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DISCRIMINATING BETWEEN FIRST AND SECOND ORDER COGNITION IN FIRST-EPISODE PARANOID SCHIZOPHRENIA

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Abstract

Introduction:

An impairment of visually perceiving backward masked stimuli is commonly observed in patients with schizophrenia, yet it is unclear whether this impairment is the result of a deficiency in first or higher order processing and for which subtypes of schizophrenia it is present.

Methods:

Here, we compare identification (first order) and metacognitive (higher order) performance in a visual masking paradigm between a highly homogenous group of young first episode patients diagnosed with paranoid schizophrenia (N=11) to that of carefully matched healthy controls (N=13).

Results:

We find no difference across groups in first order performance, but find a difference in metacognitive performance, particularly for stimuli with relatively high visibility.

Conclusions:

These results indicate that the masking deficit is present in first episode patients with paranoid schizophrenia, but that it is primarily an impairment of metacognition.

Keywords: visual perception, metacognition, schizophrenia, cognition, first-episode, paranoia
DISCRIMINATING BETWEEN FIRST AND SECOND ORDER COGNITION IN FIRST-EPISTODE PARANOID SCHIZOPHRENIA

How may one understand the psychotic symptoms of schizophrenia from the perspective of cognitive science? One approach is to look for failures in perceptual and attentional systems as these could potentially explain hallucinations. At least some cognitive tasks using backward masking seem to be solved differently by patients with psychotic illnesses (schizophrenia, schizoaffective disorder, bipolar disorder), patients with depression, and abstinent alcoholics (Chkonia et al., 2012). An altered time course of unconscious visuo-motor processing and action control has been reported in patients with schizophrenia (Kiefer et al., 2013). It was suggested that the preparation of a motor response induced by an unconscious prime would start later and last longer in the patient group compared to the controls due to deficits in unconscious response priming. This is in contradiction to other studies (Del Cul, Dehaene, & Leboyer, 2006; Huddy et al., 2009) indicating unconscious priming as intact. This discrepancy was explained by Kiefer et al. by suggesting that visual input was relatively weak and more strongly masked resulting in a smaller signal within the visuo-motor system compared to studies by Del Cul et al. and Huddy et al. However, Del Cul et al. argued that masking deficits found in their experiments related to a deficit at higher cortical stages, and characterized it as a deficit in metacognition although they found evidence that both (low-level) forced-choice identification behavior and (high-level) visibility ratings were impaired (Del Cul et al., 2006).

Herzog et al. (Herzog, Roinishvili, Chkonia, & Brand, 2013) suggest that the findings could be explained in terms of a general deficit of the cholinergic system resulting in generally less neural activity. When taking into account performance in a no-mask baseline, Thormodsen et al. (Thormodsen, Juuhl-Langseth, Holmèn, & Rund, 2012) found no difference in forced-choice
identification accuracy between young patients with early-onset schizophrenia and healthy controls using participants with ages between 12 and 18. In contrast, the participants of Del Cul et al. were between 18 and 54 years indicating that the deficit might develop at a later in life. Chris Frith suggested that metacognition is impaired in schizophrenia – much in line with Del Cul et al (C.D. Frith, 1992). Metacognition refers to a certain "type" of mental states, such as self-monitoring or introspection (Overgaard & Sandberg, 2012). Meta-analyses have shown significant and stable mentalising impairments in schizophrenia (Bliksted, Ubukata, & Koelkebeck, 2016; Savla, Vella, Armstrong, Penn, & Twamley, 2013; Sprong, Schothorst, Vos, Hox, & van Engeland, 2007), although it has been suggested that this is not the case of all reflective functions (Bliksted, Fagerlund, Weed, Frith, & Videbech, 2014; Green, Horan, & Lee, 2015). Frith pointed out that there is an asymmetry between routine actions that seem preserved in patients with schizophrenia and metacognition (e.g. mentalising) which is impaired (C.D. Frith, 1992). He argued that symptoms related to schizophrenia originate from metacognitive impairment and thus represent a "misinterpretation" of one's own "normal" first-order states (C.D. Frith, 1992). Meta-representation can be dysfunctioning in different ways (Proust, 2013). It can leave the patient with schizophrenia without the ability to monitor his or her own experiences - so that experiences are "missed" like in hypo-mentalising which is often seen in patients dominated by many negative symptoms (Abu-Akel & Bailey, 2000; C. D. Frith, 2004). However, as Sass (Sass, 2001) suggests, mental states that are normally tacit can also be "overmonitored" as seen in paranoid patients who hyper-mentalise (Abu-Akel & Bailey, 2000; C. D. Frith, 2004).

In this study we investigate first order versus higher order impairment in a highly homogeneous sample of young patients with first-episode paranoid schizophrenia. Using a first-order task (visual discrimination) and a higher-order task (confidence ratings and the Perceptual Awareness Scale) it is possible to investigate the relative impairment in the two tasks to see if one of them is
significantly worse. The hypothesis to be tested were thus: 1) Patients show impaired first order cognition, and 2) patients show impaired second order cognition.

METHODS

Participants

FES patients

Patients with first-episode schizophrenia (FES) were recruited from OPUS, Clinic for schizophrenia, Aarhus University Hospital Risskov, Denmark. All patients met the ICD-10 (International Classification of Disease 10th edition) criteria for paranoid schizophrenia (F20.0)(WHO, 1994). Patients were excluded if they had a history of neurological disorder, severe head trauma, or drug or alcohol dependency according to ICD-10. Patients were able to understand spoken Danish sufficiently to understand the testing procedures and their premorbid IQ was estimated to be above 70 based on prior history. Twelve patients were included with an age range from 19 to 38 years. One patient dropped out of the study (Table 1). All patients were right handed.

Healthy control participants

Thirteen healthy controls (HC) were recruited via advertisements in local newspapers and CNRU’s homepage. HCs had no history of mental or neurological illness, severe head injury or drug or alcohol dependency according to ICD-10. HCs were matched to the patients as well as possible regarding handedness, gender, age and educational level. They were matched according to parental, social, and economic status.

Ethics
All participants received written and verbal information about the project. Written consent was obtained before inclusion. The study was approved by The Central Denmark Region Committees on Health Research Ethics.

Measures

Clinical measures

All patients were interviewed using PSE (Present State Examination, ICD-10) at the inclusion to the OPUS Clinic by experienced psychiatrists (WHO, 1994). All subjects were rated with the SANS and SAPS (Scale for the Assessment of Negative/Positive Symptoms) (Andreasen, 1984a, 1984b) at the time of testing. Ahead of the cognitive data collection all participants were asked routinely about various background information including handedness, colorblindness, dyslexia and whether they wear spectacles. All patients were tested by the same researcher in well-known clinical surroundings in order to minimize paranoia and anxiousness.

Neuropsychological measures

Intelligence

Current functional intelligence was estimated from four subtests from Wechsler Adult Intelligence Scale (WAIS-III): Vocabulary, Similarities, Matrix Reasoning, Block Design. The four subtests were chosen based on their high correlation with the total WAIS-III IQ-score (Wechsler, 1997).

Metacognitive measures
All participants (24 in total) performed a simple visual identification task (Overgaard & Sandberg, 2012; Sandberg, Timmermans, Overgaard, & Cleeremans, 2010) (Figure 1). Stimuli were presented on a 13.3” LED screen at a resolution of 1366 x 768 and a frequency of 60 Hz. At the beginning of each trial a fixation mark appeared on the computer screen for 500, 1000, 1500 or 2000 ms. The fixation mark was followed by one of four geometrical shapes (circle, square, triangle or diamond) presented for 33.3-183.3 ms (i.e. 2-11 frames at 60 Hz) with a size of around 3 degrees of visual angle. The shape was masked by a figure consisting of all four shapes. The participants then identified the shape by pressing one of four keys (‘c’, ‘v’, ‘b’, or ‘n’) using left and right index and middle fingers. They were instructed to respond as fast and accurately as possible, prioritizing accuracy over speed. The mask was on the screen until the participant had responded, or until 3 seconds had passed. Participants had the option of discarding a trial in case they noticed a mistake. After the response, one of two scales appeared on the screen, and the participants were asked to answer questions about the former stimuli according to the presented scale. 50% of the patients and 50% of the HCs were asked to respond using the Perceptual Awareness Scale (PAS) (Ramsøy & Overgaard, 2004) and the remaining 50% were asked to respond using Confidence Ratings (CR).

(Insert Figure 1 here)

The participants using PAS reported the quality of their subjective experience of the presented stimuli on the following scale: (1) No experience, (2) A vague experience, (3) An almost clear experience, and (4) A clear experience. Participants using CR reported their confidence in having provided the correct answer in the identification task using the following scale: (1) Not confident at all, (2) Slightly confident, (3) Quite confident, and (4) Very confident.
The two types of rating scales were used as a previous study has found that the relationship between accuracy and subjective rating is better for PAS than for CR, i.e. PAS indicated a higher level of metacognitive accuracy (Sandberg et al., 2010). One intended goal of the current study was to examine if any metacognitive impairment observed in the patients was specific to the use of one type of scale. However, the number of participants did not allow for such detailed analyses (requiring splitting the sample into four groups), and instead we examined if there was an overall difference between PAS and CR users overall (i.e. not distinguishing between patients and controls).

The experiment consisted of a practice block of 40 trials and 3 experimental blocks of 80 trials each. Between blocks the participants could take a short break. In all experimental blocks, the order of presentation of stimulus duration and shape was randomized. Total duration was 30-40 minutes.

**Data analysis**

The relationship between task accuracy and reported awareness/confidence was analysed using logistic regression and a non-linear mixed effects regression method comparing mean accuracy and awareness/confidence across stimulus durations (Sandberg, Bibby, Timmermans, Cleeremans, & Overgaard, 2011). Specifically, a logistic regression model with correct identification (1/0) as response and group (patient/control), awareness scale (PAS/CR), awareness rating (1 to 4), and stimulus duration (log-transformed) as explanatory variables along with a random subject effect was used. In the non-linear mixed effects regression model, we simultaneously fitted sigmoid curves to relative accuracy frequencies and awareness ratings (Sandberg et al., 2011). The 4-parameter sigmoid function is given by the expression $a+(b-a)/(1+e^{(c-x)/d})$ where $x$ denoted the stimulus duration in milliseconds. $a$ denoted the plateau at low stimulus durations and $b$ denoted the plateau at high stimulus durations. $c$ denoted the $x$-value of the centre point of the slope (i.e. the point that is
halfway between a and b). \(d\) was a measure of the steepness of the slope. Fixed effects corresponding to group, awareness scale, and curve (accuracy/awareness) as well as random subject and curve within subject effects were included for each parameter of the four parameters describing the non-linear curve. Groups were compared with respect to accuracy and awareness by calculating the relative accuracy and awareness between the groups. This was done by simulating 5000 curves from the estimated asymptotic normal distribution of the parameter estimates and then calculating the empirical mean and 95% confidence interval of the ratio between the curves. Due to the limited number of individuals we did not include scale type (confidence/awareness) when comparing patients and controls and similarly we did not include group (patient/control) when comparing CR and PAS. This was the case for both the analysis based on the logistic regression and the non-linear regression.

RESULTS

Demographics, psychopathology and IQ

No statistically significant difference was found between patients and controls for age, gender and current functional IQ (Table 1). A difference in years of education was found between patients and controls (Table 1). This difference may partly be explained by patients’ failure to complete education due to debut of mental illness.

Visual identification performance: bias and accuracy

In order to ensure that measures of metacognition were not confounded by bias in the identification task, the distribution of responses (“square”, “circle”, “triangle”, and “diamond”) were examined across groups. On average, no response was selected on fewer than 23.4% of the trials or more than 26.6% of the trials. A chi-square test of independence across the four
experimental groups failed to refute the hypothesis of no difference across groups ($\chi^2(9)=13.8$, $p=0.13$). Overall, little or no bias was observed in the identification task, and differences in bias across groups appeared an unlikely predictor of differences in subsequent analyses.

To further ensure the validity of the measures of metacognition, identification task accuracy must be controlled for. This is automatically the case if there is no difference in accuracy across groups throughout the range of stimulus durations. To test for this, mean identification task performance was compared across groups using a non-linear regression model. Models were fitted for all groups for task accuracy and awareness rating (Figure 2), and accuracy was compared between patients and controls as well as between PAS and CR raters across stimulus durations. Specifically, this was done by calculating the relative accuracy probabilities between groups based on the non-linear accuracy models. Accuracy was comparable between patients and controls (Figure 3a) and between PAS and CR raters (Figure 3b). An overall test of no difference between accuracy for patients and controls gave a $p$-value 0.51, and the similar test comparing PAS and CR raters resulted in $p=0.14$. It is thus unlikely that differences in metacognition could be explained by differences in identification task accuracy.

(Insert Figure 2 here)

(Insert Figure 3 here)

**Metacognition**
Differences in means of awareness/confidence ratings were examined for patients versus controls and for PAS versus CR raters. As seen in Figure 3c, controls rated their awareness/confidence slightly higher than patients did in general (p=0.009 for an overall test comparing patients and controls). The difference was particularly pronounced at high stimulus durations and was statistically significant in the interval between 150 and 190ms, but not for shorter stimulus durations. A tendency for CR raters to give higher ratings than PAS raters on average was also observed (Figure 3d). The overall test comparing PAS and CR raters resulted in a p-value of 0.10. As seen in Figure 3d, this difference was found numerically across all stimulus durations, but it was only statistically significant for intermediate stimulus durations (around 60-140ms).

High metacognitive capacity is related to high accuracy for high awareness/confidence ratings and low accuracy for low awareness/confidence ratings. In the following analyses, awareness/confidence ratings of 1 and 4 are thus most interesting, but we report all results. To examine differences in metacognitive capacity, we examined the difference in accuracy across awareness/confidence ratings between patients and controls. As seen in Figure 4, the accuracy differed in general for patients and controls depending on PAS/CR rating (likelihood ratio test within the logistic regression model: p<0.0001). For PAS/CR 1 ratings, a statistically significant difference was found overall (p<0.0001). Examining individual latency segments, a significant difference was only observed for low stimulus durations (30-40 ms). This difference is difficult to interpret as performance was at chance level in this interval. For PAS/CR 2 ratings, no difference was observed (p=0.74). In contrast, controls showed statistically significantly higher accuracy levels for PAS/CR ratings of 3 and 4 for stimulus durations above 150 and 130 ms respectively (Figure 4c-d). This difference was also statistically significant overall (p=0.032 for PAS/CR 3 and p=0.0078 for PAS/CR 4).
We examined the difference in accuracy for awareness/confidence ratings between PAS and CR raters (Figure 5), and the accuracy-awareness/confidence relationship differed for the two groups overall (p=0.0060). For PAS/CR1 (p=0.84) and PAS/CR3 (p=0.50), no difference was found. For PAS/CR2, an overall difference was found (p=0.029), but this was not significant at any given stimulus duration. For PAS/CR4, the relationship was significantly different overall (p=0.0010) and specifically at intermediate and high stimulus durations (> 90 ms) (Figure 5d). For these stimulus durations, accuracy was consistently higher for PAS than for CR, i.e. PAS was associated with a higher level of metacognitive capacity.

The Del Cul et al. study (Del Cul et al., 2006) found that the sigmoid functions for patients had a higher threshold (the c parameter) than those for controls for both accuracy and awareness using a similar masking paradigm. The exact difference between c parameters was 31 ms for accuracy and 32 ms for awareness. We conducted a similar analysis for our controls, the c parameters were 62.8 ms [95% CI: (45.9; 79.6)] for accuracy and 89.5 ms [95% CI: (74.4; 104.7)] for awareness/confidence. For our patients, the c parameters were 47.2 ms [95% CI: (20.5; 73.8)] for accuracy and 78.6 ms [95% CI: (55.5; 101.7)] for awareness/confidence. The difference in threshold for our patients and controls was thus very low: 15.6 ms [95% CI: (-16.5; 47.6)] for accuracy and 10.9 ms [95% CI: (-17.2; 39.1)] for awareness/confidence with patients having a numerically lower threshold than controls (although it should be noted that this difference was not
The difference was significantly lower than the expected difference of 31 and 32 ms in the opposite direction for accuracy ($p < 0.005$, one-tailed) and awareness ($p < 0.001$, one-tailed) respectively. Overall, patients thus performed significantly better than expected relative to controls in terms of mean accuracy and awareness/confidence ratings. These results are consistent with the conclusions above that the main difference between our patients and controls is one of metacognition rather than accuracy or raw awareness/confidence ratings.

**Control analysis**

As a control analysis, we repeated the logistic regression analyses including years of education as an additional continuous explanatory variable. In the analysis of the effect of group on accuracy, years of education did not contribute significantly ($p=0.84$), and the same was the case in connection to the analysis of the effect of awareness scale ($p=0.32$). In both situations did the estimated effect of the other factors remain virtually unchanged and all conclusions were the same. These results support the assumption that onset of a mental illness interferes with education and our matching based on parental characteristics may thus provide a more adequate estimate of the potential level of function of the FES patients.

**DISCUSSION**

In this study we examined performance in a masked identification task across multiple difficulty levels (stimulus durations) in young FES patients compared to HCs. Overall, we found little or no response bias, and we found comparable task accuracy levels for patients and controls in the identification task, but the controls generally reported higher levels of confidence/awareness compared to patients. This difference was most pronounced at high stimulus durations, i.e. at
objectively more visible stimuli. The higher ratings were not simply related to a lower criterion for reporting confidence/awareness as this would result in lower accuracy levels for each of the higher ratings, and the opposite pattern was observed. The observed pattern of higher accuracy for high awareness/confidence ratings for controls compared to patients indicates a higher metacognitive capacity of the controls. This leads us to conclude that the patients participating in this study were metacognitively impaired specifically in the evaluation of relatively clear perceptions.

One previous study has examined visual backward masking using higher order (visibility) judgments and found an impairment both in terms of accuracy and reported visibility in patients with schizophrenia (Del Cul et al., 2006). In contrast, we found no such difference between groups, and the difference between groups was significantly smaller than what was expected from the Del Cul et al. study. Their sample had a large age range (18-54 years) and did not consider different subtypes of schizophrenia. In the present study, young patients with first-episode paranoid schizophrenia were investigated. Patients with paranoid schizophrenia are known to have attributional bias such as jumping to conclusions which has been suggested as related to metacognitive deficits (Garety & Freeman, 1999; Moritz & Woodward, 2007; Penn, Sanna, & Roberts, 2008). Here, we found impairment of metacognitive processes in a simple, low-level visual task indicating that metacognitive impairments may be present at many levels or cognitive domains.

Schizophrenia is a complex illness with a variable course and very different prognosis (Nordentoft, Ahlstand, Christensen, Fink-Jensen, & Glenthøj, 2004). Especially negative symptoms are associated with a poor 10 year follow-up prognosis in FES (Austin et al., 2013). Our subjects had all received a diagnosis of paranoid schizophrenia. This subgroup of patients might have a better prognosis compared to other subtypes of schizophrenia (Fenton & McGlashan, 1991) and differ from early onset schizophrenia (Werry, 1992). So even though our results could be taken to
contradict previous findings by e.g. Thormodsen et al (Thormodsen et al., 2012), the contrast could also be taken as an example of the heterogeneity of schizophrenia.

Although our sample was relatively small (N=24, 11 of which were patients), the study does not appear to have been under-powered in terms of identification of the (first order) accuracy impairment as this effect was extraordinarily large in previous studies, e.g. the Del Cul study, and our patient sample size was comparable to that used in the Thormodsen et al. study. In addition, our patients were quite homogeneous, having the same subtype of schizophrenia, and they were carefully matched to the HCs.

In sum, our results indicate that healthy participants, under the condition of this experiment, were better at matching metacognitive reports to first order performance than patients with paranoid schizophrenia. This finding seems to indicate that this difference is more pronounced for metacognitive reports than for first order reports.

On the basis of this experiment, it is not possible to make a universal claim that metacognitive reports can be used as a cognitive marker for (certain kinds of) schizophrenia. However, should future research confirm these results, they may give important insights into cognition in schizophrenia.

We propose that future research on visual backward masking should focus on clinical subgroups of schizophrenia, where patients with paranoid schizophrenia might have intact primary visual perception compared to other subtypes of schizophrenia. In addition, we propose that future research investigate not only first order accuracy and mean visibility/metacognitive ratings, but specifically examine the relationship (e.g. correlation) between the two as this provides a measure of metacognitive capacity that cannot simply be due to report bias.
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We would like to thank Charlotte Emborg, head of the OPUS Clinic at Aarhus University Hospital Risskov for help recruiting the first-episode patients.

Conflict of Interest
The authors declare that they have no conflicts of interest

Funding body agreements and policies
None

Contributors
MSO and KS designed the study. ES collected the data supervised by VB who helped recruiting the patients. BMB and KS did the statistical analysis. All authors contributed to the writing of the article.

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Del Cul, A., Dehaene, S., & Leboyer, M. (2006). Preserved subliminal processing and impaired conscious access in schizophrenia. *Arch Gen Psychiatry*, 63(12), 1313-1323.


Table 1 Comparison of FES patients and controls on demographics, psychopathology and IQ

<table>
<thead>
<tr>
<th></th>
<th>FES (N=11)</th>
<th>Healthy controls (N=13)</th>
<th>Statistical comparison P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean(95%CI)</td>
<td>23.18 (19.75; 26.62)</td>
<td>22.92 (21.47; 24.37)</td>
<td>0.32(^d)</td>
</tr>
<tr>
<td>Females, N(%)</td>
<td>7 (63.64%)</td>
<td>10 (76.92%)</td>
<td>0.48(^e)</td>
</tr>
<tr>
<td>Years of education, mean (95%CI)</td>
<td>11.36 (9.19; 13.54)</td>
<td>15.73 (14.58; 16.88)</td>
<td>&lt;0.01(^d)</td>
</tr>
<tr>
<td>SANS(^a), mean(95%CI)</td>
<td>9.18 (6.53; 11.83)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SAPS(^b), mean(95%CI)</td>
<td>9.27 (6.28; 12.26)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WAIS-III (Est func IQ)(^c)</td>
<td>91.63 (78.01; 105.26)</td>
<td>105.52 (97.87; 113.21)</td>
<td>0.05(^f)</td>
</tr>
</tbody>
</table>

\(^a\)SANS, Scale for Assessment of Negative Symptoms; \(^b\)SAPS, Scale for Assessment of Positive Symptoms; \(^c\)Wechsler Adult Intelligence Scale-III (Matrix Reasoning, Block Design, Vocabulary, Similarities); \(^d\)Mann-Whitney test; \(^e\)Chi\(^2\)-analysis; \(^f\)Students t-test.
Figure 1: Experimental paradigm. Participants performed a masked identification task. First, a fixation mark was presented for 500-2000 ms, and this was followed by the target (one of four geometric shapes) presented for 33-183 ms. A mask consisting of all four stimuli was presented after the target and remained on screen until participants reported or until 3 seconds had passed. Finally, participants reported either their confidence in being correct or the clarity of their visual experience of the stimulus on a 4-point scale.