Discriminating imagined from perceived information engages brain areas implicated in schizophrenia

Jon S. Simons,[a,*] Simon W. Davis,[a] Sam J. Gilbert,[a] Chris D. Frith,[b] and Paul W. Burgess[a]

[a] Institute of Cognitive Neuroscience and Department of Psychology, University College London, UK
[b] Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK

Some of the symptoms of schizophrenia may reflect a difficulty discriminating between information that was perceived from the outside world and information that was imagined. This study used fMRI to examine the brain regions associated with this reality monitoring ability in healthy volunteers, who recollected whether information had previously been perceived or imagined, or whether information had been presented on the left or right of a monitor screen. Recent studies have suggested that schizophrenia may be associated particularly with dysfunction in medial anterior prefrontal cortex, thalamus, and cerebellum. In our data, activation in all three of these regions of interest was significantly greater during recollection of whether stimuli had been perceived or imagined versus recollection of stimulus position. In addition, reduced prefrontal activation was associated with the same misattribution error that has been observed in schizophrenia. These results indicate a possible link between the brain areas implicated in schizophrenia and the regions supporting the ability to discriminate between perceived and imagined information.
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Introduction

How do we distinguish events we imagined from those that we actually witnessed? A rich seam of theoretical and empirical work from cognitive psychology has led to a number of cognitive models of functions that have been termed *reality monitoring* and *source monitoring*, which may contribute to discriminating between imagined and perceived information (Johnson et al., 1993; Burgess and Shallice, 1996a; Schacter et al., 1998). In terms of the neural mechanisms that might support these processes,

theorists have made great strides in understanding how the brain represents in memory information that was perceived from the outside world (Aggleton and Brown, 1999; Fletcher and Henson, 2001; Simons and Spiers, 2003), but less is known about the brain regions involved in remembering previously imagined information. An unresolved issue concerns which brain regions might be involved in discriminating between perceived and imagined information—a control function that is critical to feeling that we can trust our memories to supply us with true recollections and shield us from falsely remembering events that never occurred.

An indication of what can happen when such an ability breaks down may come from schizophrenia. Although the disorder can vary in its presentation, among the positive symptoms often reported in schizophrenia are hallucinations, whereby patients report, for example, hearing voices when none are present (Frith, 1992). It has been suggested that these symptoms may result from a difficulty in discriminating between information that is perceived in the external world and information that is imagined (Johnson and Raye, 2000), because of a deficit in monitoring the self-generation of thoughts (Frith and Done, 1989; Frith, 1992) or a bias towards misattributing internal thoughts to external sources (Bentall et al., 1991). One possibility is that this represents an intrusion of previous thoughts and experiences into current consciousness. In support of this view, schizophrenic patients with delusions and hallucinations have been shown to be impaired at judging the origin of previously encoded stimuli, often exhibiting particular difficulty in identifying the source of self-generated information (Bentall et al., 1991; Vinogradov et al., 1997; Danion et al., 1999; Keefe et al., 2002). For example, both Vinogradov et al. (1997) and Keefe et al. (2002) have reported that patients with schizophrenia were impaired at remembering the source of words they had generated themselves but performed similarly to controls at remembering the source of words they had seen or heard.

It is unclear which brain regions might be implicated in the discrimination difficulties observed in schizophrenia. Evidence from neuroimaging studies suggests that schizophrenia may be associated with changes in a number of brain regions, including lateral and medial prefrontal and temporal cortices, the thalamus, and cerebellum (Friston and Frith, 1995; Fletcher et al., 1996;

Lawrie et al., 2002; Winterer et al., 2003). However, it has proved difficult to isolate the brain regions that might be responsible specifically for an impairment in discriminating between perceived and imagined information because patients with schizophrenia often exhibit additional cognitive symptoms impacting on language, perception, attention, and problem solving (Frith, 1992; Cornblatt and Keilp, 1994; Hoff and Kremen, 2003), and, in addition, many are on anti-psychotic medication at the time of testing, known to alter the functioning of multiple brain systems (Goff and Coyle, 2001). One possible solution has been to also study unmedicated first degree relatives of schizophrenic patients, who exhibit none of the cognitive impairments associated with schizophrenia but have an enhanced genetic risk of developing the disorder (Risch, 1990), and who can, to varying extents, experience delusions or hallucinations (Callicott et al., 2003; Whalley et al., 2004).

Inspection of a number of functional neuroimaging studies involving these patient groups reveals consistent activation reductions relative to controls in three main regions: medial anterior prefrontal cortex, thalamus, and cerebellum (Andreasen et al., 1996; Callicott et al., 2003; Whalley et al., 2004; MacDonald et al., 2005; Fox et al., 2005). These activation reductions occurred reliably across groups of patients with schizophrenia as well as symptomatic and asymptomatic first degree relatives, suggesting that they are not specific to one or other participant group. In addition, dysfunction in these three regions was observed during performance of a range of cognitive tasks (story recall (Andreasen et al., 1996), n-back working memory (Callicott et al., 2003; Fox et al., 2005), sentence completion (Whalley et al., 2004), and context processing (MacDonald et al., 2005)), suggesting that the effects are independent of the task being administered. Moreover, in a number of studies (Callicott et al., 2003; Whalley et al., 2004; Fox et al., 2005), the functional disruptions occurred in the context of normal behavioral performance, suggesting that the effects were not merely secondary to poor performance on the task. A correspondence, therefore, between dysfunction in these brain regions and those involved in discriminating between perceived and imagined information may suggest an exploratory thread which links evidence from three necessary levels: evidence of dysfunction at a neuroanatomical level, cognitive substrate (or "marker"), and behavioral symptoms.

In this event-related functional magnetic resonance imaging (fMRI) study, healthy participants were scanned while recollecting whether information had previously been perceived or imagined, or recollecting which position on a monitor screen information had been presented. Our analysis examined activation changes in each of the regions identified as functionally disrupted in schizophrenics and first degree relatives (Andreasen et al., 1996; Callicott et al., 2003; Whalley et al., 2004; MacDonald et al., 2005; Fox et al., 2005), with regions of interest defined on the basis of coordinates reported in the study by Whalley et al. (2004). The coordinates reported by Whalley et al. were chosen because that experiment involved the most extensive target group of any of the studies (69 first degree relatives of patients with schizophrenia, both with and without psychotic symptoms), none of whom were on anti-psychotic medication at the time of testing and who, as a group, showed no behavioral differences relative to controls on the administered task (the Hayling sentence completion test (Burgess and Shallice, 1996b)).

If hallucinations can be attributed to difficulty in discriminating information present in the outside world from information that is imagined, and medial anterior prefrontal cortex, thalamus, and

cerebellum are the neural substrates of this ability, then we would predict that activation in all three of these regions of interest will be significantly greater in healthy volunteers during recollection of whether items had been perceived or imagined versus recollection of the items' position. Moreover, reduced activation may be associated specifically with misattributing imagined items as having been perceived, the type of error that has been observed in schizophrenia (Vinogradov et al., 1997; Danion et al., 1999; Keefe et al., 2002).

Method

Participants

Sixteen right-handed native speakers of English (6 male, 10 female), with normal or corrected-to-normal vision, took part in the experiment. The volunteers (mean age = 24.5 years, range 19–35) were screened using a comprehensive medical questionnaire and, after complete description of the study, written informed consent was obtained prior to taking part. All participants indicated that they were familiar with contemporary British culture.

Design and procedure

The stimuli consisted of 96 well-known word pairs (e.g., "Laurel and Hardy", "bacon and eggs", "rock and roll"), which were extensively pilot tested to ensure their familiarity in the target population recruited for the fMRI experiment. These word pairs were used as target items in the study and test phases. In addition, 12 naturally occurring and 12 manmade object words were used as baseline items in the test phase. The words were matched for Kucera-Francis frequency.

There were 4 scanning sessions in the experiment, each comprising a study and test phase (Fig. 1). Study phases involved 24 trials, each of which began with a fixation arrow indicating whether the stimulus was to be presented on the left or right of the monitor screen. After 500 ms, participants were presented on the designated side of the screen with either a word pair (perceive condition; e.g., "Laurel and Hardy") or the first word in a word pair and a question mark (imagine condition; e.g., "Laurel and ?"). Participants were instructed to view the presented stimulus and, in the perceive condition, to look at the second word of the word pair and count the number of letters it contained. In the imagine condition, participants were instructed to imagine the second word of the word pair and count its number of letters. A cue at the bottom of the screen in both conditions ("1 = 1–5 letters, 2 = 6–12 letters") reminded participants of which response button to press on a button box, which they were given 3 s to do. Position on the screen and perceive/imagine condition were crossed as experimental factors, with trial order pseudo-randomized such that no more than three consecutive trials were of the same condition.

Test phase trials began with a cue, presented for 1 s, which indicated the type of decision that would be required in that trial (see below). Participants were then presented with a single word in the center of the screen and were given 3 s to make their response. Twenty-four trials in each test phase involved presentation of the first word of a word pair that had been studied in the preceding study phase, 12 of which tested memory for the position in which the item had been presented in the study phase ("1 = left, 2 = right") and 12 of which tested whether the second word in the

a Study Phase

b Test Phase

Fig. 1. Examples of the cues and stimuli used during the study and test phases. (a) In the study phase, participants studied either well-known word pairs or the first word of a word pair and a question mark, which were presented either on the left or right of a monitor screen. They were cued to view each word pair and either to look at, or to imagine, the second word of each pair and to count the number of letters it contained. (b) In the subsequent test phase, the first word of each studied word pair was again presented, and participants were cued to recollect either whether the second word in the word pair had been seen or imagined, or alternatively whether the word pair had been presented on the left or right of the screen.

word pair had been perceived or imagined in the study phase ('1 = seen, 2 = imagined'). Also included were 6 baseline trials that involved making a semantic living/nonliving judgment about a non-target noun and 12 cue-only trials in which the subject simply pressed a button on the button box in response to the corresponding number displayed on the screen. Four different versions of the paradigm were created, which systematically counterbalanced the stimulus position and perceive/imagine status in the study phase, and the type of recollection cued during the test phase.

To increase the efficiency of the event-related fMRI design, the inter-trial interval in both phases was jittered according to an exponential distribution between 480 ms and 1080 ms, and additional fixation periods lasting 4 s were pseudo-randomly interspersed between trials. Participants were familiarized with the paradigm during practice sessions both prior to the experiment and inside the scanner.

Imaging acquisition and data analysis

A 3T Siemens Allegra system was used to acquire echo-planar functional images (TR = 2.34 s, TE = 30 ms, 36 sequential axial slices oriented approximately 10° to the AC–PC transverse plane, 2-mm thickness, 1-mm inter-slice skip, 4 sessions each of 180 volume acquisitions). The first 6 volumes from each session were discarded to allow for T1 equilibration.

Data were preprocessed and analyzed using SPM2 (Wellcome Department of Imaging Neuroscience, London). Images were first corrected for motion by realigning all images with respect to the first and re-sampling all slices in time to match the middle slice. The realigned images were then normalized to an EPI template in MNI stereotactic space (Cocosco et al., 1997). Normalized images were re-sampled into 3-mm cubic voxels and then spatially smoothed with an 8-mm FWHM isotropic Gaussian kernel. A high-pass filter of 1/128 Hz was used to remove low-frequency noise, and an AR(1) + white noise model corrected for temporal autocorrelation.

Random effects statistical analysis was undertaken in two stages. In the first stage, event types for each session were modeled by convolving onset times with a canonical hemodynamic response function. Parameters for each regressor were estimated using a subject-specific model, with movement parameters in the 3 directions of motion and 3 degrees of rotation included as confounds, and covariates representing the mean session effects. Linear contrasts were used to obtain subject-specific estimates for each of the effects of interest. These estimates were entered into the second stage of analysis treating subjects as a random effect, using one-sample t tests across subjects. Statistical parametric maps for each contrast were characterized using an uncorrected height threshold of $P < 0.001$ and a cluster extent threshold of $P < 0.05$, corrected for the entire imaged volume. Activations located within

the a priori regions of interest (10-mm spheres centered on the coordinates reported by Whalley et al. (2004)) were reported if they exceeded a height threshold of $P < 0.05$ corrected for voxels within the volumes of interest. The peak locations of significant activations were localized on an averaged structural scan, with approximate Brodmann areas estimated from the Talairach and Tournoux (1988) atlas, after adjusting coordinates to allow for differences between the MNI and Talairach templates (www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

Results

Behavioral results

Accuracy and reaction time data for the study and test phases are displayed in Table 1. In the study phase, behavioral differences between the perceive and imagine conditions were observed, with significantly greater accuracy ($t = 8.9$, $df = 15$, $P < 0.001$) and reduced reaction times ($t = 13.3$, $df = 15$, $P < 0.001$) associated with counting the number of letters in perceived versus imagined words. In the test phase, there was no significant difference in accuracy between recollection of perceived/imagined status and stimulus position ($t = 0.3$, $df = 15$, $P = 0.8$). Reaction times were significantly longer in the former than the latter condition ($t = 6.1$, $df = 15$, $P < 0.001$). The fMRI analysis model included correct recollection trials only.

Neuroimaging results

Looking first at the study phase conditions contrasted against fixation, counting the letters contained in target words involved activation in a number of areas previously associated with verbal processing and counting (Price, 1998; Piazza et al., 2002), such as temporal, lateral prefrontal, and parietal cortex, the cerebellum, as well as more posterior perceptual processing areas. Directly contrasting the counting task in imagined versus perceived words revealed significantly greater activation in lateral prefrontal cortex (-45, 21, 21; $Z = 4.86$ and 39, 30, -9; $Z = 3.93$), motor cortex (-3, 12, 63; $Z = 4.84$), and the globus pallidus (-3, 3, -3; $Z = 3.75$ and 12, 3, -3; $Z = 3.71$). Greater activation for perceived than imagined words was seen in areas around medial parietal (21, -57, 24; $Z = 4.42$ and -9, -39, 45; $Z = 4.21$) and occipital cortex (15, -96, 0; $Z = 4.23$ and 12, -72, -48; $Z = 3.90$).

Turning to the test phase, recollecting whether word pairs had been studied on the left or right of the monitor screen versus the semantic baseline condition provoked activation in a number of areas that closely replicated the results of previous studies

Table 1
Accuracy and reaction time (ms) data for the study and test phases

	Accuracy		Reaction time	
	Mean	SD	Mean	SD
Study phase				
Perceived	0.95	0.06	1437	253
Imagined	0.83	0.06	1799	224
Test phase				
Perceived/Imagined	0.78	0.09	1874	261
Left/Right	0.77	0.08	1687	246

Table 2
Regions of significant activation in the contrasts between correct recollection trials (perceived/imagined and left/right status) vs. the baseline condition

Brain region	Coordinates			
	x	y	z	Z
Recollection of perceived/imagined status > baseline				
Left lateral PFC (BA 45/46)	−45	27	24	4.4
Anterior cingulate cortex (BA 32)	−6	15	51	5.3
Right caudate (BA 25)	12	9	3	4.5
Left putamen (BA 25)	−12	3	−6	4.5
Right lateral parietal cortex (BA 40)	36	−45	36	4.1
Left temporal cortex (BA 21)	−48	−45	3	3.9
Left lateral parietal cortex (BA 40)	−42	−54	48	3.9
Left precuneus (BA 31)	−9	−66	27	4.0
Left medial occipital cortex (BA 17)	−6	−81	9	4.0
Recollection of left/right status > baseline				
Right anterior PFC (BA 10)	42	57	12	3.8
Left anterior PFC (BA 10)	−30	48	18	4.1
Left lateral PFC (BA 44/9)	−42	24	30	4.1
Supplementary motor area (BA 8)	−6	21	51	4.2
Right caudate (BA 25)	12	12	0	3.8
Left putamen (BA 25)	−15	9	−6	5.0
Left lateral parietal cortex (BA 40)	−33	−48	39	4.1
Posterior cingulate cortex (BA 23)	24	−57	21	4.6
Left precuneus (BA 23)	−15	−60	18	4.7
Left precuneus (BA 7)	−9	−69	51	4.1

Not. Coordinates are in MNI atlas space (Cocosco et al., 1997), with brain regions and Brodmann areas (BA) estimated from the Talairach and Tournoux (1988) atlas.

investigating memory for spatial position (Rugg et al., 1999; Simons et al., 2005b). As can be seen in Table 2, these included left and right anterior PFC, lateral PFC, lateral parietal cortex, and precuneus. The contrast between recollection of whether words had previously been perceived or imagined versus semantic baseline produced significant activation (Table 2) in regions including left lateral PFC, anterior cingulate, right caudate, bilateral parietal cortex, and precuneus (see Lundstrom et al., 2003; Vinogradov et al., 2006, for similar results).

The contrast of most relevance to understanding the discrimination difficulties sometimes associated with schizophrenia was the comparison between recollection of the perceived/imagined status of words versus their spatial position. Such a contrast should isolate the brain regions specifically associated with remembering whether information was perceived or imagined, over and above those regions that might support processes involved generally in the retrieval of details about the context in which previous events occurred. As illustrated in Fig. 2, activation was significantly greater in all three of the regions of interest identified on the basis of dysfunction in schizophrenics and first degree relatives (Andreasen et al., 1996; Callicott et al., 2003; Whalley et al., 2004; MacDonald et al., 2005; Fox et al., 2005) – medial anterior prefrontal cortex, thalamus, and cerebellum – during recollection of perceived/imagined status versus left/right spatial position of words ($F = 111.7$, $df = 1$, 15, $P < 0.001$). This result suggests that the regions disrupted in both diagnosed schizophrenia and high genetic predisposition to the disorder are among the very same regions as are recruited by healthy volunteers to discriminate between perceived and imagined information (see Table 3 for full whole-brain results).
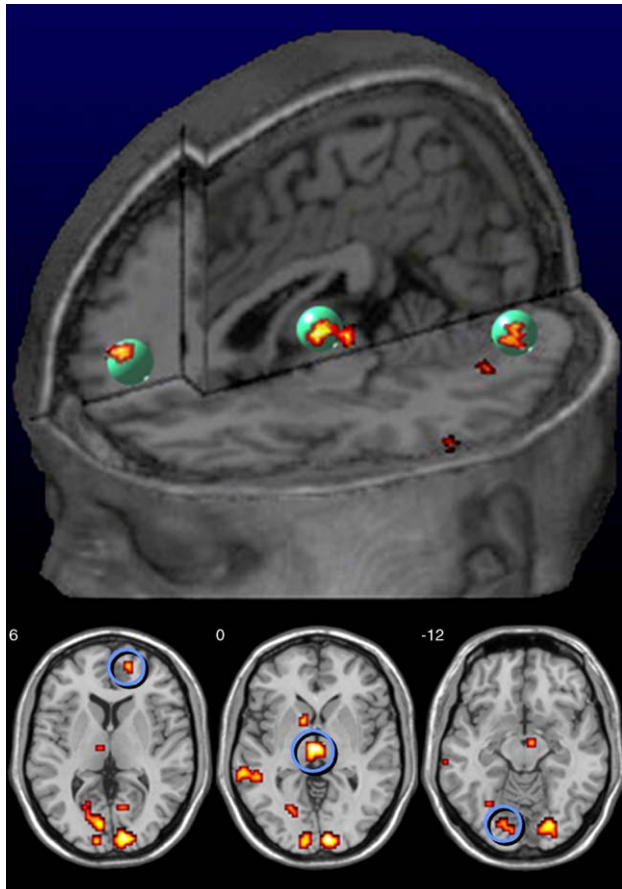
Fig. 2. All three of the regions of interest (depicted as green spheres) identified by Whalley et al. (2004) as functionally disrupted in individuals at enhanced genetic risk of schizophrenia also exhibit significant activation in healthy volunteers associated with remembering whether stimuli were previously perceived or imagined. Significant activation in the regions of interest (medial anterior prefrontal cortex, thalamus, and cerebellum) resulting from the contrast between recollection of perceived/imagined status versus left/right status is plotted onto a three-quarter cut-out projection, and on three separate axial slices (highlighted with blue circles), of a template human brain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Activation in these regions of interest was not related to overall recollection accuracy across subjects ($M = 0.77$, SD = 0.07; $r <$ 0.17, $P > 0.54$). Further analysis of specific types of error centered on misattributions of imagined items as having been perceived (mean proportion of imagined items endorsed as perceived = 0.19, SD = 0.11) and of perceived items as having been imagined (mean proportion of perceived items endorsed as imagined = 0.26, SD = 0.21). This analysis revealed that activation in the medial anterior PFC region of interest was significantly negatively correlated with the likelihood of misattributing imagined items as having been perceived (Fig. 3; $r = -0.54$, $P < 0.05$). In other words, reduced engagement of this medial anterior PFC region relative to other participants in the sample was associated with the same type of error in attributing imagined information to an external source as has been observed in schizophrenia (Frith and Done, 1989; Frith, 1992; Bentall et al., 1991; Vinogradov et al., 1997; Danion et al., 1999; Keefe et al., 2002). The brain–behavior correspondence was specific to this type of misattribution error: there was no significant correlation between anterior PFC signal and the likelihood of

incorrectly endorsing perceived items as having been imagined ($r = 0.18$, $P = 0.5$). There were no significant correlations between signal in thalamus or cerebellum and misattribution error.

As described earlier, our regions of interest were centered on the coordinates reported by Whalley et al. (2004) but were derived from multiple previous studies that had used a number of different cognitive tasks to identify functional disruption. To further ensure that the present results could not be in some way attributable to the particular cognitive task that Whalley et al. used to identify functional disruption in their participants, we also examined activation in our data in regions of interest defined by the results of Nathaniel-James et al. (1997), who characterized activation in healthy volunteers during performance of the same task as used by Whalley et al. (the Hayling sentence completion test (Burgess and Shallice, 1996b)). In contrast to the results based on Whalley et al.'s coordinates, activation in these "control" regions of interest was not significantly sensitive to the discrimination between perceived/imagined versus left/right status of stimuli (F = 1.2, $df = 1, 15$, $P = 0.3$), confirming that a task-specific factor is unlikely to account for the present results.

A final analysis considered whether activation in any of the regions of interest defined on the basis of the results of Whalley et al. (2004) could be attributable to time on task, given that reaction times were significantly longer during recollection of perceived/imagined status than stimulus position. However, this possibility was shown to be unlikely since there was no significant correlation between reaction time and signal change in the regions of interest across subjects ($r = -0.18$, $P = 0.5$).

Discussion

The main finding of this experiment is that three brain regions – medial anterior PFC, the thalamus, and cerebellum – were involved in discriminating information that had previously been perceived from information that had been imagined. Activation in these regions was significantly greater when participants recollected the perceived/imagined status of words versus remembering the spatial position in which the words had been presented, indicating that their role in recollection is more important for the former type of distinction. Furthermore, all three of these brain regions have been identified as dysfunctional in previous studies of schizophrenia and

Table 3
Regions of significant activation in the contrast between correct recollection of perceived/imagined status vs. left/right status

Brain region	Coordinates			
	x	y	z	Z
Regions of interest based on results of Whalley et al. (2004)				
Medial anterior PFC (BA 10)	18	54	6	3.6
Mediodorsal thalamus	3	−15	0	4.6
Cerebellum/Medial occipital cortex (BA 18)	−9	−84	−12	3.1
Additional significant regions				
Left lateral temporal cortex (BA 21)	−51	−42	−6	4.3
Left occipital cortex (BA 18)	−24	−81	−6	4.9
Right occipital cortex (BA 18)	24	−81	−12	4.3
Left medial occipital cortex (BA 18)	−9	−81	9	4.0
Right cuneus (BA 17)	9	−93	0	5.0

Note. Coordinates are in MNI atlas space (Cocosco et al., 1997), with brain regions and Brodmann areas (BA) estimated from the Talairach and Tournoux (1988) atlas.
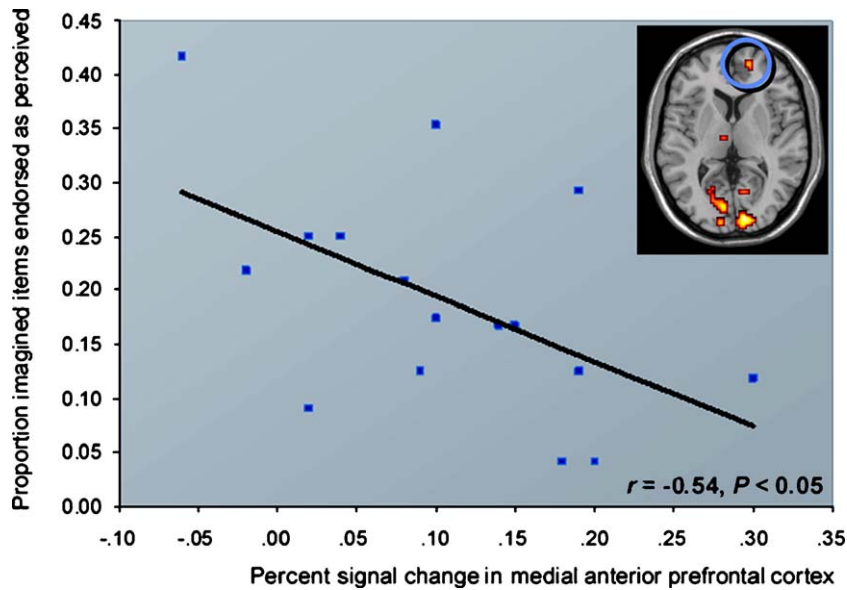
Fig. 3. Scatter plot illustrating the significant correlation across participants between reduced activation in medial anterior prefrontal cortex (pictured) and likelihood of misattributing imagined stimuli as having been perceived. This is the same type of error as has been observed in schizophrenia.

first degree relatives of schizophrenics (Andreasen et al., 1996; Callicott et al., 2003; Whalley et al., 2004; MacDonald et al., 2005; Fox et al., 2005), suggesting that disruption to medial anterior PFC, thalamus, and cerebellum may be at least partly responsible for an impairment in making similar discriminations that might account for the hallucinations associated with schizophrenia (Frith and Done, 1989; Frith, 1992; Bentall et al., 1991; Vinogradov et al., 1997; Danion et al., 1999; Keefe et al., 2002). The data indicate that medial anterior PFC may be of particular importance, since correlation analysis demonstrated that reduced activation in this region was associated with greater likelihood of misattributing imagined items as having been perceived—the precise type of error that has been observed in schizophrenia.

The prominent role for anterior PFC in the present data is consistent with previous results from our laboratory (Simons et al., 2005a,b) and others (Rugg et al., 1999; Ranganath et al., 2000; Dobbins et al., 2002) that this region is key for recollecting the context in which previous events occurred. Recent evidence has suggested a distinction between the lateral and medial aspects of anterior PFC. The lateral aspect appears to play a general role in contextual recollection regardless of the type of context being retrieved (e.g., where and when an event occurred, and our thoughts and feelings at the time) (Rugg et al., 1999; Dobbins et al., 2002; Simons et al., 2005a,b). The medial region, by contrast, has been demonstrated to be sensitive specifically to the recollection of the kind of context details that a number of cognitive theories (Johnson et al., 1993; Burgess and Shallice, 1996a; Schacter et al., 1998) consider to have been internally generated at the time of encoding (Simons et al., 2005a,b), such as what thought processes were engaged when a stimulus was presented. Thus, we have previously shown that medial anterior PFC is engaged to a significantly greater extent during recollection of the type of encoding task that was previously undertaken with stimuli than when recollecting either where (Simons et al., 2005b) or when (Simons et al., 2005a) the stimuli were encountered. Our finding in the present study that medial anterior PFC was recruited when discriminating whether stimuli had been imagined or

perceived is consistent with the hypothesis that the region is important for recollecting contextual details that were generated internally at the time of encoding (Simons et al., 2005a,b).

This hypothesis is in line with previous observations of activation in anterior PFC associated with functions involving the processing of internally generated thoughts such as remembering to carry out intentions after a delay (Burgess et al., 2003), goal/ subgoal processing (Koechlin et al., 1999), integrating internally represented information (Reynolds et al., 2006), self-referential mental activity (Gusnard et al., 2001), and forming a theory of mind about the mental states of others (Frith and Frith, 2003). Other research suggests that medial anterior PFC is involved in processing that is particularly oriented towards external stimuli (Small et al., 2003; Gilbert et al., 2005; Burgess et al., 2005), for example, exhibiting greater activation when participants perform a task on the basis of externally presented stimuli rather than performing the same task in their heads (Gilbert et al., 2005). A full account of these results requires a model in which anterior PFC biases attention between internally generated and externally derived information (see Burgess et al., 2005, for one such model). A general information processing capacity of this sort may be expressed in a recollective memory paradigm like that used in the present experiment as modulation of the attentional balance between externally presented stimuli and the internally generated thoughts that were previously provoked by them (Simons et al., 2005a; Burgess et al., 2005).

One outstanding question concerns which stage of the episodic retrieval process might be supported by the anterior PFC region that was observed in the present study. A number of cognitive theories indicate that pre-retrieval cue specification processes may be separable from post-retrieval monitoring processes (Burgess and Shallice, 1996a; Rugg and Wilding, 2000). Although the present data cannot address this issue directly, previous results suggest that lateral anterior PFC may support cue specification processes that occur prior to commencement of a retrieval search, whereas medial anterior PFC may be involved in a later stage of the recollection process

(Simons et al., 2005a). Further studies are required to elucidate the precise nature of these later processes, but it is possible that they contribute to the monitoring and evaluation of retrieved information, in which case differences in activation may be seen in future experiments if correct responses which subjects are unsure about are contrasted with responses in which subjects indicate higher confidence (cf., Henson et al., 2000).

The thalamus and cerebellum have also both been linked with episodic memory, although their precise functional roles have yet to be described conclusively. Thalamic activation has been observed in a number of studies of recollection (Dobbins et al., 2002; Simons et al., 2005b), and damage to the region has been associated with marked amnesia in humans (Winocur et al., 1984) and non-humans (Aggleton and Brown, 1999). Similarly, activation in the cerebellum is often reported in neuroimaging studies of memory (Henson et al., 1999; Simons et al., 2001; Velanova et al., 2003), although its functional significance is rarely considered. One hypothesis has been that the cerebellum acts in a coordinating capacity (Andreasen et al., 1999), as part of a prefrontal–thalamic–cerebellar functional network (Andreasen et al., 1996). There is much evidence for extensive connections between the prefrontal cortex and cerebellum, mediated by subcortical regions such as the thalamus (Goldman-Rakic and Porrino, 1985; Middleton and Strick, 1994). Of relevance to the present data, recent anatomical findings suggest that prominent connections exist between anterior PFC and the mediodorsal nucleus of the thalamus (Johansen-Berg et al., 2005), the subregion in which activation was centered in the present perceived/imagined versus left/right contrast (Table 3).

To conclude, we have shown that the brain regions which have been found to be dysfunctional in neuroimaging studies involving both patients with schizophrenia and individuals at enhanced genetic risk of developing the disorder – medial anterior PFC, thalamus, and cerebellum – are among the very same regions recruited by healthy individuals when recollecting whether stimuli had been perceived or imagined during encoding. Reduced PFC activation was associated with misattributing imagined items as having been perceived, the same kind of error that has been reported in schizophrenia. Further studies are required to confirm any putative impairment on our particular recollection task in patients with schizophrenia. However, as described above, greater deficits have been reported in such patients at recollecting the source of self-generated words than of words that were perceived by the participant or presented by an experimenter (Bentall et al., 1991; Vinogradov et al., 1997; Keefe et al., 2002). An impairment in discriminating between internal and external sources of information could potentially account for the hallucinations and delusions that are often observed in the disorder (Frith and Done, 1989; Frith, 1992; Bentall et al., 1991; Johnson and Raye, 2000). As such, our findings suggest a possible link between function of the prefrontal–thalamic–cerebellar network in which activation was observed in the present experiment and some of the key symptoms of schizophrenia.

Acknowledgments

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