Episodic memory-related activation in schizophrenia: meta-analysis

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Background Numerous studies have examined the neural correlates of episodic memory deficits in schizophrenia, yielding both consistencies and discrepancies in the reported patterns of results.

Aims To identify in schizophrenia the brain regions in which activity is consistently abnormal across imaging studies of memory.

Method Data from 18 studies meeting the inclusion criteria were combined using a recently developed quantitative meta-analytic approach.

Results Regions of consistent differential activation between groups were observed in the left inferior prefrontal cortex, medial temporal cortex bilaterally, left cerebellum, and in other prefrontal and temporal lobe regions. Subsequent analyses explored memory encoding and retrieval separately and identified between-group differences in specific prefrontal and medial temporal lobe regions.

Conclusions Beneath the apparent heterogeneity of published findings on schizophrenia and memory, a consistent and robust pattern of group differences is observed as a function of memory processes.

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Although several studies have been performed to assess the neural correlates of memory encoding and retrieval in schizophrenia, there is still no consensus on the specific brain regions that seem most affected. A new quantitative meta-analytic method is available for combining the results from different functional brain imaging studies (Chein *et al*, 2002; Turkeltaub *et al*, 2002). This type of meta-analysis is theoretically and methodologically different from standard meta-analyses based on effect size (Fox *et al*, 1998). In contrast to the typical pooling of effect sizes from different studies, this new technique assesses whether the peaks of activation reported in different studies are significantly clustered (agglomerated) in certain brain regions. We used this technique to review published reports of functional brain imaging studies of episodic memory in schizophrenia; our aim was to identify the brain regions that are consistently affected during the performance of episodic memory tasks.

METHOD

Literature search and criteria for inclusion

A literature search was performed to retrieve studies that compared the brain activation elicited by an episodic memory task between a group of people with schizophrenia and a control group of healthy people. Our inclusion criteria were:

(a) participation of a group of people with an established diagnosis of schizophrenia (or schizophrenia-spectrum disorders) and a healthy control group;

(b) administration of a target episodic memory task (encoding or retrieval) and a reference (baseline) task concomitant to the acquisition of functional neuroimaging data;

(c) direct statistical comparison between the pattern of activation elicited by this memory task (relative to the reference task) in the schizophrenia group *v*. the control group;

(d) reporting of the focus of the peaks of differential activation between the two groups according to the Talairach/Montreal Neurological Institute (MNI) coordinate system (Talairach & Tournoux, 1988; Evans *et al*, 1993).

Data extraction and processing

Eighteen studies published between January 1996 and October 2004 met the criteria for inclusion in our meta-analysis (Table 1). Other studies meeting our inclusion criteria except for the absence of Talairach/MNI coordinates (Ragland *et al*, 1998; Shihabuddin *et al*, 1998; Hazlett *et al*, 1999, 2000; Nohara *et al*, 2000) were reviewed but were not included in the meta-analysis. Altogether, 228 foci reported in these studies corresponded to a between-group difference in brain activation during the performance of a memory task. Studies often used different methods of analysis and different thresholds and so we included all foci reported to be significant using the criteria designated in the individual studies. Following a technique similar to that used by other groups (Chein *et al*, 2002; Turkeltaub *et al*, 2002; Wager *et al*, 2003, 2004), we created a three-dimensional file with a value of 1 at each of these 228 foci and smoothed it to model each focus as a Gaussian sphere with a full width at half-maximum of 14 mm. After smoothing, the overlap of neighbouring Gaussian spheres led to greater values, termed activation likelihood estimate (ALE) values by Turkeltaub *et al* (2002), in certain brain regions where multiple foci agglomerated.

Statistical significance of these ALE values was then determined using 1000 simulated sets of 228 randomly distributed foci throughout the brain. Based on these simulations, two methods were used to determine a significance threshold. First, following the method described by Turkeltaub *et al* (2002), we used as a threshold the ALE value that was observed with a voxel probability of 0.001 (i.e. obtained by chance only once in every 1000 voxels in the simulations). Second, we also extracted the value corresponding to 0.05 simulations (i.e. obtained by chance in at least 1 voxel in only 5% of the simulations). This threshold was found to be more restrictive than the voxel threshold and the regions that met this

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Table 1 Studies included in the meta-analysis

Reference	Sample size		Probability threshold	Extent threshold	ROI	Imaging threshold	Target task	Reference task
	Sz *n*	Co *n*						
Encoding > low-level baseline							**Encoding**	**Baseline**
Eyler Zorrilla *et al* (2002)	9	10	0.025	7 voxels	Hippocampus, parahippocampal gyrus, inferior frontal gyrus and fusiform gyrus	fMRI	Novel picture encoding	Presentation of a repeated picture
Hofer *et al* (2003*a*)	10	10	0.001	No	No	fMRI	Like/dislike judgements for words	Rest
Hofer *et al* (2003*b*)	10	10	0.05 corrected	No	No	fMRI	Like/dislike judgements for words	Rest
Jessen *et al* (2003)	12	12	0.05	10 voxels	Hippocampus	fMRI	Internally associate another noun to the presented word	Presentation of XOXO and OXOX in alternation
Kubicki *et al* (2003)	9	9	0.001	0.05 corrected	No	fMRI	Deep encoding (abstract/concrete judgements for words)	Rest
Leube *et al* (2003)			0.05 corrected	0.05 corrected	No	fMRI	Encoding unfamiliar faces	Fixation cross
Ragland *et al* (2001)	23	23	0.005	50 voxels	No	PET	Encoding words presented twice	Motor baseline task
Ragland *et al* (2004)	14	15	0.005	8 voxels	Regions activated in either group	fMRI	Encoding words presented twice	Average prestimulus baseline response
Retrieval > non-episodic retrieval							**Retrieval**	**Non-episodic retrieval**
Andreasen *et al* (1996)	14	13	0.005	No	No	PET	Recall of story learned once	Rest
Andreasen *et al* (1996)	14	13	0.005	No	No	PET	Recall of well-learned story	Rest
Crespo-Facorro *et al* (1999)	14	13	0.005	50 voxels	No	PET	Recall of words learned to 100% recall	Rest
Crespo-Facorro *et al* (1999)	14	13	0.005	50 voxels	No	PET	Recall of words learned once	Rest
Ganguli *et al* (1997)	8	8	0.05?	In 2 slices	Regions activated in either group	PET	Recall of words	Fixation cross
Heckers *et al* (1998)	13	8	0.001	No	No	fMRI	Stem-recall for words encoded once	Stem completion (from semantic memory)
Hofer *et al* (2003*a*)	10	10	0.001	No	No	fMRI	Forced-choice word recognition	Rest
Hofer *et al* (2003*b*)	10	10	0.05 corrected	No	No	fMRI	Forced-choice word recognition	Rest
Jessen *et al* (2003)	12	12	0.05	10 voxels	Hippocampus	fMRI	Recognition of unstudied words	Null event (interstimulus interval)
Jessen *et al* (2003)	12	12	0.05	10 voxels	Hippocampus	fMRI	Recognition of studied words	Null event (interstimulus interval)
Ragland *et al* (2001)	23	23	0.005	50 voxels	No	PET	Recognition of studied and unstudied words	Motor baseline task
Ragland *et al* (2004)	14	15	0.005	8 voxels	Regions activated in either group	fMRI	Recognition of studied and unstudied words	Average prestimulus baseline response

(*Continued*)

Table 1 (*Continued*)

Reference	Sample size		Probability threshold	Extent threshold	ROI	Imaging threshold	Target task	Reference task
	Sz *n*	Co *n*						
Weiss *et al* (2003)	12	12	0.001 in hippocampus and prefrontal cortex, 0.05 corrected in other brain areas	No	Different thresholds	PET	Stem-recall for words encoded four times	Stem-completion (from semantic memory)
Weiss *et al* (2003)	12	12	0.001 in hippocampus and prefrontal cortex, 0.05 corrected in other brain areas	No	Different thresholds	PET	Stem-recall for words encoded semantically	Stem-completion (from semantic memory)
Wiser *et al* (1998)	15	29	0.005	No	No	PET	Recognition of words studied to 100% performance and of unstudied words	Reading words
Retrieval: high > low							**High retrieval**	**Low retrieval**
Crespo-Facorro *et al* (2001)	19	34	0.005	50 voxels	No	PET	Recognition of well-learned words[1]	Recognition of words learned once[1]
Heckers *et al* (1998)	13	8	0.001	No	No	PET	Stem-recall for words encoded four times	Stem-recall for words encoded once
Heckers *et al* (2000)	9	8	0.001	No	No	PET	Recognition of studied images	Recognition of unstudied images
Ragland *et al* (2004)	13	15	0.005	8 voxels	Regions activated in either group	fMRI	Word recognition hits	Word recognition correct rejections
Weiss *et al* (2003)	12	12	0.001 in hippocampus and prefrontal cortex, 0.05 corrected in other brain areas	No	Different thresholds	PET	Stem-recall for words encoded semantically	Stem-recall for words encoded perceptually
Weiss *et al* (2004)	15	16	0.01	5 voxels	Hippocampus	fMRI	Recognition of mainly studied words[1]	Recognition of mainly unstudied words[1]
Other studies								
Kubicki *et al* (2003)	9	9	0.001	0.05 corrected	No	fMRI	Deep encoding (abstract/concrete judgements for words)	Shallow encoding (lower/upper-case judgements)
Barch *et al* (2002)	38	48	0.0025	9 voxels	No	fMRI	Conjunction of encoding > fixation and recognition > fixation for both verbal and figural stimuli	

Co, controls; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; ROI, region of interest; Sz, schizophrenia.

1. These contrasts were reversed so that they could be included in one of our contrast categories.

Table 2 Thresholds associated with each category of contrasts to which the meta-analysis procedure was applied

Category	Studies *n*	Foci *n*	Voxel threshold[1]	Simulation threshold[1]
Overall	18	229	0.005140	0.006206
Encoding > baseline				
Controls > schizophrenia	8	29	0.002380	0.003116
Schizophrenia > controls	2	9	0.002030	0.002417
Retrieval > baseline				
Controls > schizophrenia	10	115	0.003920	0.004844
Schizophrenia > controls	5	20	0.002280	0.002509
Retrieval: high > low				
Controls > schizophrenia	5	17	0.002160	0.002463
Schizophrenia > controls	6	30	0.002410	0.002981

1. The activation likelihood estimate value thresholds reported in this table correspond to a voxel threshold of 0.001 and a simulation threshold of 0.05.

threshold are highlighted in bold characters in Tables 3 and 4.

After applying this procedure for all 228 foci regardless of the tasks, we grouped the individual contrasts into independent categories:

(a) memory encoding *v*. low-level baseline (8 studies);

(b) memory retrieval *v*. non-episodic retrieval comparison tasks (11 studies);

(c) high *v*. low retrieval conditions (6 studies).

Only two studies used contrasts that did not fit into any of these categories (see Table 1).

For the studies using high *v*. low levels of retrieval conditions, some between-group contrasts were performed using the within-group contrast in one direction (high retrieval > low retrieval), whereas others were in the other direction (low retrieval > high retrieval). To combine the different studies while taking the direction of the group difference into account, within-group contrasts that were in the low > high retrieval direction (Crespo-Facorro *et al*, 2001; Weiss *et al*, 2004) were reversed by also reversing the group comparison. (Between-group functional neuroimaging analyses are in fact group by task interactions, i.e. a contrast of contrasts. Within-subject contrasts have to be performed first and the output of these contrasts are then used for the between-group comparisons: it is a difference of differences. For two groups (A and B) and two tasks (1 and 2), we can say that mathematically (A1 − A2) − (B1 − B2)=(B2 − B1)

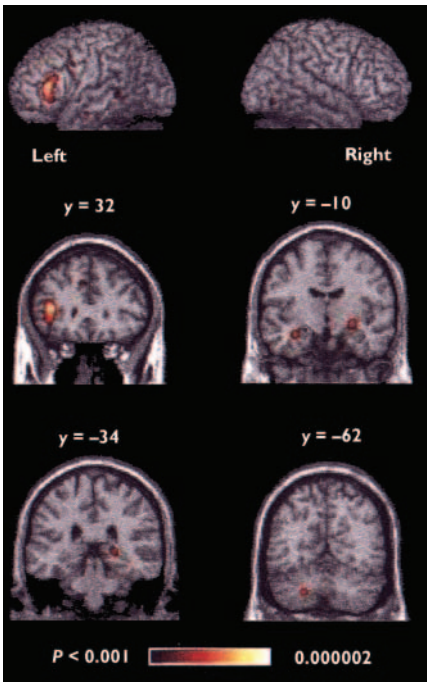

Fig. 1 Regions of significant agglomeration of foci in the overall meta-analysis. The *y* values given for the coronal slices denote the coordinates in the Talairach/MNI system; the colour range represents the above threshold voxel probability.

Table 3 Overall regions of significant agglomeration of foci of differential activation between participants with schizophrenia and controls during the performance of memory tasks. The foci reported in bold also met the simulation threshold

x[1]	*y*[1]	*z*[1]	Region	BA	ALE value[2]	Associated voxel probability
−4	54	4	Left medial frontal	10	0.005534	0.000510
−40	**32**	**8**	**Left inferior frontal**	**45**	**0.008400**	**0.000002**
−6	30	36	Anterior cingulate	32	0.005962	0.000237
−38	4	34	Left precentral/middle frontal gyrus	9	0.005600	0.000452
−32	**−12**	**−20**	**Left anterior hippocampus**		**0.007379**	**0.000016**
−50	−42	0	Left middle/superior temporal gyrus	22	0.005830	0.000300
−38	−44	−22	Left fusiform gyrus	37	0.005237	0.000844
−22	**−62**	**−42**	**Left cerebellum**		**0.006390**	**0.000108**
16	44	20	Right medial frontal	9	0.005336	0.000711
28	**−10**	**−8**	**Right anterior medial temporal lobe**		**0.006885**	**0.000042**
22	**−32**	**2**	**Right posterior hippocampus**		**0.006390**	**0.000108**
24	−72	−10	Right fusiform gyrus	19	0.005699	0.000378

ALE, activation likelihood estimate; BA, Brodmann area.
1. Reported according to the Talairach/Montreal Neurological Institute system.
2. The ALE value is a measure of agglomeration.

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Table 4 Regions of significant agglomeration of foci of differential activation between participants with schizophrenia and controls for three categories of contrasts. The foci reported in bold also met the simulation threshold

x	*y*	*z*	Region	BA	ALE value	Associated voxel probability
Encoding > baseline						
Controls > schizophrenia						
−42	30	6	Left inferior frontal gyrus	45	0.00285	0.000319
24	**54**	**2**	**Right anterior middle frontal gyrus**	**10**	**0.003886**	**0.000025**
20	**44**	**20**	**Right medial frontal gyrus**	**9**	**0.003139**	**0.000172**
20	**−34**	**2**	**Right posterior hippocampus**		**0.003231**	**0.000141**
Schizophrenia > controls			No significant clusters of activation			
Retrieval > baseline						
Controls > schizophrenia						
−4	**54**	**4**	**Left medial frontal gyrus**	**10**	**0.005294**	**0.000059**
−38	36	36	Left middle frontal gyrus	9	0.004315	0.000437
−42	**26**	**16**	**Left inferior frontal gyrus**	**45**	**0.006221**	**0.000008**
−40	2	26	Left precentral gyrus	6	0.004024	0.000804
−4	−12	14	Left thalamus		0.004315	0.000437
−30	**−14**	**−20**	**Left hippocampus**		**0.005559**	**0.000034**
−22	**−62**	**−42**	**Left cerebellum**		**0.00675**	**0.000003**
−2	−80	−14	Cerebellum/lingual gyrus	18	0.004632	0.000229
4	26	−8	Subgenual	32	0.004791	0.000166
8	−24	10	Right thalamus		0.004738	0.000183
26	**−74**	**−8**	**Right fusiform gyrus**	**18**	**0.0054**	0.000047
Schizophrenia > controls						
28	**−8**	**−10**	**Right anterior medial temporal lobe**		**0.004105**	**0.000004**
Retrieval: high > low						
Controls > schizophrenia						
24	**−28**	**0**	**Right posterior hippocampus**		**0.003679**	**0.000014**
Schizophrenia > controls						
−8	**30**	**36**	**Anterior cingulate**	**32**	**0.004212**	**0.000011**
38	−16	−34	Right parahippocampal gyrus	20	0.002659	0.000508
44	−54	52	Right superior parietal lobule	40	0.002510	0.000718

ALE, activation likelihood estimate; BA, Brodmann area.

−(A2−A1) and (A2−A1)−(B2−B1)=(B1−B2)−(A1−A2). It is thus possible to reverse a within-subject contrast by also reversing the group contrast.) Three-dimensional maps of smoothed foci were then created and thresholded for each of the three categories and each between-group contrast direction (Table 2) with the same valid method that could also be used for combining within-group contrasts.

RESULTS

Overall meta-analysis

When all foci were included in the meta-analysis, the areas of significant agglomeration were located in the left inferior prefrontal cortex, bilateral medial frontal cortex, anterior cingulate, left precentral/middle frontal gyrus, bilateral anterior medial temporal lobe, right posterior hippocampus, left superior temporal gyrus, bilateral fusiform gyrus and left cerebellum (Table 3, Fig. 1).

Specific contrasts

The clustering into three categories allowed us to identify the regions that were either more or less active in the schizophrenia group relative to the control group.

For the encoding *v.* low-level baseline category (Table 4, Fig. 2a), the control group exhibited greater activation across studies in the left inferior prefrontal cortex, right anterior middle frontal gyrus, right medial frontal gyrus and right posterior hippocampus relative to people with schizophrenia. No region showed significant agglomeration for the schizophrenia group relative to controls.

For the retrieval *v.* non-episodic retrieval comparison tasks category (Table 4, Fig. 2b), control participants had clusters of greater activation in the left inferior prefrontal cortex, left middle frontal gyrus, left medial frontal gyrus, right subgenual region, left precentral gyrus, bilateral thalamus, left anterior hippocampus, right fusiform gyrus and bilateral cerebellum. The only region to show significant agglomeration for people with schizophrenia relative to controls was the right anterior medial temporal lobe

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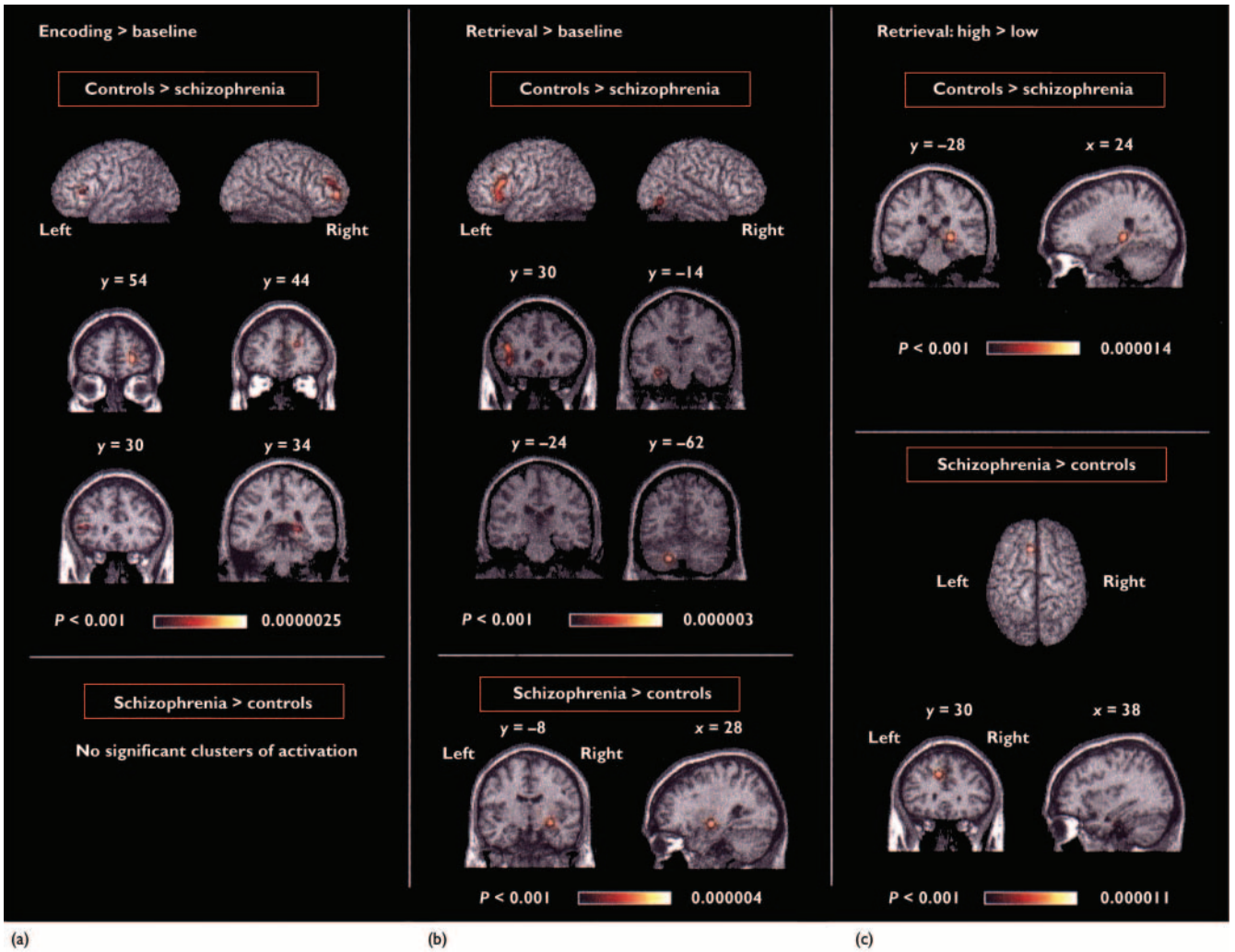

Fig. 2 Regions of significant agglomeration of foci in category of contrasts: (a) encoding *v.* low-level baseline; (b) retrieval *v.* non-episodic retrieval baseline; (c) high *v.* low retrieval. The *y* and *x* values denote the coordinates in the Talairach/MNI system for the coronal slices and sagittal slices, respectively; the colour ranges represent the above-threshold voxel probability.

(border between hippocampus and amygdala).

For the high retrieval *v.* low retrieval category (Table 4, Fig. 2c), a cluster of greater activation for the control participants was observed in the right posterior hippocampus. For participants with schizophrenia, clusters were observed in the cingulate gyrus, right parahippocampal gyrus and right superior parietal cortex.

DISCUSSION

Using a new meta-analytic approach, we performed a quantitative review of functional neuroimaging studies of episodic memory in schizophrenia. This meta-analysis revealed a set of brain regions showing consistent patterns of differential activation between people with schizophrenia and healthy individuals during the performance of diverse memory tasks. Consistent with previous models of brain dysfunctions in schizophrenia and qualitative reviews on this same topic (Weiss & Heckers, 2001), the regions that showed the most consistent differences between people with schizophrenia and healthy participants were located in the prefrontal cortex and in the temporal lobe. Hypotheses relating to the potential causes of this differential frontal and temporal activity in schizophrenia are discussed below. Foci of consistent differential activation between groups were also observed in the thalamus and cerebellum and provide support for abnormalities in the cortical–thalamic–cerebellar–cortical circuit in schizophrenia.

Left inferior prefrontal cortex

The left inferior prefrontal cortex was the main region that distinguished between control and schizophrenia groups in this meta-analysis. This region showed the most significant agglomeration of foci in the overall meta-analysis, and was found to be consistently more active in controls relative to people with schizophrenia during both encoding and retrieval relative to baseline conditions. The region is involved in elaborative semantic or phonological processing and in the implementation of strategies (e.g. organisation) during episodic memory encoding (Dempster & Brainerd, 1995; Simons & Spiers, 2003); it is also active during strategic search, the maintenance of successfully retrieved information and response selection during

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retrieval (Badre & Wagner, 2002; Petrides, 2002; Petrides *et al*, 2002; Simons & Spiers, 2003). Interestingly, it has been postulated that during encoding, people with schizophrenia fail to engage spontaneously in efficient elaborative processing. Ragland *et al* (2001) have suggested that people with schizophrenia process stimuli on a more superficial level and do not spontaneously use semantic processing to guide memory encoding and retrieval. None the less, it seems that people with schizophrenia can use specific cues or strategies to improve their performance when they are provided with them (Kubicki *et al*, 2003; Ragland *et al*, 2003). For example, Ragland *et al* (2003) used a level of processing paradigm (Craik & Lockhart, 1972) to study verbal recognition memory in schizophrenia. During encoding, participants were instructed to make either 'upper case' *v*. 'lower case' judgements (shallow encoding) or 'concrete' *v*. 'abstract' judgements (deep encoding). On a subsequent recognition memory test there was no significant difference in performance between control participants and those with schizophrenia, and both groups benefited from deeper encoding. Similarly, Paul *et al* (2005) observed a modulation of recognition memory performance by the level of processing in schizophrenia, although in their study patients performed more poorly on the recognition tasks relative to the control group. It follows that it is not primarily the capacity to use elaborative processing to improve memory performance that is affected in schizophrenia, but rather the tendency to use a deep elaborative encoding strategy when no specific instructions are provided.

In healthy participants a relationship between left inferior prefrontal cortex activity and the use of deeper processing during encoding has been extensively reported (e.g. Kapur *et al*, 1994; Kubicki *et al*, 2003; Petersson *et al*, 2003). This same relationship was examined in people with schizophrenia by Kubicki *et al* (2003), who contrasted the neural correlates of elaborative semantic processing with those related to perceptual processing. Relative to controls, people with schizophrenia showed reduced activation of the left inferior prefrontal cortex for the contrast between semantic and perceptual encoding, despite their normal performance and despite the normal modulation of memory performance by level of processing (Craik & Lockhart, 1972). This difference in activation may stem from a between-group difference in stimulus processing, reflecting either relatively reduced processing during semantic encoding or relatively increased processing during perceptual encoding, even if this difference does not affect subsequent recognition performance.

It has been suggested that some of the cognitive impairments in schizophrenia might be secondary to patients' impaired ability to use organisational strategies to maximise performance (Bauman, 1971; Koh *et al*, 1976; Iddon *et al*, 1998; Hazlett *et al*, 2000). For instance, people with schizophrenia do not spontaneously use semantic clustering as a strategy to improve their memory performance (Gold *et al*, 1992; Paulsen *et al*, 1995; Brebion *et al*, 1997, 2004; Hazlett *et al*, 2000; Nohara *et al*, 2000). Organisational strategies are thought to rely at least in part on the left inferior prefrontal cortex during both encoding and retrieval (Fletcher *et al*, 1998; Wagner *et al*, 1999; Simons & Spiers, 2003). With regards to retrieval, Nohara *et al* (2000) have observed a significant correlation between categorical clustering and the activation in this cortical region in control participants that was not observed in people with schizophrenia. Taken together, these results suggest that the differential activation of this region in people with schizophrenia could be related to their inability to use efficient strategies spontaneously during both encoding and retrieval.

Another possibility is that the decreased activation of the left inferior prefrontal cortex is related to memory performance because this region has also been thought to be involved in retrieval success (Habib & Lepage, 2000; Konishi *et al*, 2000). The region was, however, observed to be deactivated in schizophrenia even when there was no significant difference in performance between groups (Andreasen *et al*, 1996; Wiser *et al*, 1998; Ragland *et al*, 2001; Hofer *et al*, 2003*a*; Kubicki *et al*, 2003). Even if it has been shown that people with schizophrenia are less likely to base their recognition judgements on conscious recollection relative to control participants (Huron *et al*, 1995; Danion *et al*, 1999), it is unlikely that the deactivation of this cortical region observed in this group relates to the reduced proportion of successfully or consciously recollected items, because there was no significant clustering of differential activation between groups in that region for the contrast between high and low retrieval conditions.

Medial temporal lobes

Functional neuroimaging studies in healthy individuals have consistently implicated the medial temporal lobes in both memory encoding and memory retrieval (Lepage *et al*, 1998; Schacter & Wagner, 1999). During encoding, the hippocampal formation is thought to support the encoding of information in a meaningful way, such as creating new associations (Vandenberghe *et al*, 1996; Henke *et al*, 1997, 1999; Lepage *et al*, 2000; Davachi *et al*, 2001; Davachi & Wagner, 2002; Achim & Lepage, 2005*b*). Medial temporal activation during encoding has also been shown to predict subsequent recognition success (Brewer *et al*, 1998; Wagner *et al*, 1998; Davachi *et al*, 2003; Chua *et al*, 2004; Jackson & Schacter, 2004), supporting the implication of this structure in the creation of durable memory traces. Our meta-analysis revealed a significant agglomeration of foci of reduced activation in people with schizophrenia in the right hippocampus during encoding, possibly reflecting the less efficient or less associative encoding strategies used by people with schizophrenia.

Different lines of evidence suggest that during memory retrieval the hippocampus supports conscious recollection of information from memory, whereas the parahippocampal gyrus is involved in familiarity assessment (Yonelinas, 2002). It has also been suggested that people with schizophrenia could have a specific deficit in conscious recollection (Huron *et al*, 1995; Danion *et al*, 1999; Weiss *et al*, 2003). The results from our meta-analysis support this idea by showing that people with schizophrenia present a deactivation of the region implicated in conscious recollection (i.e. the hippocampus) when exposed to conditions favouring the recovery of information from memory (high *v*. low retrieval). Moreover, this hippocampal deactivation is accompanied by an overactivation of the region implicated in familiarity assessment (i.e. the parahippocampal gyrus), suggesting that people with schizophrenia use familiarity assessment rather than conscious recollection as a basis for retrieval.

Another interesting observation is a focus of agglomeration of greater activation in schizophrenia relative to controls during memory retrieval *v*. baseline, centred in the

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right anterior medial temporal lobe. In contrast, control participants show greater left lateralised activation in this region for the same comparison. This pattern of activation is consistent with the idea that people with schizophrenia show less lateralised medial temporal activation as a function of stimulus type (verbal and non-verbal) (Crow *et al*, 1989; Gur *et al*, 1994), because all studies included in the retrieval *v*. baseline category used verbal stimuli.

Other frontal regions

A few other prefrontal regions showed significant agglomeration of foci in our meta-analysis. For instance, the left middle frontal gyrus showed significant agglomeration of foci in the controls relative to people with schizophrenia for the retrieval *v*. baseline contrast. This region is known to support post-retrieval monitoring during episodic memory retrieval, with activation typically in the right middle frontal gyrus for more simple monitoring and additional involvement of the left middle frontal gyrus for more complex tasks (Achim & Lepage, 2005*a*). The observation that the left middle frontal gyrus shows a greater activation in controls suggests a specific impairment of more complex post-retrieval monitoring processes in schizophrenia, a view consistent with the finding that more complex tasks reveal greater memory impairment (Danion *et al*, 1999).

The anterior medial prefrontal cortex also showed significant agglomeration in the general meta-analysis as well as in encoding *v*. baseline and retrieval *v*. baseline. This region is thought to be involved in the retrieval of self-relevant or self-generated information (Simons & Spiers, 2003; Fossati *et al*, 2004), although the specific mechanisms remain to be understood. Failure to activate these regions in people with schizophrenia could reflect their difficulty in using sources of information other than the ones provided by the task.

The anterior cingulate also showed significant agglomeration in both the overall meta-analysis and the high *v*. low retrieval category. Paus *et al* (1998) have suggested that the anterior cingulate has a role in memory and cognitive effort. It could be the case that this activity reflects the greater effort needed by people with schizophrenia to perform these memory tasks.

Other regions: cerebellum, thalamus

The cerebellum projects to motor and prefrontal regions of the cerebral cortex through synapses in the thalamus. Through this circuit, the cerebellum is thought to modulate and coordinate both motor and cognitive functions (Andreasen *et al*, 1996, 1998, 1999). Converging evidence has pointed to dysfunctions of this cortical–cerebellar–thalamic–cortical circuit in schizophrenia, and our findings of significant agglomerations of foci observed in the cerebellum and thalamus are consistent with this notion. The specific neural mechanisms underlying the coordination of cognitive activity by the cerebellum, however, remain to be clarified. It has been proposed that the cerebellum could modulate memory processing through a mechanism for correction of discrepancies (Schmahmann, 1991; Fink *et al*, 1996; Greve *et al*, 1999) or through a mechanism for coordination between different pieces of information (Fabbro, 2000).

Studies without Talairach/MNI coordinates

Five functional neuroimaging studies of memory in schizophrenia could not be included in the meta-analysis because no Talairach/MNI coordinates were reported (Ragland *et al*, 1998; Shihabuddin *et al*, 1998; Hazlett *et al*, 1999, 2000; Nohara *et al*, 2000). Two of these studies used restricted regions of interest either in the thalamus (Hazlett *et al*, 1999) or in the striatum (Shihabuddin *et al*, 1998) and observed decreased activation in these regions in schizophrenia relative to controls. The other three studies examined the entire brain and, consistent with our results, reported reduced activation in participants with schizophrenia in the left inferior frontal gyrus and other frontal regions (Ragland *et al*, 1998; Hazlett *et al*, 2000; Nohara *et al*, 2000) as well as in the temporal lobe (Ragland *et al*, 1998; Hazlett *et al*, 2000) during episodic memory tasks. Overall these results are consistent with those that reported Talairach/MNI coordinates for peaks of activation, making it unlikely that the exclusion of these five studies from our meta-analysis biased our results.

Future research

In summary, the quantitative aspect of this meta-analytic method represents an improvement over current qualitative methods because it offers an objective way of regrouping studies and summarising results. However, it must be noted that most of the studies reviewed here compared a memory task (encoding or retrieval) with a low-level baseline. Such contrasts are not ideal for discriminating the neural correlates of specific memory processes and instead are likely to reflect several cognitive and perceptual processes (Stark & Squire, 2001). More sophisticated experimental designs would increase our chances of identifying selective deficient processes in schizophrenia and ultimately the neural correlates of these abnormal processes.

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CLINICAL IMPLICATIONS

- People with schizophrenia have abnormal patterns of brain activation during both memory encoding and retrieval.
- Several brain regions, including the prefrontal cortex and hippocampus, are implicated in these abnormal memory functions.
- One challenge to the cognitive remediation of memory problems in schizophrenia will be to take into consideration these multiple faulty memory processes and possibly executive dysfunctions when devising an intervention.

LIMITATIONS

- It was not possible to integrate the results from studies that did not report specific coordinates for their activation foci.
- The results obtained using this meta-analytic approach might have been biased by the inclusion of studies that used regions of interest (e.g. the hippocampus).
- The number of studies in each category was insufficient to assess the effect of important variables such as medication status or age on the pattern of agglomeration of activation foci.

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