group and Spatial-frequency ($F(1,33) = 3.80$, $p = .060$), suggesting that Patients did not statistically differ from Controls in their perceptual performance. There was a main effect of Spatial-frequency ($F(1, 33) = 4.33$, $p = .045$, partial $\eta 2 = .116$), which was due to generally lower d' with LSF relative to HSF stimuli. Note that this main effect alone cannot account for the aforementioned group difference in metacognitive performance because of at least two reasons. First, meta-d'/d' already takes the variability in d' into account when assessing metacognitive efficiency [9]. Second, if the difference in d' accounts for the results in meta-d'/d', then we would expect that the result of meta-d'/d' (i.e., yes-response advantage) would differ between HSF and LSF stimuli for Patients rather than for Controls. This is because, although the interaction was non-significant, it was Patients who primarily showed difference in d' between HSF and LSF stimuli (Supplementary Figure 2). However, the results of meta-d'/d' showed that it was Patients who showed equivalent yes-response advantage between Spatial-frequency levels.

The calibrated stimulus contrast tended to be higher for Patients relative to Controls (M = 9.79% ± s.d. 2.78, M = 8.27% ± 1.55, respectively), but did not statistically differ across Groups (a main effect; $F(1,33) = 4.05$, $p = .052$). There was no significant main effect of Spatial-frequency (a main effect; $F(1,33) = 2.43$, $p = .135$) or two-way interaction ($F(1, 33) = .18$, $p = .677$). The analysis of meta-d' (Supplementary Figure 2) alone revealed a qualitatively similar result as that of meta-d'/d'. A potential relationship between hallucination severity (measured with Positive and Negative Syndrome Scale (PANSS) [25]) and metacognitive performance among Patients, although tentative, can be found in Supplementary material.

Taken together, the results suggest that insensitivity to spatial-frequency modulation may characterize the metacognitive performance among patients (Figure 3).

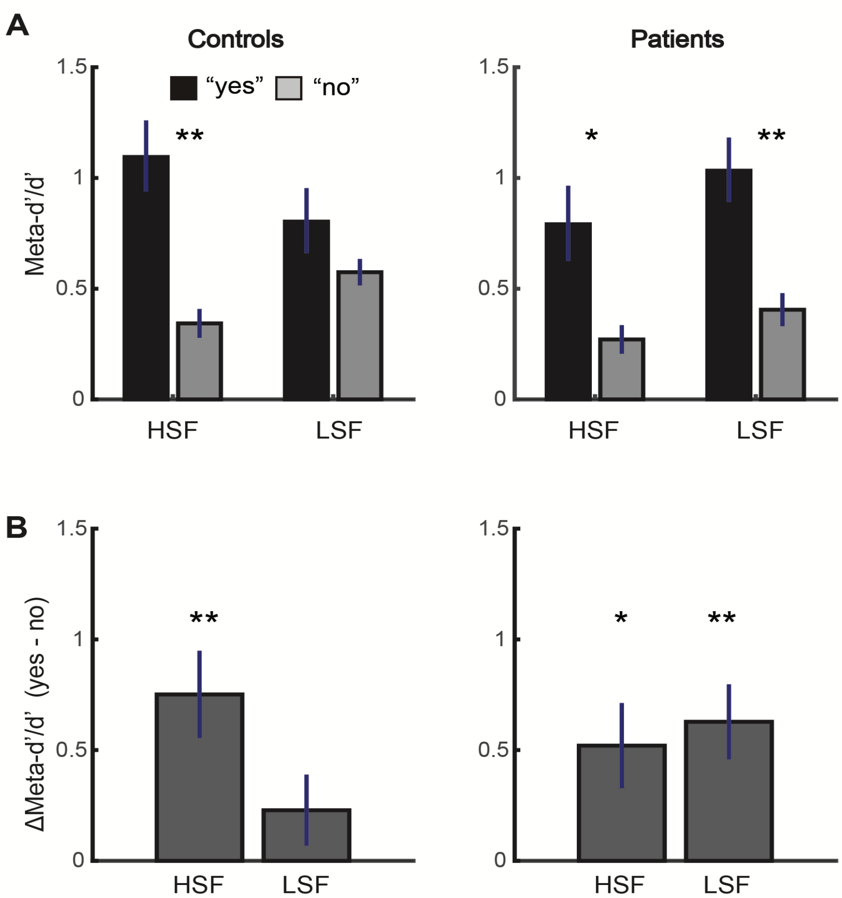

Figure 3. Differences in Meta-d' between patients with schizophrenia and control participants as a function of response type ("yes"/"no") and that of spatial-frequency (HSF/LSF) in Experiment 2. **A.** Controls showed advantageous metacognitive performance with yes- relative to no-responses only during HSF target detection task but not during LSF target detection task, whereas patients showed advantageous performance with yes-response irrespective of the target spatial-frequency. There was a significant spatial-frequency x response type x group interaction ($F(1, 33) = 4.6$, $p = .039$). The results of post-hoc t-tests are shown. **B.** Same result as in A. Differences in meta-d'/d' between "yes" and "no" responses are shown for demonstrative purpose. Here, larger value indicates more advantageous metacognitive performance with yes- than no-responses Error bar indicates standard error of means. ** p<.01, * < p<.05.

Experiment 3

As described above, Experiment 2 indicated that only Controls show spatial-frequency dependency in their metacognitive performance, while Patients do not. Based on this result, we predicted that Controls, but not Patients, may rely less on the neural circuit typically supporting metacognition with LSF stimuli. A large body of literature has shown that the dorsolateral prefrontal cortex (DLPFC) plays a central role in metacognition [26-32]. However, these studies have only demonstrated such role of DLPFC among individuals without schizophrenia. Whether it differently contributes to metacognition among patients remains unknown. We here particularly predicted that DLPFC may be a potential source of group difference in metacognitive function. To test this, we next conducted the same experimental task as Experiment 2 in an fMRI scanner.

Methods and Materials

Participants

Seventeen patients with schizophrenia diagnosed with DSM-IV Axis I Disorders Patients Edition, Version 2.0 (SCID-P) (6 males, mean age = 42.8 ± 9.5) and seventeen healthy controls (7 males, mean age = 40.2 ± 10.1) were enrolled in this study. The data from two male patients were excluded from the analyses because they were unable to register their key responses within the limited response windows (< 2 s). The data from remaining fifteen patients (4 males, mean age = 44.7 ± 8.4) were analyzed. These patients were medicated with antipsychotics (atypical, N = 12, typical + atypical, N = 3). Those patients and controls did not statistically differ in their age ($t(30)=1.35$, $p = .186$) and gender ratio ($\chi 2 = .74$, $p = .388$). As expected, the IQ estimated with JART [23, 24] was significantly higher for controls (M = 110.5 ± 5.7) than for patients (M = 98.9 ± 9.0) ($t(30) = 4.42$, $p < .001$). Nine patients and seven controls were also enrolled in Experiment 2, and the ratio of overlapped participation did not statistically differ between the groups ($\chi 2 = 1.13$, $p = .288$). Other demographic information is summarized in Supplementary Table 1. See Supplementary material for the details on participant recruitment.

Procedure

The task procedure was similar to that of Experiment 2 with a few exceptions. The runs were blocked for HSF and LSF stimuli and the order of Spatial-frequency level was counterbalanced order across participants. See Supplementary material for further details.

ROI definition

The DLPFC ROI was functionally defined. Specifically, the clusters of voxels that were significantly activated for the confidence rating relative to the fixation period from all the trials ($p < .01$, Bonferroni-corrected) were selected, which were located within Brodmann area (BA) 46 (MRIcron, Brodmann 48 Area Atlas Template, https://people.cas.sc.edu/rorden/mricron/index.html) (Figure 5A). The left and right clusters were combined to form the DLPFC ROI for the subsequent analyses. Note that bias in voxel selection for any particular experimental condition (e.g., HSF) or group was minimized, as all the trials including all the conditions from all participants were included in a GLM. To further ensure this, we ran an analysis of covariance (ANCOVA) examining the effects of Group, Spatial-frequency, Response-type in BrainVoyager to show that no voxel survived the cluster-threshold enhancement [33, 34] at liberal criteria ($p < .01$) with a mask of DLPFC ROI. This was consistently the case when examining a main effect of Group, Spatial-frequency, Response-type, and the interactions among any combinations of the variables.

As a control ROI which is related with visual processing but not directly with metacognitive processing [26], the clusters of voxels that were significantly activated for the stimulus period relative to the fixation from all the trials ($p < .01$, Bonferroni-corrected) were selected within visual cortex (Supplementary Figure 5). See Supplementary material for further details on ROI definition.

Analyses

The fMRI data were preprocessed and analyzed with BrainVoyager 21.0 (Brain Innovation, the Netherlands). We aimed to examine whether functional connectivity between DLPFC and some other brain areas were modulated as a function of Spatial-frequency, Response-type, and Group. With this aim, we first conducted a whole-brain Generalized form of context-dependent psychophysiological interaction analysis (gPPI) analysis [35] with DLPFC as a seed ROI to quantify its functional integration with other brain areas as a function of Spatial-frequency and Response-type at the participant level. In addition, to binary decode the trial-by-trial confidence level (high or low) from the multivoxel activation pattern in DLPFC during the confidence rating period, we built a decoder with sparse logistic regression (SLR) which automatically selects relevant features (i.e., voxels) [36]. See Supplementary material for more details.

Results and discussion

Behavioral results

The behavioral data were not of main interest in Experiment 3, given that there were too small trial numbers in Experiment 3 (96 trials) relative to Experiment 2 (360 trials) to properly fit the data to estimate Meta-d'. Nevertheless, we analyzed the behavioral data to check if the result was qualitatively similar to that of Experiment 2.

Overall, the result of Meta-d'/d' qualitatively mirrored that of Experiment 2. Yet, the result in Experiment 3 was noisier (i.e., larger variability), which was well expected due to fewer trial numbers, tighter response time constraint, and being in a physically constrained fMRI (Supplementary Figure 3). That is, Meta-d'/d' was numerically larger for yes than no-responses (i.e., yes-response advantage), although this difference did not reach significance (a main effect of Response-type, $F(1, 30) = 3.39$, $p = .075$). Only Controls showed numerically larger Meta-d'/d' for yes- than no-responses (i.e., yes-response advantage) with HSF (Δ Meta-d'/d': M = 0.908 ± s.e. 0.489, $p = .175$) but not with LSF (M = -0.009 ± s.e. 0.212, $p = .975$). Meanwhile, Patients showed similar yes-response advantage with HSF (M = 0.725 ± 0.853, $p = .306$) and LSF (M = 0.460 ± 0.367, $p = .136$). There was no significant interaction between Spatial-frequency, Response-type, and Group ($F(1,30) = .48$, $p = .493$).

The detection sensitivity d' did not differ as a function of Spatial-frequency ($F(1, 30) = .02$, $p = .899$), that of Group ($F(1, 30) = 1.39$, $p = .247$), and their interaction ($F(1, 30) = .13$, $p = .721$). This result suggests that calibration of stimulus contrast was comparable across all experimental conditions. The mean contrast levels of Controls and Patients were 5.4% ± s.e. 0.42 and 4.78% ± 0.46, respectively. There was neither a significant main effect of Group ($F(1,30) = .98$, $p = .330$) nor that of Spatial-frequency ($F(1, 30) = 2.80$, $p = .105$). The interaction between Group and Spatial-frequency was also non-significant ($F(1, 30) = 1.09$, $p = .305$).

fMRI results

The group-level analysis of gPPI effect revealed that the DLPFC ROI showed altered functional connectivity with the clusters in parietal and visual cortices, as a function of Spatial-frequency, Response-type, and Group ($p < .01$, corrected with cluster-level thresholding, [33, 34]) (Figure 4). The bilateral clusters in parietal cortex were located posterior of BA 7 (MRIcron, Brodmann 48 Area Atlas Template) and their centers of gravity for the left and right clusters were [X = -21.34 (± 4.76), Y = -68.37 (± 4.18), Z = 38.32 (± 3.40)] and [X = 10.50 (± 2.28), Y = -61.86 (± 3.13), Z = 36.32 (± 2.41)], respectively. The bilateral clusters in visual cortex were located ventral of BA18 and their centers of gravity for the left and right clusters were [X = 17.13 (± 4.62), Y = -72.81 (± 2.71), Z = -16.73 (± 2.92)] and [X = -24.0 (± 5.21), Y = -77.51 (± 3.22), Z = -19.52 (± 1.93)], respectively. There were also bilateral significant clusters in motor cortex overlapping BA 6 (Figure 5), which may reflect mere motor-related consequences of the metacognition-level effect (e.g., reduced motor fluency in responding with difficult metacognitive judgement).

A previous study has demonstrated the altered functional integration between prefrontal areas and visual areas during metacognitive judgement [29]. Similarly, the current study revealed the condition-specific group difference in the functional integration of DLPFC with parietal and visual cortices. While parietal cortex has been implicated in perceptual decisions [37], visual cortex has been implicated in representing sensory evidence with little additional contribution to metacognition [26]. Together with these previous findings, the current results suggest that Patients and Controls may differ in the degree to which their DLPFC integrates information on perceptual decision (in parietal cortex) and sensory evidence (in visual cortex) during metacognitive judgement, and such group difference may depend on Spatial-frequency and Response-type.

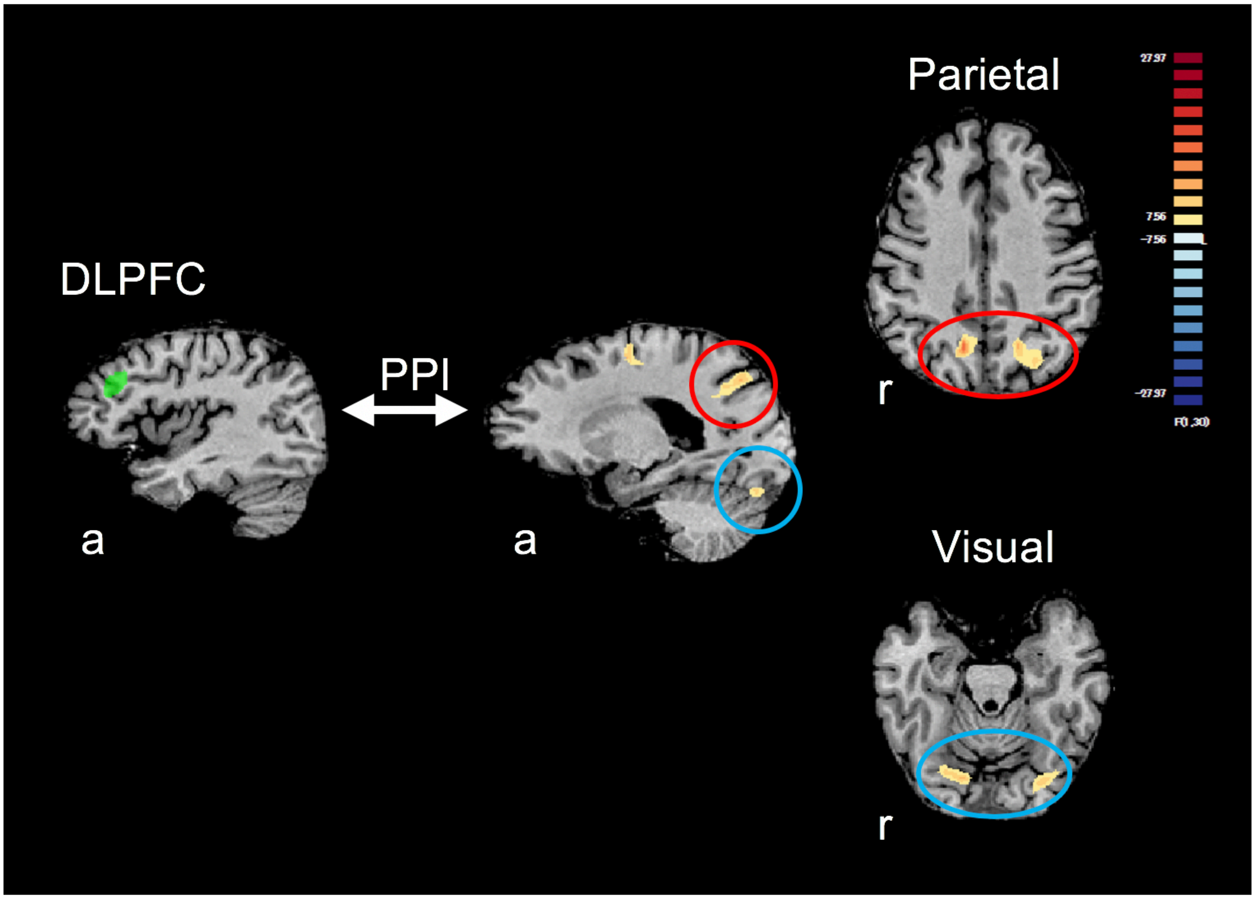

Figure 4. The results of a whole-brain analysis examining where in the brain showed altered functional connectivity with the DLPFC during confidence rating as a function of Spatial-frequency, Response-type, and Group. Here, the degree of functional connectivity was estimated with a general form of context-dependent psychophysiological interaction (gPPI, [35]). The functional connectivity between the DLPFC and bilateral clusters in parietal and visual cortices were significantly modulated as a function of interaction between Spatial-frequency, Response-type, and Group ($p < 0.01$, corrected with cluster-size thresholding). a: anterior, r: right, PPI: psychophysiological interaction.

For illustrative purposes only, the parameter estimates (Beta) for PPI terms in the parietal and occipital clusters (averaged between the hemispheres) are visualized separately for each level of Spatial-frequency, Response-type, and Group in Supplementary Figure 4. This result, although illustrative, shows that the functional connectivity between DLPFC and parietal or visual cortex was more enhanced following no- relative to yes-responses with the HSF stimuli among Controls. Considering the behavioral results from Experiment 2 and 3 that Controls show yes-response advantage in metacognitive performance with the HSF stimuli, one interpretation of this functional integration effect may be that there was more effortful (thus enhanced) integration of sensory and decision information by the DLPFC following no-response to the HSF stimuli.

The results of multivoxel decoding analysis also supported the possibility that Patients and Controls may differ in the DLPFC recruitment during metacognitive judgement (Figure 5). That is, the decoding analysis with the DLPFC ROI revealed a significant interaction between Group and Spatial-frequency ($F(1, 27) = 5.08$, $p = .032$, partial $\eta2 = .158$). This interaction was due to higher decoding accuracy with HSF relative to LSF stimuli among Controls ($p = .043$, partial $\eta2 = .144$), while there was no such Spatial-frequency dependence of decoding accuracy among Patients ($p = .289$). There was no significant main effect of Group ($F(1, 27) = .07$, $p = .799$) and that of Spatial-frequency ($F(1, 27) = 2.81$, $p = .105$). Unlike with DLPFC, there was no significant difference in decoding accuracy as a function of Group and Spatial-frequency within the control ROI in a visual cortex (Supplementary Figure 5). There was no significant main effect of Group ($F(1, 27) = 2.33$, $p = .138$), that of Spatial-frequency ($F(1, 27) = 0.10$, $p = .751$), and their interaction ($F(1, 27) = 2.15$, $p = .154$). Note that the factor of Response-type was not considered in the decoding analysis due to the limits in trial number (see Supplementary material on *Decoding analysis*).

As described above, the behavioral results showed that there was neither a significant main effect of Group nor a Group by Spatial-frequency interaction in both meta-d'/d' and detection sensitivity d'. These behavioral results are consistent with Experiment 2 and suggest that Patients and Controls did not differ in their overall performance in metacognition and perception (i.e., unless considering response-type), regardless of Spatial-frequency level. Thus, it is unlikely that the decoding accuracy difference merely reflected the metacognitive performance difference. Instead, such results more likely reflect the group difference in the involvement of DLPFC in metacognition, as a function of Spatial-frequency.

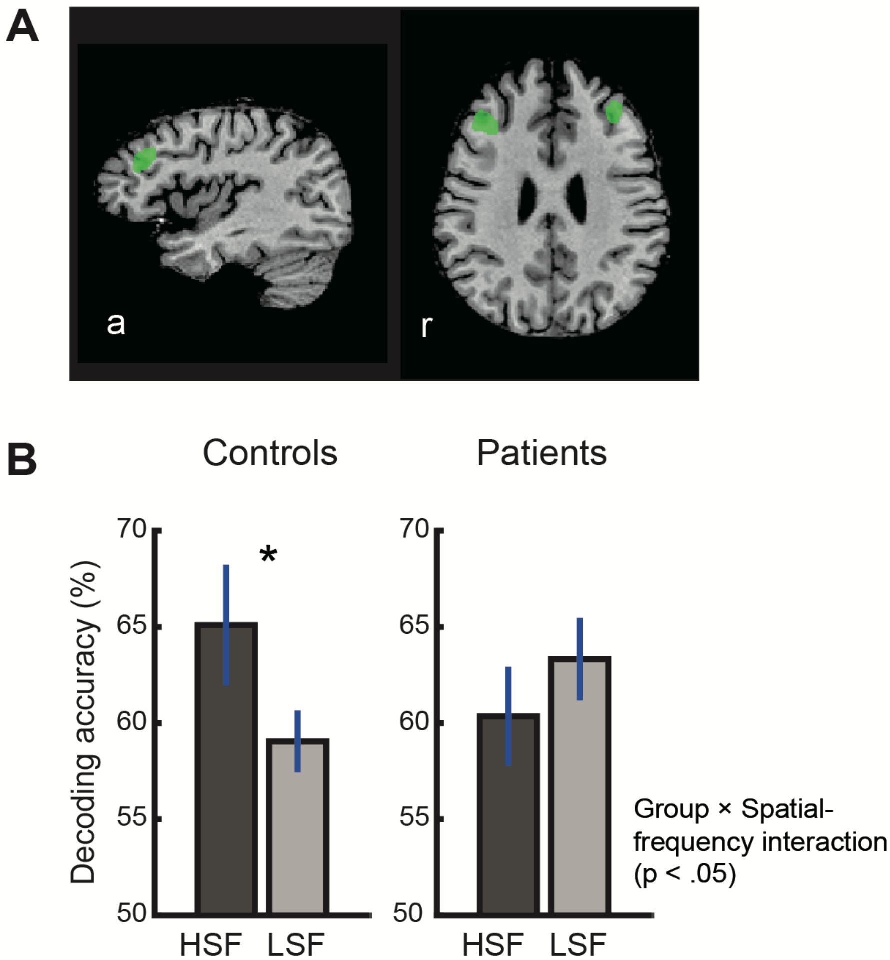

Figure 5. A. DLPFC ROIs functionally defined from a group GLM. ROIs include the voxels that showed significantly larger activity during the confidence rating period relative to fixation in a group GLM ($p < .01$, Bonferroni corrected). There was no statistical difference between the groups in terms of activation level across the whole brain including DLPFC, even when considering the interaction with the spatial-frequency level and/or response type (yes/no). **B.** Although the activation level did not differ between the groups, there was a significant interaction between group and stimulus spatial-frequency in the decoding accuracy of the trial-wise confidence level (high/low) from the multivariate activation patterns in DLPFC. Only among

controls, decoding accuracy was significantly higher with HSF than LSF stimulus judgement, whereas it was statistically similar between the spatial-frequency levels among patient group. During metacognitive judgement, controls may strategically rely on different neural computations depending on the spatial-frequency of target visual stimuli, whereas patients may more uniformly rely on a similar computation involving DLPFC regardless of such stimulus property. a: anterior, r: right, * $p < .05$.

Discussion

While a potential relationship between schizophrenia and atypical metacognitive function has been speculated for decades [4], whether patients with schizophrenia have altered metacognitive ability to introspect perception has remained inconclusive [5, 6]. We here showed that patients and controls generally perform equally well in a visual metacognitive task. However, the groups differed in both behavioral performance and neural activity in terms of their dependency on spatial-frequency.

One consistent result across three experiments was that metacognitive efficiency to introspect one’s perceptual accuracy is overall superior with yes-responses (i.e., perception of target presence) relative to no-responses (i.e., absence). That is, it is generally easier to discriminate one's correct versus incorrect yes-responses (i.e. by giving higher confidence rating to hit vs false alarm) than to discriminate no-responses (i.e., correct rejection vs miss) when detecting a visual target. This yes-response advantage itself is in agreement with earlier studies [18, 19].

A novel finding of this study was that patients and control subjects differ in spatial-frequency range where they display yes-response advantage in metacognition. Specifically, control subjects showed such yes-response advantage only when detecting a higher spatial-frequency visual target but not when detecting a lower spatial-frequency target. Meanwhile, patients showed yes-response advantage irrespective of the spatial-frequency level. An fMRI study (Experiment 3) further supported such spatial-frequency independence of metacognitive function among patients. The functional connectivity between DLPFC and parietal or visual cortex during the metacognitive judgement was differently modulated as a function of the groups, spatial-frequency, and response-type. Moreover, among control participants, trial-by-trial confidence level could be more accurately decoded from the multivoxel patterns in DLPFC with higher than lower spatial-frequency stimuli. Meanwhile, decoding accuracy was similar between the spatial-frequency levels among patients.

To provide explanations for the group difference in spatial-frequency dependence, we first turn to why there is generally yes-response advantage in metacognition. It has been repeatedly demonstrated that metacognitive judgements are mainly based on perceptual evidence that contributed to finalize perceptual decisions [38-41]. For instance, confidence in a perceptual decision that motion was rightward is proportional to the amount of perceptual evidence for rightward motion but not that of other evidence in irrelevant motion directions. While these findings are mainly based on discrimination tasks, a similar mechanism may be at play with a detection task. In a detection task, there is perceptual evidence to support yes-responses (stimulus presence) but no evidence to support no-responses (stimulus absence). Thus, perceptual confidence for yes-responses likely reflects the amount of supporting evidence, which is typically larger for correct than incorrect responses. However, confidence for no-responses could be more difficult to estimate, because supporting evidence for no-responses is absence of evidence, which might have less discriminatory ability to discern correct versus incorrect responses [9]. Thus, yes-response advantage in a given perceptual condition may be considered as an index for the degree to which supporting perceptual evidence is directly translated to metacognitive judgements (i.e., confidence rating).

Considering this, one possibility is that the group difference in yes-response advantage reflects the degree to which metacognitive judgement is based on perceptual evidence in a given spatial-frequency range. Typically, when people make perceptual decisions, e.g., to identify an object, they rely on perceptual evidence in higher spatial-frequency range, while they would also rely on evidence in lower spatial-frequency to rapidly prime their forthcoming perceptual decisions [13]. However, studies have shown that patients with schizophrenia are more dependent on evidence in lower spatial-frequency range when making perceptual decisions, relative to control subjects [10, 11]. Considering this group difference at the level of perceptual judgements, individuals *without* schizophrenia may base their metacognitive judgements more on higher spatial-frequency evidence because it typically contributes more to finalize perceptual decisions. Meanwhile, patients with schizophrenia may also rely on evidence in lower spatial-frequency range, because it generally contributes to finalize perceptual decisions too.

This group difference in the use of perceptual evidence at the level of perceptual decision may at least partly contribute to the difference at the level of metacognitive decision. As described above, metacognitive judgement over yes-responses is more likely to depend on perceptual evidence. Given this, it could be that control subjects show yes-response advantage only with higher spatial-frequency stimuli because they tend to base their metacognitive judgements on perceptual evidence in higher spatial-frequency range more directly than that in lower spatial-frequency range. Meanwhile, the result that patients with schizophrenia show yes-response advantage irrespective of the spatial-frequency level could be because patients tend to base their metacognitive judgements on evidence irrespective of its spatial-frequency.

The results of fMRI (Experiment 3) suggested that the group difference in metacognition may be at least partly related to the functional difference in the DLPFC. First, the result of gPPI analysis showed that control subjects and patients differ in how the functional connectivity between the DLPFC and parietal or visual cortex is modulated during metacognitive judgement, as a function of the stimulus spatial-frequency and the response type (yes or no) (Figure 4). Given that parietal cortex and visual cortex are each involved in perceptual decisions [37] and sensory evidence processing [26], the result suggests that the degree to which the DLPFC engages to integrate the perceptual-level information in parietal and visual cortices differs between the groups, depending on whether they perceived stimulus presence (yes- or no-responses) and on whether the stimulus was high or low in its spatial frequency. Whether the degree of such functional connectivity reflects more elaborative metacognitive processing (Supplementary Figure 4) or other computational differences remain to be further examined in the future.

The result of decoding analysis further supported the possibility that the DLPFC may at least partly contribute to the group difference in metacognition. The decoding result showed that, among control subjects, metacognitive judgements (i.e., trial-wise confidence ratings) are more accurately decoded from the activation patterns in DLPFC during the detection of high spatial-frequency stimuli than that of low spatial-frequency stimuli. Meanwhile, the decoding accuracy was similar between the spatial-frequency levels among patients with schizophrenia. It has been repetitively shown that DLPFC serves a central role in metacognition [26, 28-32]. These results could not be accounted for by any difference in behavioral performance, as patients and controls did not differ in their overall performance in metacognition and perception regardless of spatial-frequency level (unless response-type was considered). One of the postulated functional contributions of DLPFC is to compute perceptual confidence based on perceptual evidence available in sensory areas [26, 28]. Considering this role of DLPFC, one explanation for the lowered decoding accuracy with lower spatial-frequency stimuli among control subjects could be that they relied on DLPFC when estimating confidence for perception in a spatial frequency-specific manner. Meanwhile, patients with schizophrenia may rely on DLPFC in a more uniform manner across the spatial-frequency range. Although speculative, such atypical dependence on DLPFC among patients may have developed due to their reduced dependency on high spatial frequency information when making perceptual decisions [10]. That is, while individuals without schizophrenia may develop their DLPFC-dependent metacognitive functions through their repetitive experiences in making perceptual decisions based more on high spatial-frequency information, patients may develop the functions through their perceptual decisions which do not particularly favor high spatial-frequency information. Potentially because of this, patients may not develop their DLPFC-dependent metacognitive functions in a typical spatial-frequency dependent manner.

Lastly, whether patients show atypicality in metacognitive performance with other sensory modalities such as auditory modality remains one important question to be examined, as hallucinations among patients with schizophrenia are even more prevalent in the auditory domain than the visual domain (59% and 27% prevalence, respectively) [42]. As a previous study demonstrated that one's metacognitive performance correlates across the sensory modalities [43], metacognitive function among patients may also show atypical dependence on some auditory conditions. Future studies may examine which stimulus properties in auditory domain, if any, may relate with atypical metacognitive performance. For example, metacognitive performance among patients may be atypically modulated by some auditory properties that are supported by magnocellular function such as temporal features [44, 45], which would suggest that altered magnocellular function may underlie the metacognitive atypicality among patients across sensory modalities.

Taken together, the results demonstrated that patients with schizophrenia do not show spatial-frequency dependence in their metacognitive performance, while controls show differential metacognitive performance as well as differential reliance on DLPFC across spatial-frequency levels. The finding among controls is itself novel and may suggest that they can flexibly shift their metacognitive strategy depending on the surrounding viewing conditions. It may be adaptive to rely less on perceptual evidence in some viewing conditions, e.g., where misty air renders perceptual evidence to be blurry (i.e., lower spatial-frequency) than in other conditions where perceptual evidence with sharp edges (higher spatial-frequency) is ample in a clear bright air. Inability of patients to adaptively shift their metacognitive strategy across visual conditions might contribute to their altered subjective experience of sensory world.

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Disclosures

We disclose no conflict of interest.

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