Impairment of perceptual metacognitive accuracy and reduced prefrontal grey matter volume in first-episode psychosis

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Introduction: Metacognition, or 'thinking about thinking' is a higher-order thought process that allows for the evaluation of perceptual and cognitive processes for accuracy. Metacognitive accuracy is associated with the grey matter volume in the prefrontal cortex (PFC), an area also found to be affected in schizophrenia. The present study set out to investigate whether deficits in metacognitive accuracy are present in the early stages of psychosis.

Method: Metacognitive performance on a perceptual decision task was investigated in first-episode psychosis (FEP) (N=31) and performance compared to age, gender and level of education matched healthy control participants (N=18). A novel signal detection theory approach was used to model metacognitive sensitivity independently from objective perceptual performance. A Voxel-Based Morphometry investigation was also conducted on grey matter volume (GMV).

Results: We found that the FEP group demonstrated significantly worse metacognitive accuracy compared to controls (p=.039). Importantly, GMV deficits were also observed in the superior frontal gyrus. The findings suggest a specific deficit in this processing domain to exist at first episode compared to control participants however no relationship was found between GMV and metacognitive accuracy.

Conclusions: Our findings support the notion that a selective inability to accurately scrutinise perception may underpin functional deficits observed in later schizophrenia development however the exact neural basis of metacognitive deficits in FEP remains elusive

Keywords: schizophrenia, psychosis, first episode, metacognition, consciousness, voxel-based morphometry

Introduction

Metacognition refers to 'thinking about thinking' (Flavell, 1979) and is a fundamental component of higher order cognition (Rosenthal, 2000) facilitating successful learning and completion of daily tasks. The monitoring and control of cognitive processes are dependent on subjective appraisals of cognitive products, may be explicit (conscious) or implicit (feeling driven or 'gut instinct') and are pertinent to successful social interactions (Frith, 2000). Basic cognitive and perceptual operations are scrutinised for accuracy by a higher-order, hierarchal processing system and the self-knowledge an individual has into the 'metacognitive report' produced has become an area of interest in itself separate from the accuracy of objective task performance (Fleming & Dolan, 2012). These implicit, perceptual metacognitive appraisals are not necessarily available to the individual however they may inform more conscious, synthetic metacognitive judgements relevant to social interactions as discussed in Frith's early model. A greater understanding of the unconscious perceptual judgements, and the potentially hierarchical relationship to the more pronounced, declarative metacognitive reports relevant to social recovery (Lysaker et al., 2013) may be critical to understanding the social dysfunction so endemic to schizophrenia. Linking these perceptual processes to their relevant neural foundations may serve as a valuable first step to differentiating processing routes in the metacognitive system.

Dysfunction in metacognition has been found in a number of neuropsychiatric disorders (David et al., 2012) and specifically in schizophrenia (Vargas et al., 2012). People with schizophrenia have been found to have deficits in reflecting back on their own mental states (Lysaker et al., 2013), overconfidence in erroneous conclusions (Köther et al., 2012) and these deficits have been associated with a jumping to conclusions bias (Buck et al., 2012) due to inaccurate assessments of self-knowledge (Lysaker et al., 2013).

Research has investigated these metacognitive judgements through prospective learning assessments (Do Lam, 2012), feelings of knowing (Bacon & Izaute, 2009) and (typically) retrospective reports of confidence in perceptual performance as a means to calculate metacognitive performance (Fleming et al., 2010). One method of modelling this relationship is by employing signal detection theory (SDT) to provide an estimation of the ability for the individual to discriminate signal from noise (Maniscalco & Lau, 2012). To have good metacognitive sensitivity, an individual should be confident in correct responses and unconfident in incorrect decisions.

The study of the neural basis of these metacognitive judgements has frequently reported a relationship with the frontal cortex (for a review, see Fleming & Dolan, 2012; Frith & Frith, 2003). The processing of self-referential information, engaging in introspective behaviours (Schmitz et al., 2004), and retrospective confidence judgements in perceptual decision-making (Fleming et al., 2012) have all been associated with the PFC (Fleming et al., 2010; Morales, Lau & Fleming, 2017). .

In schizophrenia, studies suggest the presence of enlarged ventricles and reduced hippocampal (Radulescu et al., 2014), basal ganglia, medial temporal, prefrontal (Shenton et al., 2001) thalamus and striatal (Gaser et al., 2004) volume. Metacognition has been investigated in relation to GMV in schizophrenia through structured interviews (*Metacognitive Assessment Scale* (MAS) (Semerari et al., 2003)) and self-rated questionnaires (*Insight Scale* (Marková & Berrios, 1992)). Spalletta et al., (2014) found poor self-reflection (as measured by a self-rated questionnaire) associated with reduced volume in the ventrolateral and right dorsolateral PFC. The aforementioned studies have adopted more synthetic models of metacognition, using methods of assessment such as the MAS and Beck Cognitive Insight scale which may draw upon a broad range of social, emotional and linguistic metacognitive processes. The

investigation of perceptual metacognitive judgement may allow these processes to be separated and a cleaner relationship to symptom pathology elucidated. Interestingly, previous studies suggest that metacognitive abilities may differ across processing routes (e.g. performance on memory and perceptual decision making were independent of each other and relied on differing neural networks) (Baird et al., (2013) suggesting a delineated metacognitive processing system. Further evidence into differing metacognitive processing systems is found in TMS research where spatial and tactile neural substrates were found to function independently of each other in a metacognitive, working memory task (Gogulski et al., 2017). These moment-to-moment, more perception-based judgements may replicate more ecologically relevant errors which occur in the real-world where one is not required to explicitly verbalise and construct an internal mental world. However no investigation into perceptual metacognitive accuracy has taken place to date in schizophrenia.

Zipursky et al., (2013) also warn that studies employing chronic cohorts demonstrating a longer term degenerative process must be considered with the fact that the further degeneration may be due to effects of continued exposure to antipsychotic mediation and substance abuse rather than psychosis per se.

A strategy to avoid the aforementioned confounding variables has been adopted by investigating non-chronic samples, in particular, first-episode psychosis (FEP) groups. In FEP, reduced GM volume has been observed in limbic structures (Watson et al., 2012), frontal, temporal, occipital and cerebellum regions compared to controls and more severe GM reduction has been associated with earlier onset of psychosis (Tordesillas-Gutierrez et al., 2015). Vohs et al., (2015) found improved synthetic metacognition related to greater GM density in the medial PFC and the ventral striatum and Buchy et al., (2015) found a relationship in a clinically high risk (CHR) group

between cortical thickness, the inferior and middle frontal gyri and insula regions, and synthetic metacognition. In CHR groups those that converted into psychosis demonstrated a higher decline in overall GM volume than those that did not (Borgwardt et al., 2008), although other studies have only found this effect in specific brain regions such as the prefrontal cortex (Sun et al., 2009). These relationships are yet to be investigated in relation to perceptual metacognitive accuracy however.

The previous evidence motivates several specific hypotheses; that GM differences can be present at early stage of illness and that these deficits are more subtle than at chronic stages. Metacognition has been linked to frontal regions which have also been proposed to be deteriorated in FEP, however the nature of this relationship between GM volume in FEP and perceptual metacognitive accuracy dysfunction compared to controls is yet to be investigated. This paper will focus on cognitive-perceptual metacognition whilst the role and impact social-emotional-interpersonal metacognition in psychosis is reported elsewhere (Davies, Fowler and Greenwood 2016).

To address these questions, the present study will investigate (i) whether patients with FEP have a deficit in metacognitive accuracy compared to matched healthy controls, using a perceptual decision task; (ii) investigate structural GM differences between FEP and healthy controls and iii) whether there is a correlation between structural GM volume and perceptual metacognitive accuracy in FEP will also be investigated. The present study focused on the PFC, as there are clear a priori implications for this region in both metacognitive processing.

Methods and Materials

Participants

Ethical approval was obtained from the London-Camden and Islington NHS Research and Ethics Committee (Ref: 11/LO/1877, project ID 72141) and a local NHS research governance committee. Forty-one patients with first-episode psychosis (32 male, age 19 to 39; mean 25.95) and twenty-one controls matched on age, gender and years of education (15 male, age 18 to 38; mean 24.43) participated in a behavioural testing session and underwent a T1-weighted structural MRI scan.

Patients were recruited through Early Intervention in Psychosis (EIP) services in Sussex NHS Partnership Trust. Participants had received a diagnosis of first-episode psychosis by a UK psychiatrist, and were directly under the care of the EIP service as a first psychotic episode. Inclusion criteria were a primary diagnosis of first-episode psychosis, aged 18+, no history of organic neurological impairment, and no primary diagnosis of substance misuse.

Thirteen patients were medication free for one month or more and 28 were receiving antipsychotic medication (see table 1 for demographic and clinical information pertaining to the final scanned cohort). Four patients did not complete the metacognition task due to fatigue and four were excluded from analysis due to being unable to complete the task with suitable accuracy. One patient was excluded from further analysis due to poor quality T1 MPRAGE and one due to atypical neurology (subarachnoid cyst).

[Table 1: FEP and control participant demographic information]

Eighteen matched control participants were recruited from the community through local media outlets and were screened for any psychiatric, neurological, or substance

misuse history. All participants were screened for MRI safety compatibility. There were no significant differences between the FEP and control populations on age, gender composition, or years of education ($p>.05$).

Participants were compensated for their time by £20. Written informed consent was obtained on the day of the study.

Patients' symptoms on the day of the study were assessed with the short version of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Neuroleptic medication information was taken and converted to Olanzapine equivalent doses (leucht et al., 2014).

Perceptual metacognitive accuracy task

Participants performed a perceptual metacognitive accuracy task adapted from a previous study (Fleming et al., 2010) outside of the scanner. The task was programmed and administered on MATLAB 8 (Mathworks Inc., Natick, MA, USA) using the COGENT 2000 toolbox. Participants undertook a forced choice visual perception task in which they were presented with 2 sequential displays. Each display contained 6 Gabor patch stimuli (circular patches containing alternate black and white vertical bars presented at 1.5 visual angle, 2.2 cycles per degree) arranged around a central fixation point (see figure 1). One of the Gabors in each screen was manipulated to 'pop-out' by increasing the contrast in the patch itself compared to neighbour patches. The contrast of the background Gabors was set to 20% of maximum luminance (bar to background contrast), and the target Gabor was set to vary from 40% (little difference) to 100% (large difference) contrasts. All stimuli and instructions were presented on a grey background and presented on a Viewsonic Graphics Series G90fB 18" CRT monitor in a darkened room with participants placed 60 cms from the screen

Stimuli arrays were presented for 200ms with an interval of 300ms between the two sequential stimuli displays. The target Gabor's location was randomly alternated both in terms of Gabor patch location (1 of 6) and which of the two sequential displays (first or second) it would appear. Participants were requested to state which display they believed the target Gabor had appeared in (first or second) by pressing an assigned key on a standard qwerty keyboard. Participants were given 2500ms to respond or a message stating 'too slow' would appear. Participants were then asked to report their confidence regarding their decision on a scale of 1 (low confidence) to 6 (high confidence) by pressing a labelled key on the computer keyboard. Participants were given 4000ms to make this decision before the next trial commenced. Participants were encouraged to use the full range of the scale and a red box would surround their selected responses. The response window was increased from the original study (Fleming et al., 2010) (stimuli response was 2000ms and confidence response was 4000ms) to account for the potentially slower FEP sample response speed and ensure a suitable level of accuracy was achieved.

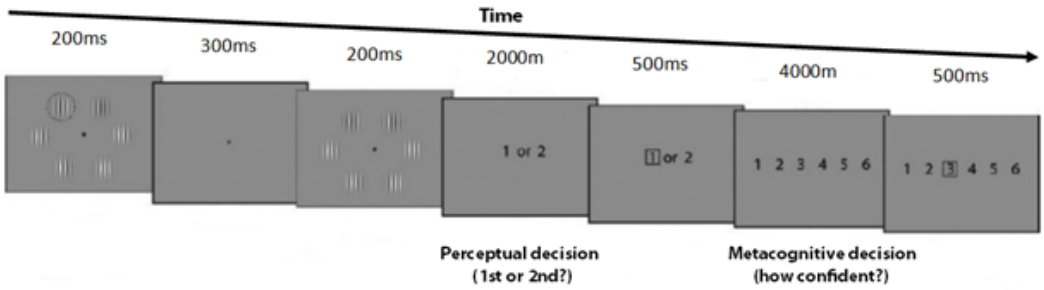

Figure 1: Perceptual metacognition 'pop out' task sequence

As a first measure to ensure that metacognitive accuracy is not confounded by general performance, the target Gabor patch contrast was set using a 1-up-2 down staircase procedure to maintain participant accuracy at ~70% in the perceptual decision task. One incorrect response would lead to a 3 % increase in contrast and two consecutive correct

judgements would lead to a 3% decrease in contrast, on the subsequent trial. All participants received a practice block containing 10 trials to familiarise themselves with the procedure and ensure task comprehension. The main task consisted of 4 blocks of 50 trials with a short break between each block. Due to the clinical sample, the number of trials was reduced to 200 from the 600 included in the original study, to reduce task demands.

To quantify perceptual sensitivity *d*' we used signal detection theory (Green & Swets, 1966). Here, trials are classified into hits (H), misses (M), false alarms (FA) or correct rejections (CR). We can then calculate the following

$$d' = Z(Hit\ rate) - Z(False\ alarm\ rate)$$

where

$$Hit\ rate = \frac{\sum H}{\sum H + \sum M}$$

$$False\ alarm\ rate = \frac{\sum FA}{\sum FA + \sum CR}$$

When metacognitive sensitivity is high, this correspondence should be high, and correct trials (hits and correct rejections) should be accompanied by high confidence, whereas incorrect trials (misses and false alarms) should be accompanied by low confidence. To further ensure specificity in measuring metacognition, we used the measure meta-*d*'/*d*' (Maniscalco & Lau, 2012). This measure is the current 'gold-standard' for quantifying metacognition, because it is invariant to biases in decision accuracy and confidence (Barret et al., 2013) and quantified as meta-*d'*/*d'*. Meta-*d'* is a measure of the correspondence between trial-by-trial accuracy and trial-by-trial confidence. More specifically, it is the *d*' (performance) that the SDT-optimal observer would need in order to achieve the confidence-accuracy correspondence the participant has

demonstrated. Dividing this value of meta-*d*' by *d*' therefore gives the optimality of a participant's confidence judgements. A value of 1 equates to 'perfect' or optimal metacognitive awareness where confidence tracks accuracy in response to the task, whilst values less than 1 demonstrate lack of metacognitive awareness or suboptimal metacognition. Meta-*d'* is modelled in the same units as *d'* (modelled in standardised units on a Gaussian distribution) and therefore calculating meta-*d'* as a proportion of *d'* allows for the direct comparison between objective and subjective sensitivity referred to as metacognitive efficiency. Meta-*d'* was calculated using a Matlab code available at http://www.columbia.edu/~bsm2105/type2sdt/ (13) and meta-*d'*/*d'* was employed in analysis.

[Table 2: Type 2 SDT response table]

MRI Acquisition

Structural MRI scans were obtained using a Siemens Avanto 1.5 T scanner. A T1-weighted MPRAGE sequence was performed with the following parameters: TR/TE = 2730ms/3.57ms, GRAPPA acceleration 2, an in-plane matrix of 256x 256 pixels over a FOV of 256mm x 240mm, flip angle 7°, slice thickness 1mm yielding 192 sagittal plane slices, coronal and axial resolution 1mm, acquisition time 5 min 58 seconds. All images were inspected for image and motion artefacts prior to analysis.

Voxel-Based Morphometry

Structural data was preprocessed and analysed using FSL-VBM (Douaud et al., 2007, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM) with an optimised Voxel-Based Morphometry (VBM) protocol (Good et al., 2001) in FMRIB software library (FSL) version 5.0.7 (Smith et al., 2004). For the purpose of creating the study template, a sub-sample (n=18) of the FEP patients were randomly selected to match the number of

controls (n=18), using an in-house MATLAB script. In the first stage of FSL-VBM, the T1 images were skull-stripped using the FSL Brain Extraction Tool (BET). In the next step of FSL-VBM, the skull-stripped images were segmented to extract grey matter only and registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007). The resulting images were then averaged and flipped along the x-axis to create a left-right symmetric study-specific grey matter template. A modulation process was then applied to compensate for the enlargement/contraction required for non-linear spatial registration wherein each voxel of each grey matter image was divided by the Jacobian of the warp field (Good et al., 2001). All normalised GM images were then smoothed with an isotropic Gaussian kernel with a sigma value of 3 (equal to a full width half maximum of 7 mm). Finally using FSL 'randomise' voxelwise GLM was applied using permutation-based non-parametric inference testing, correcting for multiple comparisons across voxels with threshold-free cluster enhancement (Smith et al., 2009) Whole-brain analyses were conducted across all GM template voxels. In addition, given the clear role for prefrontal cortex in metacognition (Fleming et al., 2010), region of interest analyses were conducted across GM voxels within a frontal lobe mask, as defined by the frontal lobe region in the FSL Harvard-Oxford Cortical Atlas.

Design matrix

A design matrix was compiled with the FSL general linear model tool. In the first two columns, images were categorised according to participant group (FEP patient or control). Metacognitive accuracy was entered as a covariate of interest, and age and gender were entered as nuisance covariates. All covariates were demeaned before entering to the design matrix (http://mumford.fmripower.org/mean_centering/).

Statistical analysis was conducted using FSL randomise, with 5000 permutations and correction for multiple comparisons with Threshold-Free Cluster Enhancement (TFCE) at a family-wise error rate (FWE) of $p<0.05$ (Smith et al., 2009). The following contrasts were examined; (1) the main effect of group on GM volume, (2) the main effect of metacognitive accuracy on GM volume, and (3) the interaction between group and metacognitive accuracy in GM volume. In the main effect and interaction contrasts, age and gender were controlled by their inclusion in the design matrix as covariates.

Results

Perceptual metacognitive accuracy

Variables were inspected for normal distribution prior to analysis through histogram distribution inspection and K-S tests, despite a slight positive skew, no significant violations were observed. An analysis of covariance was run to investigate metacognitive accuracy between the control (N= 18) and FEP (N=31) samples with age and gender controlled for to match the structural analysis. A significant difference was found between groups ($F(1, 45)= 4.53$, $p=.039$) with the control sample demonstrating increased metacognitive accuracy (M=.44, SD=.34) compared to the FEP sample (M=.23, SD=.37), despite equivalent performance accuracy as ensured by the staircase procedure built into the task (table 3). The magnitude of the effect size indicates a medium sized effect of group on metacognitive accuracy (partial eta squared = .09). Interestingly, the FEP group were not significantly worse on the perceptual decision-making task as demonstrated by the non-significant *d'* result ($p=.751$) or was this deficit attributable to a general tendency to be more confident. This suggests that the deficit is exclusively in the metacognitive sensitivity estimation rather than the ability to complete the task or generally be over or under confident. This also testifies to the staircase procedure working successfully. Medication dose was not correlated with perceptual metacognitive accuracy (p=.421). No significant relationship was found between symptoms, and perceptual metacognitive accuracy.

[Table 3: Performance by group on perceptual accuracy task]

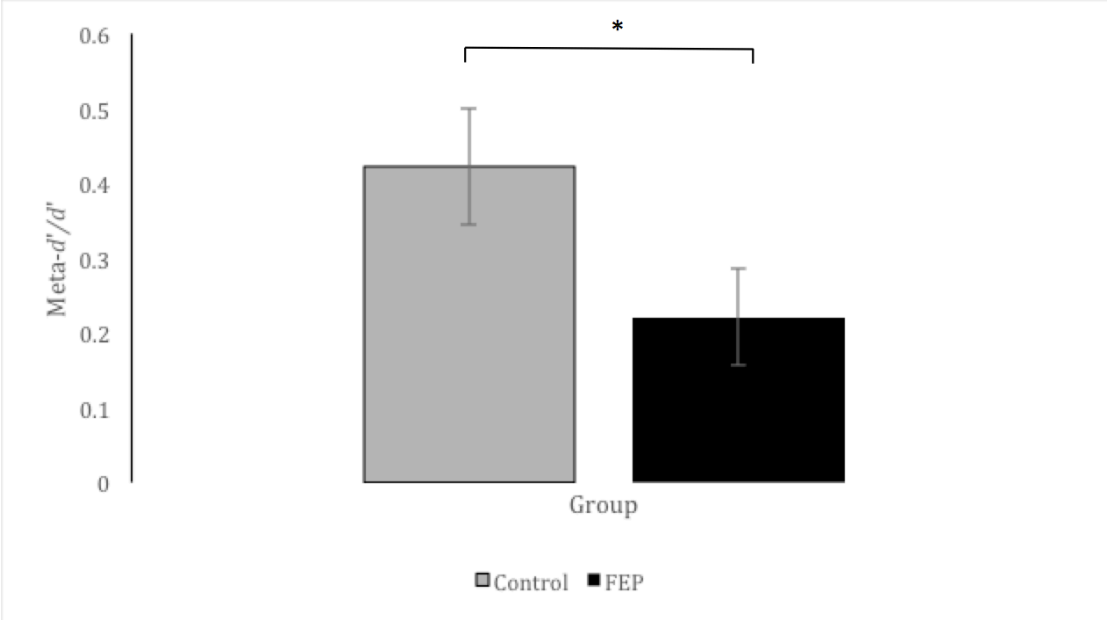

Figure 2 Perceptual metacognitive accuracy between FEP and control participants. Error bars represent standard error of the mean.

Voxel-based morphometry

Given the a priori interest in the frontal lobe including the frontal pole region previously highlighted as specifically relevant for metacognition (Fleming et al., 2010; Fleming et al., 2014; Buchy et al., 2015) we used the frontal lobe mask from the FSL Harvard-Oxford Cortical Atlas as a region of interest, performing permutation tests only on GM voxels within this region. Within the frontal lobe there was a significant group difference, with the FEP sample having significantly lower GM volume in the right superior-medial frontal gyrus ($p<.05$ FWE) (figure 3).

Relationship between perceptual metacognitive accuracy and grey matter volume

No significant relationship was found between GM volume and perceptual metacognitive accuracy. No interaction effect was observed between group, perceptual metacognitive accuracy and GMV.

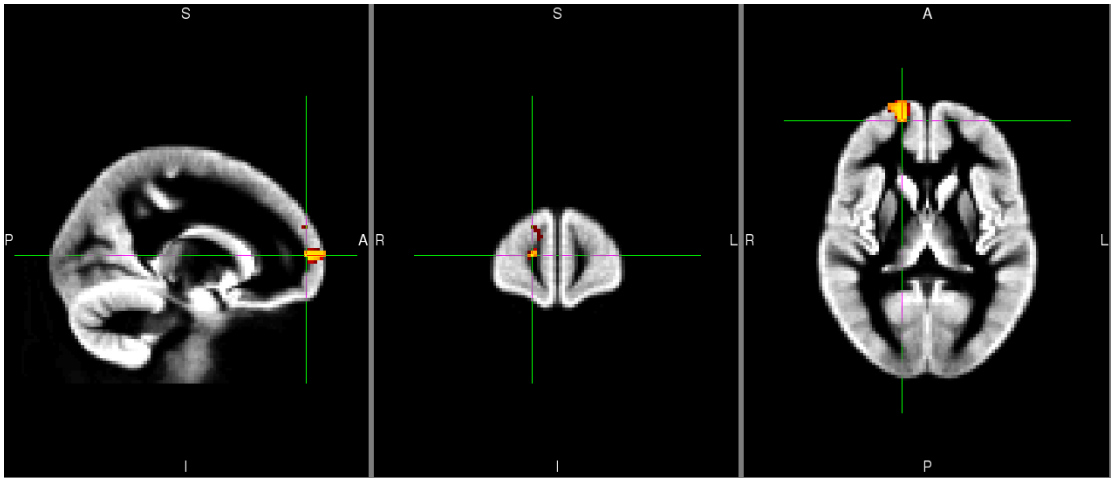

Figure 3: Significant 117 voxel cluster from frontal mask region of interest analysis, peak coordinate 16 56 08, shown at p<0.05 FWE

[Table 4 Contrast results for GM volume and relationship to variables (FWE corrected). Regions localised according to the Harvard-Oxford atlas in FSL]

Discussion

Patients with first-episode psychosis had significantly worse metacognitive accuracy compared to healthy controls matched on age, gender and education level. This is indicative of a specific processing deficit in the metacognitive domain and not attributable to objective task ability. We then examined differences between FEP and control participants in relation to grey matter structure and found significantly reduced volume in the frontal gyrus compared to controls. No significant relationship was found between metacognitive accuracy and GM volume and no interaction was found between group and metacognitive accuracy. No relationship was found between medication and perceptual metacognitive accuracy.

Our observation of impaired perceptual metacognitive accuracy in first-episode psychosis corroborates the metacognitive deficits observed in other studies of schizophrenia. Köther et al., (2012) found a similar effect in overconfidence in relation to incorrect decisions on a social cognition task compared to controls and Warman et al., (2007) found less self-reflectivity and increased certainty in patients versus control participants. Cartwright-Hatton and Wells (1997) found differences in patients compared to controls for a metacognition questionnaire relating to worry and, in another questionnaire design, Bacon et al., (2001) found patients to have less awareness of their mental state than controls. The present study also corroborates findings in FEP in relation to metacognition with a specific deficit being found in FEP compared to non-clinical controls (Trauelsen et al., 2016). Importantly, whilst the above measures relate to social cognitive insight and more synthetic metacognition, this study is the first to experimentally demonstrate metacognitive deficits in FEP in perceptual decision-making, and in a de novo population uncontaminated by years of antipsychotic treatment. This study furthermore does this through advanced SDT theory therefore

employing a sensitive, rigorous and validated model of metacognitive sensitivity (Barrett et al., 2013).

In relation to the neural underpinnings of metacognition, Fleming and colleagues (2010) found an association between metacognitive accuracy and the BA10 and precuneus regions. The present study failed to replicate Fleming's findings. *Whilst* Fleming et al did remove the potentially confounding factors of overall brain volume and gender in their analysis, they did not remove age. There are well known relationships between reduced grey matter and metacognition and age (Smith et al., 2007; Palmer et al., 2014). A relationship between age and decreased grey matter structure has also been found in psychosis (Tordillas-Gutierrez et al., 2017 and removing this as a confound is common practice in structural neuroimaging studies (Boekel et al., 2015). In performing an interaction analysis between group and the correlation between metacognition and grey matter volume, it is therefore crucial to preclude a general effect on grey matter structure of accelerated aging effects in the patients. In addition to inclusion of relevant confounding variables in structure-function studies, there are a number of other factors that can affect the potential for replication, including power of the original and (non)-replicating study, MRI acquisition parameters, analysis options, and statistical inference methods (Boekel et al, 2015). Multi-site studies and pre-registered reports are routes by which replicability of structural brain-behaviour correlations can be investigated, though beyond the scope of our present investigation.

The group difference in GM volume appears in line with other VBM studies (Watson et al., 2012; Buchy et al., 2015) however in an attenuated form. The lower GM volume in the frontal gyrus in the present study is an interesting finding; Lesion studies have found a deficit in the frontal gyrus region compared to controls which related to reduced inhibitory control (Aron et al., 2004). This reduced volume in the frontal gyrus may

account for the observation that people with FEP struggle to inhibit competing cognitive responses and this contributes to a process of tangential thought or *hypermentalization* observed in schizophrenia (Schimansky et al., 2010).

There could, however, be a number of reasons behind the less pronounced cortical differences found compared to other existing studies: the healthy controls to whom the FEP sample was compared were a better match in terms of education level and demographic information and half the FEP sample were not exposed to antipsychotic medication. Previous studies, such as Rosa et al., (2015), have failed to match on education level or studied long-term populations (Douaud et al., 2007). The more severe deficits reported elsewhere could be attributed to these factors rather than FEP status alone. In relation to the more attenuated grey matter differences found in the paper, the main research in the area has been conducted in chronic samples and has found more pronounced deficits in GMV (eg. Shenton et al., 2001). More chronic populations may be a more homogenous sample of those who originate in FEP but go on to have the worst outcomes. FEP as a first point of onset, will have a more heterogeneous composition of those who may make a full recovery, and those who may gone onto longer term symptoms and later schizophrenia diagnosis. If GMV deficits are associated with greater propensity to develop schizophrenia, only a small proportion of an FEP sample should demonstrate these deficits and the correlation may be lost in the present analysis. Other authors focusing on prefrontal cortex GMV have found similar findings where no deficit has been observed in FEP but deficits present in chronic cohorts (Torres et al., 2016). Volumetric differences may be more subtle and Torres et al., only found these when investigated with small volume corrected analysis with a large multicenter investigation in FEP.'

In relation to the relationship between GMV and metacognition, one hypothesis for the lack of substantiation between density and metacognitive capacity could be due to this relationship developing over time rather than being present at first episode. Metacognitive deficits may relate to cortical changes with symptom expression and time; for example those with more pronounced metacognitive dysfunction at FEP may develop greater symptoms (or manage symptoms less well), have increased exposure to neuroleptic medication and neuro-inflammation (Zhang et al., 2016) which may account for the greater deficits in chronic samples. The causal factor in GM atrophy post illness may have a multifaceted aetiology which includes illness trajectory, symptoms, changes in IQ and access to treatments. The mean level of education in the present sample was higher than other studies (Rosa et al., 2015) which may also explain the attenuated structural deterioration despite every precaution being made to find matched controls. Future studies may wish to control for both years of education and take a measure of IQ.

Finally, whilst the present study recruited those from FEP and medication information was taken, inclusion in analysis would have been difficult to do due to the group comparison as the healthy control participants were medication free due to the inclusion criteria. Medication dose was investigated in relation to metacognitive accuracy and no significant relationship was noted suggesting that metacognitive dysfunction in FEP is not attributable to medication alone. None of the controls were on medication so an analysis would have been reflective of group membership rather than impact of medication. Fusar-Poli and colleagues (2014) suggest that detecting group differences increases with sample size in VBM investigations; recruitment of more participants may have revealed more pronounced group differences.

As the study also recruited FEP participants, in order to minimise the potential distress caused the number of trials completed in the perceptual task was reduced from Fleming's original study's 600 to 200. The present study's mean performance was lower than in other studies employing a similar design. Whilst this could be due to a clinical population, the matched controls were also lower which could be an artefact of the reduced number of trials. This may have impacted on the GM investigation. However as both comparison groups completed the same task, this should not have affected the group comparison analysis in which a significant difference was observed.

In conclusion, the present study offers new insights into the structural differences at early stages of illness and into metacognitive deficits in schizophrenia compared to controls. The profile of GM volume change in FEP appears less straightforward and more subtle than in other studies and the nature of GM atrophy in psychosis is likely not a definitive trajectory. The metacognitive deficits, which the present study demonstrates are evident in FEP, were not explained through structural difference as previous work suggests. The cognitive deficits observed in psychosis may be more subtle than existing research suggests and targeting metacognitive rather than cognitive components of disability in psychosis may address longer-term social dysfunction. The implicit perceptual metacognitive accuracy investigated in the present study may better account for higher-order assessments of cognition without the confounds of language deficits and emotional awareness required in more synthetic versions of metacognition. How these differences interact with community function would be a useful next step as the real-life social cost of psychosis should be of the upmost importance to researchers adopting an anatomical approach.

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Footnotes

Tables

Table 1: FEP and control participant demographic information

	FEP (N=31)	HC (N=18)
Age (SD)	26.16 (5.69)	24.06 (4.87)
Gender (female/male)	7/24	5/13
Education (years) (SD)	13.58 (1.71)	13.67 (1.68)
Medication (olanzapine equivalent mg/day) (SD)	13.97 (7.51)	N/A
PANSS (3 item) positive symptoms (mean) (SD)	5.43 (2.44)	N/A
PANSS (2 item) cognitive disorganisation (mean) (SD)	3.1 (1.43)	N/A
PANSS (3 item) negative symptoms (mean) (SD)	5.40 (2.8)	N/A

Table 2: Type 2 SDT response categories

	Correct	**Incorrect**
High confidence	*Hit*	*False alarm*
Low confidence	*Miss*	*Correct rejection*

Table 3: Performance by group on perceptual accuracy task

	FEP	**Healthy control group**	
% Correct (SD)	68.62 (1.6)	69.39 (1.08)	p=.08
Mean confidence (SD)	3.89 (.71)	3.57 (.67)	p=.127
d'	.74 (.12)	.75 (.06)	p=.751

Table 4: Contrast results for GM volume and relationship to variables (FWE corrected). Regions localised according to the Harvard-Oxford atlas in FSL (all contrasts significant at p<.05)

Contrast	*Peak voxel coordinate (x y z)*			*Cluster size (voxels)*	*Region*
HC>FEP	16	56	08	117	Right superior medial gyrus
HC>FEP	12	54	26	32	Right superior medial gyrus
HC>FEP	20	62	28	2	Right middle frontal gyrus

Supplementary materials

PANSS negative symptoms	PANSS cognitive disorganisation	PANSS positive symptoms	Olanzapine equivalent	Diagnosis
9.00	3.00	5.00	20.00	First Episode Psychosis (F29)
3.00	2.00	5.00	10.00	First Episode Psychosis (F29)
9.00	3.00	5.00	.00	First Episode Psychosis (F29)
3.00	2.00	4.00	15.00	Acute Transient Psychosis (F23) / previously substance induced psychotic disorder (cannabis) (F12.9)
5.00	2.00	4.00	.00	First Episode Psychosis (F29)
9.00	3.00	6.00	30.00	First Episode Psychosis (F29)
4.00	3.00	6.00	.00	Asperger's (F84.5) and First Episode Psychosis (F2
7.00	3.00	5.00	.00	First Episode Psychosis (F29)
7.00	4.00	5.00	.00	Substance induced psychotic disorder (cannabis) F1
7.00	3.00	5.00	.00	Paranoid schizophrenia (F20.0) / previously substance induced psychotic disorder (cannabis) (F12.9)
3.00	2.00	3.00	30.00	Bipolar Affective Disorder (F31)
6.00	5.00	8.00	0	Bipolar Affective Disorder (F31)
3.00	2.00	4.00	.00	Bipolar Affective Disorder (F31) and Autism Spectrum

4.00	2.00	6.00	.00	Acute Transient Psychosis (F23)
9.00	5.00	9.00	10.00	Schizophrenia (F20)
3.00	3.00	7.00	14.81	First Episode Psychosis (F29)
3.00	2.00	3.00	11.11	Acute Transient Psychosis (F23)
6.00	5.00	5.00	18.52	First Episode Psychosis (F29) and depression (F32)
5.00	3.00	4.00	.00	Bipolar Affective Disorder in remission (F31.7)
10.00	4.00	6.00	7.41	Schizophrenia (F20)
3.00	2.00	3.00	.00	First Episode Psychosis (F29)
4.00	4.00	8.00	10.00	First Episode Psychosis (F29)
6.00	2.00	5.00	.00	First Episode Psychosis (F29)
3.00	2.00	3.00	.00	Psychotic episode - relapse (F29)
3.00	5.00	6.00	10.00	First Episode Psychosis (F29)
9.00	6.00	12.00	7.69	Asperger's (F84.5) and First Episode Psychosis (F2
3.00	4.00	5.00	15.00	First Episode Psychosis (F29)
7.00	2.00	4.00	3.70	First Episode Psychosis (F29)
3.00	2.00	3.00	.00	Emotionally Unstable Personality disorder (F60.3)
5.00	4.00	9.00	10.26	Paranoid schizophrenia (F20.0)
8.00	4.00	5.00	.00	First Episode Psychosis (F29)