Patterns of anterior cingulate activation in schizophrenia: a selective review

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Background: Anterior cingulate cortex (ACC) dysfunction is implicated in schizophrenia by numerous strands of scientific investigation. Functional neuroimaging studies of the ACC in schizophrenia have shown task-related hypo-activation, hyper-activation, and normal activation relative to comparison subjects. Interpreting these results and explaining their inconsistencies has been hindered by our ignorance of the healthy ACC's function. This review aims to clarify the site and magnitude of ACC activations in schizophrenia, and sources of their variation.
Method: 48 studies of mnemonic and executive task-related activations in schizophrenia using both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) were analyzed.
Results: Abnormal activations in schizophrenia were not restricted to the "cognitive" part of the ACC. Hypoactivations were most common, and were found in all types of tasks. Hyperactivations when found, were largely in n-back tasks.
Conclusions: Hypoactivations cannot be explained by poor performance, more demanding control conditions or chronicity of illness alone. Patients on anti-psychotic medication tended to show both greater ACC activation and better performance, although whether this is directly due to their medication or the resultant reduction in symptoms is unclear. The relationship between ACC rCBF and task performance is not straightforward. Future research should better control confounding factors and incorporate different levels of difficulty.
Keywords: functional magnetic resonance imaging, positron emission tomography, schizophrenia, anterior cingulate cortex

Introduction

Pathology in the anterior cingulate cortex (ACC) is widely believed to have a significant part to play in the disease process of schizophrenia. There is much anatomical and physiological evidence for this. Densities of neurons, interneurons, axons and synapses have all been found to be abnormal in the ACC's of people with schizophrenia (Arnold and Trojanowski 1996), as has both the micro- and macro- circuitry involving both ordinary neurons and neuromodulators (Benes 2000). Abnormal activations are often found in the ACC in neuroimaging studies in schizophrenia (see below for references), which may then normalise upon administration of antipsychotic medication (Braus et al 2002; Ngan et al 2002).

Currently, however, the functional implications of these pathological findings are unknown. This is largely because realtively little is known of the function of the healthy ACC. There are several competing theories about ACC function which we shall briefly outline here; they are more extensively reviewed elsewhere (Bush et al 2000; Paus 2001; Frackowiak et al 2004; Vogt 2005). Structurally, the ACC is a large area of cortex, subdivided into affective (BA 25 and 33, and rostral 32 and 24) and cognitive (including caudal BA 32 and 24) divisions (Devinsky et al 1995). The ACC has extensive interconnections with other brain areas; the rostral, affective part

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(rCZa) with limbic areas, the caudal, cognitive part (rCZp) with prefrontal and motor areas.

Theories of ACC function tend to concentrate on its possible cognitive roles, of which there are many. Its proposed cognitive functions are more 'attentive' than "executive"; these include monitoring for errors, monitoring for conflicting responses, and attention to actions, in particular "willed", non-automated actions (Paus 2001). It also seems to provide an important, high-level bridge between stimuli and responses; Petit et al (1998) suggest that ACC activity during working memory delays reflects neither memory nor response preparation per se, but rather "a state of preparedness for selecting a motor response based on the information held on-line". Whether the ACC performs similar functions in regard to its affective inputs is unknown, although it seems that its emotional and cognitive domains are mutually inhibitory (Bush et al 2000). What is certain is that ACC is activated by arousal and stress, presumably via its projections from the midbrain: it receives the highest concentration of dopaminergic innervation in primate cerebral cortex (Paus 2001). The difficulty of assigning the ACC a particular function is illustrated by Paus et al's (1998) review of 107 PET studies. They found that the single most important factor contributing to ACC activation was the level of task difficulty, especially in BA 24/32. It is obvious that this variable subsumes a wide variety of monitoring, attentive, mnemonic, response, and arousal-related processes.

Both hypo-activation and hyper-activation of the ACC are found in neuroimaging studies of schizophrenia. It could be that an abnormal ACC in schizophrenia is hyperactive at rest, but is unable to activate further in response to increasing task demands, thereby becoming relatively hypoactive. Such a relationship has been found in the medial temporal lobe in schizophrenia (Honey et al 2003). Manoach (2003) has described this relationship in the dorsolateral prefrontal cortex (DLPFC) in schizophrenia, and relates task-related DLPFC hypoactivity to decreased task performance. Other imaging studies in schizophrenia, however, have found that the ACC is hypoactive, not hyperactive, at rest (Siegel et al 1993; Haznedar et al 1997). Investigators have also looked at the effect of antidopaminergic medications on the ACC's activation patterns. Reductions in cortical dopaminergic neurotransmission cause a reduction in resting ACC hyperactivity (Ngan et al 2002), and a normalization of task-related ACC hypoactivity (Fletcher et al 1996). Such effects are significant as they may eventually demonstrate a link between dopamine dysfunction, abnormal ACC activation, impaired task performance and their correction by neuroleptic medications in schizophrenia.

The ACC does not always show a task-related hypoactivation; indeed, it can be hyperactive (see Results). This inconsistency may be due to a large number of variables. These include: different cognitive demands made by different tasks, how well subjects perform the task, the nature of the control task, whether subjects are on typical, atypical or no medication, and whether subjects are acutely psychotic or chronically ill. It has also been suggested that the scanning time (longer in PET than fMRI) may make a difference, if people with schizophrenia become hyperactive at the start of the task and then slump into hypoactivity (Callicott et al 2000). It is also worth remembering that just because an area shows neither hyper- nor hypoactivation, it does not imply that that area is doing its normal job perfectly satisfactorily.

Functional neuroimaging experiments in schizophrenia tend to fall into two broad categories. These are:

1. Imaging patients performing cognitive psychological tests, finding areas of abnormal activation, and trying to relate these to anatomical or behavioral abnormalities.
2. Imaging patients with specific symptoms, to try to find the physiological basis for those symptoms (especially auditory verbal hallucinations).

This review will concentrate on a subset of the first category of experiments, so that valid comparisons between experiments can be made. It will ignore work in the fields of: eye movements, facial, and emotional processing, oddball target detection, logic/decision-making, theory of mind, and symptom-based experiments because we wish to concentrate on tasks with a mainly cognitive basis that have been published in significant numbers.

The review has two broad aims; one anatomical, the other functional. First, it examines the sites of functional abnormality in a range of imaging experiments to see whether they localise to one or more particular areas of ACC. Second, it attempts to clarify the reasons why ACC activation may vary from one experiment to the next. One final point regarding "activations" must be clarified. fMRI can only compare relative changes in activations, eg, patients (task activation—control activation)—comparison subjects (task activation—control activation). It cannot compare absolute activations, eg, patients (task activation)—comparison subjects (task activation). PET can compare both relative and absolute activations.

When the terms "hyperactivation" or "hypoactivation" are used in this paper, these refer to relative changes in

activation, not absolute activations. Indeed, when a schizophrenia cohort is said to show task-related hypoactivity, their average brain activation during the task may well be *higher* than that of comparison subjects.

The review sets out to examine the following aspects of ACC activations:

Location

Areas of abnormal activation during cognitive tasks may congregate in the "cognitive" domain of the ACC (rCZp), the affective domain of the ACC (rCZa), or may be distributed throughout.

Direction

The ACC may be hypoactive, hyperactive or of normal activation during task performance in schizophrenia.

Relationship to performance/other variables

Abnormal activity in schizophrenia may be associated with impaired task performance, chronicity of illness, type of task, current symptoms, or scanning method.

Effect of anti-psychotic medication on ACC activity and task performance

Administration of anti-psychotic medication may normalise (ie increase or decrease), hyperactivate, or hypoactivate the ACC during task performance. Medication may also alter task performance itself.

Method

Papers were selected from the PubMed database (www.ncbi.nlm.nih.gov/entrez/query.fcgi) from January 1990 to July 2005 using the following search terms:

- Schizophrenia AND fMRI
- Schizophrenia AND functional magnetic
- Schizophrenia AND PET
- Schizophrenia AND positron emission

Of these papers, those using fluorinated deoxyglucose (FDG) were eliminated as we wished to concentrate on studies which employed measures of activation inferred from regional blood flow. Studies of mnemonic tasks (2-back or encoding/recognition/retrieval tasks), and studies of executive functions (the Stroop, verbal fluency, Stop or Go-No-Go, and Continuous Performance tasks), 49 altogether, were selected from the remaining (69) papers. Unfortunately, formal meta-analysis was precluded because of insufficient and inconsistent reporting of useable summary data, and the diverse methodologies employed. The results are therefore represented in a simple, vote-counting style.

Results

Results of these 49 studies are tabulated below (Tables 1–4). The sites of normal and abnormal activations of ACC in the memory and executive experiments are shown in Figures 2 and 3, respectively. Regarding ACC activations, one can make the following comments:

Location

All of the points of maximal activation in comparison subjects in both mnemonic and executive tasks lie in rCZp

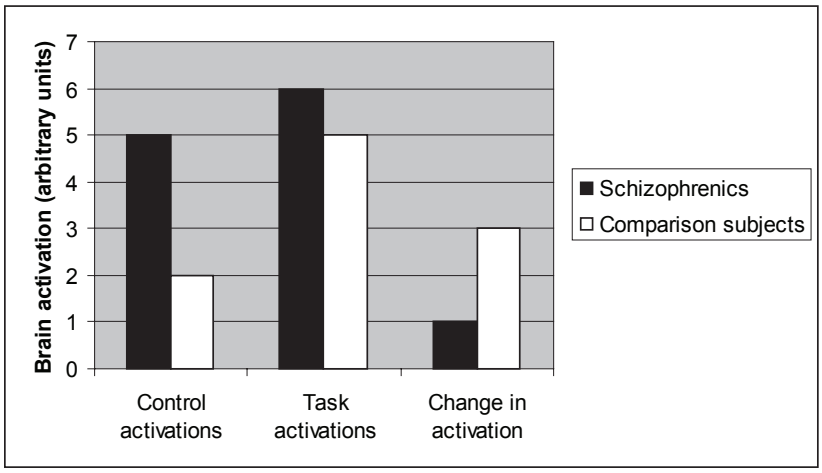

Figure 1 This graph illustrates how schizophrenic subjects might show a relative task-related hypoactivation, while being hyperactive in absolute terms.

(Figures 2 and 3). The areas of over- and underactivity in schizophrenia are less congregated. The Go/NoGo and verbal fluency hypoactivation points cluster in rCZa and rCZp respectively, but the points of differential activation in the other tasks are distributed throughout the ACC.

Direction

The ACC was found to be hypoactive in schizophrenia much more often than it was hyperactive (16/49 and 6/49 experiments, respectively).

Relationship to performance/other variables

Possible factors affecting ACC activation include: task performance, the cognitive requirements of both the experimental and control tasks, length of illness, scanning times (PET taking longer than fMRI), and patients' medication status.

In 9/14 of the hypoactivations, the schizophrenic subjects' performance was equal to that of the controls. There were hypoactivations in all of the tasks, and hyperactivations in three (four in the n-back, and one each in the recognition and Stroop tasks). 4/17 studies of patients with illness of <6 years showed a hypoactive ACC, compared with 8/26 studies of patients with illness of >6 years. 13/17 short-illness patient groups performed worse than comparison subjects, compared with 15/26 long-illness patient groups, an indication that the younger patients were more psychotic and hence more impaired. 6/42 fMRI studies showed hyperactivations, versus 0/14 PET studies.

Medication effects

All of the ACC hyperactivations reviewed here occurred in patients taking anti-psychotic medication. Medicated patients also exhibited proportionally less hypoactivations (10/44) than unmedicated ones (5/11), and less poor performances (26/46 vs 9/11). Being on an atypical rather than a typical antipsychotic seemed to marginally improve performance (11/25 did worse on an atypical, 6/9 on a typical), but made no difference to the number of hypoactivations (if anything, increasing them from 1/9 to 6/25).

Discussion

Before speculating upon why the schizophrenia patients' ACC might be both over- and underactive, one must ask two questions about ACC activation in normal subjects. The first is anatomical: how do the areas of abnormal ACC activation in schizophrenia compare with those areas activated in normal subjects performing the same tasks? The second is functional: what is the putative role of the normal ACC in mnemonic and executive tasks? The first question is important because abnormal neural circuitry in schizophrenia may alter the brain's functional neuroanatomy: both how and where information is processed may change. Tasks may even be carried out in different ways. In an insightful review of prefrontal dysfunction in working memory tasks in schizophrenia, Manoach (2003) points out that the common finding of schizophrenic hypofrontality may merely reflect more variable and more disparate cortical activations, and not decreased cortical activation.

The points of maximal activation in comparison subjects during all of the cognitive tasks reviewed here lie in rCZp (Figures 2 and 3). Contrary to expectations, areas of abnormal activation within schizophrenics' ACC's were not confined to rCZp. This does not support Manoach's (2003) theory that activations in schizophrenia are more widespread, however, as there are far more *hypo*activations (10) than *hyper*activations (2) in rCZa. Rather, this review agrees with the meta-analysis of Hill et al (2004), which proposes that frontal activations in schizophrenia are generally lower, but not more disparate.

Regarding the second question, the ACC's role in both mnemonic and executive tasks is unclear. Its proposed roles in attention and in holding information online in order to make a response (Petit et al 1998) are obviously highly relevant to working memory tasks like the n-back. Desgranges et al's review (1998) notes that ACC activation is "almost constant" in episodic memory tasks, including encoding, recognition and retrieval, which they put down to its many proposed cognitive roles. Likewise, Ragland et al (2000) explain ACC activation during recognition with reference to its information-holding, monitoring and response selection capacities. A primate ACC lesion study implies that the ACC is more important for task performance in general than working memory specifically (Rushworth et al 2003). Indeed, Peterson et al (1999) claim that it is involved in almost all stages of an executive task (the Stroop).

We may now ask why, in schizophrenia, the ACC can be both hyper- and hypoactive? When frontal hypoactivity is found in association with impaired performance, it can be argued that either a frontal abnormality impaired performance, or that the subjects "gave up" on the task, leading to frontal hypoactivity (Frith et al 1995). If decreased task performance were responsible for hypoactivity, one would expect that subjects would perform worse on those tasks in which they

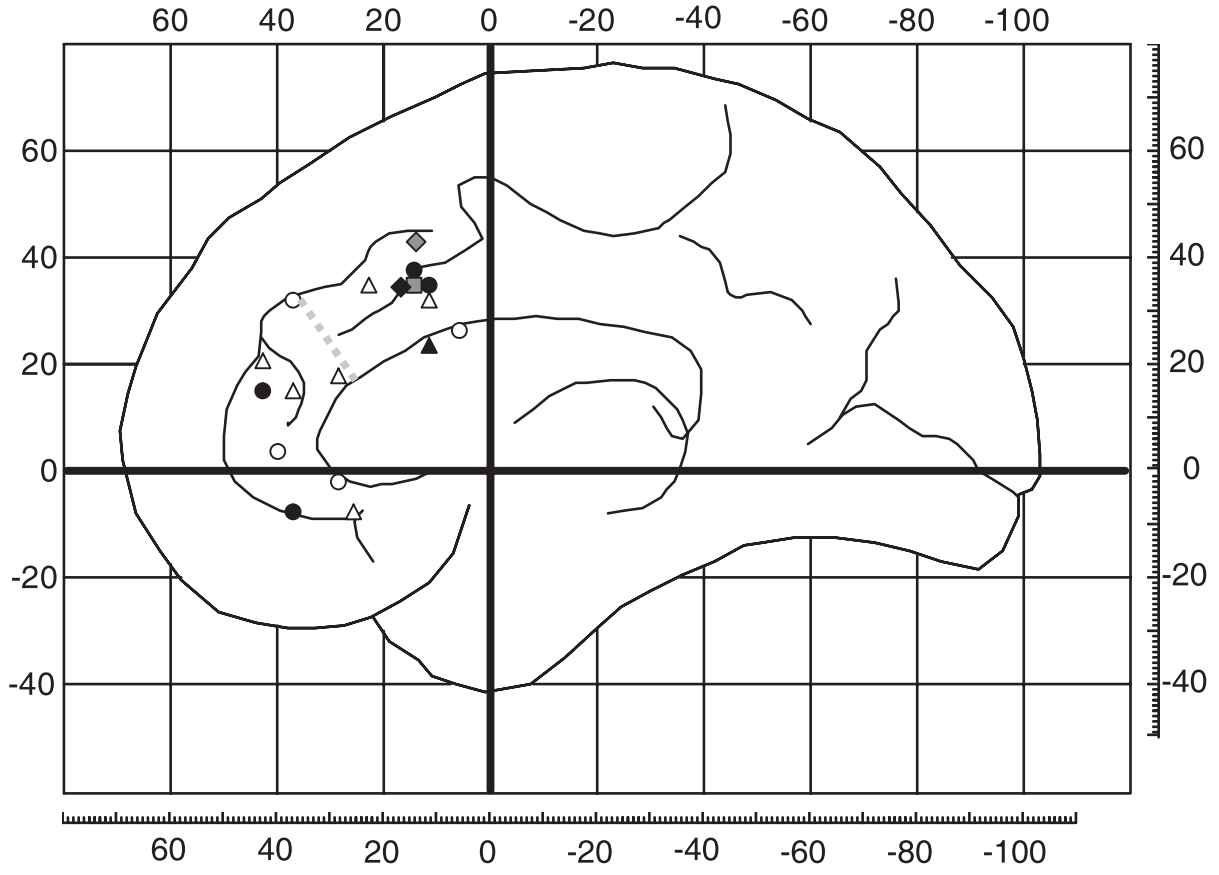

Figure 2 Sites of hyperactivation and hypoactivation in schizophrenia and mean activation in controls during mnemonic tasks (n-back and encoding, recognition and retrieval tasks). Most experiments gave just one point of maximal activation in the ACC but a few gave more. All are listed in Tables 1–3. The points anterior to the dashed grey line lie in rCZa, those posterior to the line lie in rCZp.

showed ACC hypoactivity (as was predicted in the introduction). But this was not observed consistently. It therefore seems unlikely that task performance accounts for the observed activations. ACC hypoactivations do not appear to be related to particular tasks, whereas hyperactivations do. This finding echoes Glahn et al's (2005) meta-analysis which showed the ACC to be regularly hyperactive in n-back tasks. The reason for this is uncertain. One might argue that this demonstrates a hyperactive tendency in mnemonic tasks, but as the n-back task also makes considerable executive demands, this conclusion would not be valid. Task-related hypoactivity could be an artefact of the subtraction of a large control activation from a normal task-related activation. Unfortunately, none of the PET experiments compared control-related activations, so one cannot dismiss this possibility. In the majority of the encoding/retrieval/recognition experiments showing ACC hypoactivity, however, the control task was just "REST", which makes minimal demands on an attentional/task-monitoring system. In fact, the n-back control (a 0-back task) requires much more attention and response preparation, but in this case the task-control subtraction gave several hyperactive results.

The Go/NoGo task is the only one in which it is possible that a hyperactive control condition was responsible for an overall hypoactive Task-Control subtraction. Here,

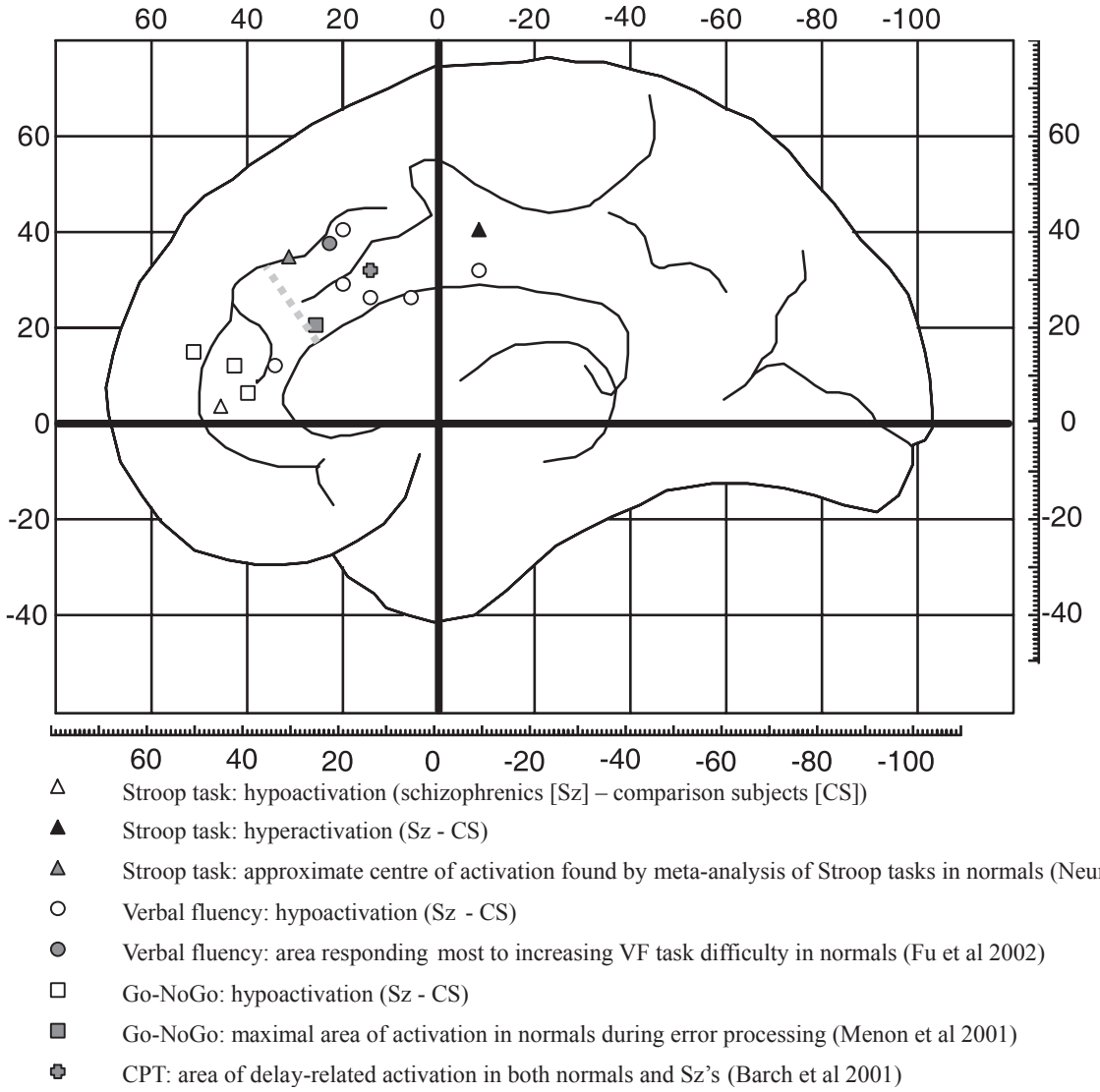

Figure 3 Sites of hyperactivation and hypoactivation in schizophrenia and mean activation in controls during executive tasks (the Stroop, Verbal Fluency, Go-NoGo and Continuous Performance tasks). Most experiments gave just one point of maximal activation in the ACC but a few gave more. All are listed in Tables 1–3. The points anterior to the dashed grey line lie in rCZa, those posterior to the line lie in rCZp.

the only experiment in which the ACC was not hypoactive was the one in which the patients performed worse than the controls, hence, in the other three sets of experiments the patients may have been "trying harder" throughout, leading to hyperactivations during the control condition and an apparent overall hypoactivity.

Callicott et al (2000) mention the possibility that scanning time could affect the activation result if schizophrenia patients' activations started off hyperactive and then became hypoactive. As PET scans last longer, it would average a lower activation than fMRI if they both began at the start of the experiment. Although none of the 14 PET experiments showed a hyperactivation, only 6 of the 42 fMRI experiments did, so, without greater numbers of PET studies, one cannot attribute this distribution to scanning method.

Hill et al (2004), in their review of hypofrontality in schizophrenia, found that increased length of illness was the biggest contributor to hypofrontality, although they were careful to point out that increased age is a confound which is very difficult to factor out. Age is an especially important factor when considering ACC activation, as Buchsbaum et al (1997) found that the ACC is one of two brain areas showing the greatest age-related metabolic decline in healthy subjects. This observation led Schultz et al (2002) to dismiss their finding that the ACC's rCBF declines in proportion to duration of schizophrenic illness as an age-related effect.

Table 1 Results of the verbal, picture, and spatial 2-back mnemonic tasks

Study	Task/ Symptom	PET/ fMRI	Mean duration of Sz, yrs (sd)	Medication	Sz Performance	ACC	ACC x, y, z	PFC L	PFC R
Callicott et al (2000)	verbal 2-back	fMRI	10.0 (6.0)	on	worse	↑	–2,14,40		
						↓	4,28,0;		
							20,38,4	↑↓	↑
Meyer-Lindeburg et al (2001)	verbal 2-back	PET	?	off	worse			↓	↓
Perlstein et al (2001)	verbal 2-back	fMRI	13.9 (8.4)	on typ	worse	↑	–14,42,15		↓
Barch et al (2002)	verbal & facial								
	2-back	fMRI	13.0 (11.5)	on atyp	?			↓	↓
Honey et al (2002)	verbal 2-back	fMRI	11.8 (7.3)	on typ	same				
Wykes et al (2002)	verbal 2-back	fMRI	>2/3 were >10 yrs	on typ	worse			↓	↓
Honey et al (2003)	verbal 2-back	fMRI	13.0 (9.8)	on	worse			↓	↓
Kim et al (2003)	picture 2-back	PET	2.8 (3.2)	on atyp	same	↓	6,32,36	↑↓	↑↓
Perlstein et al (2003)	verbal 2-back	fMRI	14.1 (2.2)	on typ	worse				↓
Walter et al (2003)	verbal 2-back	fMRI	5.5 (6)	on atyp	worse	↑	–3,12,36	↓ L dominance	
Walter et al (2003)	spatial 2-back	fMRI	5.5 (6)	on atyp	worse			↓ R dominance	
Jansma et al (2004)	spatial 3-back	fMRI	?	on atyp	worse			↓	↓
Mendrek et al (2004)	verbal 2-back	fMRI	1st episode	started atyp	worse			↓	↓
Mendrek et al (2004)	verbal 2-back	fMRI	1st episode	on atyp	worse			↓	
Kindermann et al (2004)	spatial 3-back	fMRI	21.1 (9.0)	aty > typ	same	↓	16,6,24	↑	
Mendrek et al (2005)	verbal 2-back	fMRI	? (stable outpts)	on atyp	same	↑	12,36,-8	↑↓	
Thermenos et al (2005)	verbal 2-back	fMRI	?	?	same			↑	↑

Notes: Arrows indicate whether the result of the comparison "Sz (Task–Control)–Comparison subjects (Task–Control)" was a hyperactivation (↑), hypoactivation (↓), or normal activation (no arrow).
Abbreviations: a/typ, a/typical neuroleptics; ACC, anterior cingulate cortex; PFC, prefrontal cortex; x, y, z, Talairach coordinates.

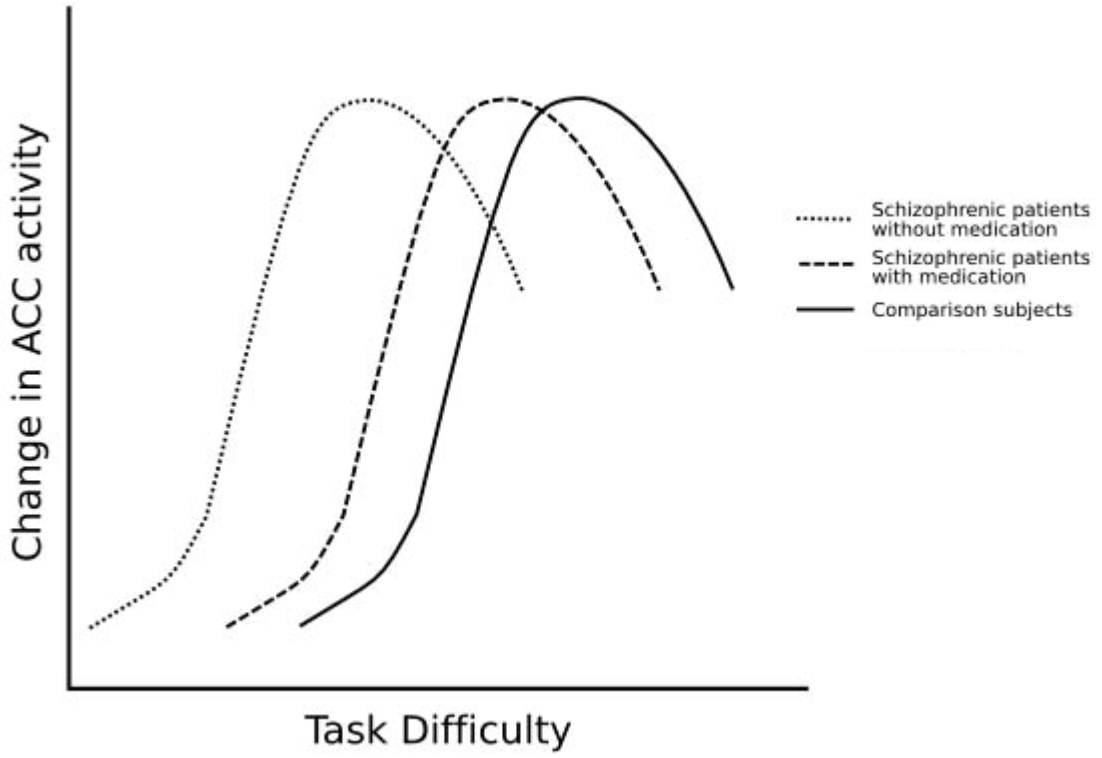

Figure 4 A graph illustrating one possible relationship between ACC activity, task difficulty and schizophrenia. Adapted from Manoach's (2003) theory of DLPFC activation in schizophrenia.

This review found no evidence that longer illness leads to a more hypoactive ACC. There is a probable confound present, however, as the short-illness patient groups performed worse than the long-illness patient groups, an indication that the younger patients were more psychotic and hence more impaired. If acute psychosis were also associated with task-related ACC hypoactivation, this would mask a chronicity effect, as both younger, more psychotic patients and older, chronic patients would hypoactivate. Unfortunately there was insufficient information about patients' symptoms given in many studies, so this factor could not be assessed independently.

The relationship between rCBF and anti-psychotic medications is a complex and poorly characterized one. It is also uncertain what changes in rCBF mean in terms of underlying brain activity, for instance, whether an increase implies that the brain is doing its job more productively or less efficiently. To help decide this, one must compare schizophrenic brain activity (and task performance) pre- and post-medication with that of normal subjects, both at rest and during tasks. It is a common finding that anti-psychotics increase rCBF in the striatum and parts of the frontal cortex, both at rest (Lahti et al 2003; Sharafi et al 2005) and during a task (Jones et al 2004), although this is not always the case (either at rest—Miller et al 2001; or during a task—Liddle et al 2000). Atypical anti-psychotics are thought to increase rCBF more than typical anti-psychotics in the prefrontal cortex (Honey et al 1999), including the ACC (Lahti et al 2003). Lahti et al (2004) found that clozapine increased ACC activation in schizophrenics performing an auditory discrimination task, and that this increase was a *normalization* of activity, not a hyperactivation.

Although most conclude that the increased frontal rCBF must be cognitively beneficial, it has been difficult to show a concomitant increase in task performance (Honey et al 1999; Jones et al 2004), despite the abundant evidence that treatment with atypical anti-psychotics does improve performance, eg, at verbal fluency tasks and the Stroop (Velligan et al 2002) and at a CPT and a spatial working memory task (Harvey et al 2003). It is not just atypical anti-psychotics that present this problem, however. Schizophrenics treated with cognitive enhancers also show increases in prefrontal (Nahas et al 2003) and ACC activity (Spence et al 2005) during task performance, but fail to demonstrate an increased aptitude for the task. It is therefore interesting to note that all of the ACC hyperactivations reviewed here occurred in patients

Table 2 Results of the encoding, recognition, and retrieval mnemonic tasks

Study	Task/ Symptom	PET/ fMRI	Mean duration of Sz, yrs (sd)	Medication	Sz Performance	ACC	ACC x,y,z	PFC L	PFC R
Fletcher et al (1998)	verbal enc/retr	PET	>2	on typ	worse			↓	↓
Crespo-Facorro et al (1999)	verbal retr	PET	10.6 (12.2)	off	same	↓	0,10,32	↓	
Heckers et al (2000)	picture recog	PET	16.2	on typ	worse			↑	
Manoach et al (2000)	item recog	fMRI	?	on typ	same	↑	3,12,25	↑↓	↑↓
Crespo-Facorro et al (2001)	verbal recog	PET	?	off	worse	↓	6,42,20	↓	↓
Ragland et al (2001)	verbal enc	PET	12.2 (9.2)	50% on	same			↓	
Ragland et al (2001)	verbal recog	PET	12.2 (9.2)	50% on	same			↓	
Barch et al (2002)	verbal & facial enc/recog	fMRI		on atyp	?				
Hofer et al (2003)A	verbal enc	fMRI	6.3 (3.5)	on atyp	same	↓	14,30,18		↓
Hofer et al (2003)A	verbal recog	fMRI	6.3 (3.5)	on atyp	same			↓	↓
Hofer et al (2003)B	verbal enc	fMRI	4.3 (5.1), 6 1st ep	off	worse				↓
Hofer et al (2003)B	verbal recog	fMRI	4.3 (5.1), 6 1st ep	off	worse	↓	6,21,36	↑↓	↑↓
Ragland et al (2004)	verbal enc	fMRI	12.2 (7.6)	on atyp	worse			↑↓	↑
Ragland et al (2004)	verbal recog	fMRI	12.2 (7.6)	on atyp	worse			↑↓	↑↓
Ragland et al (2004)	verbal retr	fMRI	12.2 (7.6)	on atyp	worse			↑	↑↓
Bonner-Jackson et al (2005)	verbal enc	fMRI	? (outpts)	on atyp	worse			↑	↑

Notes: Arrows indicate whether the result of the comparison "Sz (Task–Control)–Comparison Subjects (Task–Control)" was a hyperactivation (↑), hypoactivation (↓), or normal activation (no arrow).
Abbreviations: enc, encoding task; recog, recognition task; retr, retrieval task; a/typ, a/typical neuroleptics; ACC, anterior cingulate cortex; PFC, prefrontal cortex; x, y, z, Talairach coordinates.

Table 3 Results of the executive tasks

Study	Task/ Symptom	PET/ fMRI	Mean duration of Sz, yrs (sd)	Medication	Sz Performance	ACC	ACC x, y, z	PFC L	PFC R
Carter et al (1997)	Stroop	PET	chronic	typ > aty	worse	↓	12,46,4	↓	
Yucel et al (2002)	Stroop	PET	11.5 (8.5)	on	?	↓	-	↓	↑
Weiss et al (2003)	Stroop	fMRI	6.2 (4.7)	on atyp	same	↑	0,–8,40	↑	↓
Volz et al (1999)	CPT	fMRI	?	on	same	↓	-	↓	↓
Barch et al (2001)	CPT	fMRI	1st episode	off	worse		↓	↓	
MacDonald et al (2003)	CPT	fMRI	16.0 (9.0)	on	worse		↓		
Salgado-Pineda et al (2004)	CPT	fMRI	1.9	on atyp	worse			↓	
Eyler et al (2004)	CPT	fMRI	33	aty > typ	same			↑ ↓	
MacDonald et al (2005)	CPT	fMRI	1st episode	off	worse		↑ ↓	↑ ↓	
Holmes et al (2005)	CPT	fMRI	? (inpts)	off > on	worse		↑	↓ ↑	
Fletcher et al (1996)	Verbal fluency	PET	4.3 (6.0)	off	same	↓	–4,–6,32; 6,16,28; 6,6,28		
Curtis et al (1998)	Verbal fluency	fMRI	10.8 (3.6)	on atyp	same		↓		
Dye et al (1999)	Verbal fluency	PET	chronic	on typ	same				
Artiges et al (2000)	Verbal fluency	PET	chronic	on	worse		↓	↓	
Spence et al (2000)	Verbal fluency	PET	16.3 (7.6)	on	same				
Jones et al (2004)	Verbal fluency	fMRI	1st episode	off	worse		↓	↓	
Jones et al (2004)	Verbal fluency	fMRI	1st episode	on atyp	worse				
Weiss et al (2004)	Verbal fluency	fMRI	1st episode	on atyp	same				
Boksman et al (2005)	Verbal fluency	fMRI	1st episode	off	worse	↓	6,20,42		↓
Fu et al (2005)	Verbal fluency	fMRI	11	aty > typ	same	↓	–24,20,32; 9,26,32	↑	↓
Rubia et al (2001)	Go-No-Go	fMRI	1.3 (0.8)	on atyp	same	↓	–5,42,18		
Erkwoh et al (2002)	Go-No-Go	PET	5.7	on	worse		↑		
Laurens et al (2003)	Go-No-Go	fMRI	11.0 (3.6)	on atyp	same	↓	–8,52,16		↑
Ford et al (2004)	Go-No-Go	fMRI	17.3 (13.9)	on atyp	same	↓	-	↓	↓

Notes: Arrows indicate whether the result of the comparison "Sz(Task–Control)–Comparison subjects(Task–Control)" was a hyperactivation (↑), hypoactivation (↓), or normal activation (no arrow).
Abbreviations: CPT, Continuous Performance Task; a/typ, a/typical neuroleptics; ACC, anterior cingulate cortex; PFC, prefrontal cortex; x, y, z, Talairach coordinates.

Table 4 Overall results

		Medication	Sz Performance	Relative ACC activations in schizophrenia
Medicated		47 on	26/47 worse	6↑, 10↓
Non-medicated		11 off	9/11 worse	5↓
Medicated (typical)		9	6/9 worse	2↑, 1↓
Medicated (atypical)		25	11/25 worse	3↑, 6↓
		17 on		3↑, 7↓
Equal performers	19	2 off		2↓
		21 on		3↑, 2↓
Worse performers	30	9 off		3↓
Illness < 6 yrs		10 on, 7 off	4/17 same	
			13/17 worse	1↑, 4↓
Illness > 6 yrs		24 on, 2 off	15/26 same	
			11/26 worse	3↑, 8↓
PET	15			6↓
fMRI	42			6↑, 10↓

Notes: When there was insufficient information given in a study to assign it to a particular group, it was left out of the total; eg, there were 47 studies involving medicated patients, but only 34 of these specified that their patients were all on typical or atypical neuroleptics, hence the remaining 13 studies are not included in the medicated (typical) and medicated (atypical) subtotals.
Abbreviations: on/off, on or off neuroleptics; ACC, anterior cingulate cortex.

taking anti-psychotic medication. Medicated patients also showed less hypoactivations and better performance, and those on atypical medication performed best of all. As all of the hyperactivations occurred in fMRI experiments, one cannot be sure whether the greater task-related activation in schizophrenics was due to a lower resting activation or a higher task-related activation (or both). As anti-psychotics are thought to increase frontal rCBF, one must presume the latter. Unfortunately, as was the case with the length of illness, these data might well be confounded with the patients' current symptoms. Nevertheless, a patient's medication status must remain of prime importance when one seeks to interpret their ACC activation state.

Investigators have attempted to explain the inconsistency of frontal activation findings in schizophrenia in several ways. I shall address two questions on this subject: why ACC activations vary (from hyper- to hypo-) between experiments, and why prefrontal activations vary (from hyper- to hypo-, and from location to location) within experiments. Manoach (2003) and Callicott et al (2003) have both put forward theories as to why the DLPFC can be both hyperactive and hypoactive in schizophrenia. It would be interesting to see if these theories could also explain the behavior of the ACC. Manoach (2003) proposes that both variable DLPFC activations and inconsistent relationships of DLPFC activation to performance (from direct to inverse, or neither) can be explained by one theory. This states that the normal DLPFC increases its activation in response to increasing task demand up to a maximum point, after which both DLPFC activation and performance decline. Manoach (2003) proposes that in schizophrenia, the same relationship exists, but with its maximal activation and performance at a lower level of task demand, ie the curve is shifted to the left. Would this relationship in the ACC explain the pattern of activations we have seen? The answer is no. Lahti et al (2004) claim that, in schizophrenic patients, clozapine reduces resting ACC hyperactivity and increases task-related activity, ie, it shifts the curve (illustrated in Figure 4) to the right. This would certainly be an important finding, as it relates task difficulty and ACC activation to each other and demonstrates how antipsychotic medication may change them.

There are two problems with this conclusion. The first is as follows: at high levels of task difficulty, patients' ACC's become comparatively hypoactive. If one assumes (as Manoach's (2003) model of the DLPFC does) that task performance declines once the ACC becomes hypoactive, then one must conclude that whenever the ACC is hypoactive, performance must similarly decline. In this review, however, 9/19 experiments showed ACC hypoactivity and *identical* performance, compared with 5/29 experiments showing ACC hypoactivity and impaired performance. Performance obviously has a much more complex relationship with rCBF than this graph indicates.

The second problem is that if medication does shift the curve to the right, then one would expect that patients taking anti-psychotic medications would show less ACC hyperactivations

in response to tasks, not more. The opposite relationship exists, however, as all 6 hyperactivations occurred in those on medication, not off. A possible objection to this point could be that medication might shift the curve upwards (ie activating the ACC more at all levels of difficulty) and not to the right, this, however, is not what Lahti et al (2004) found. A further objection would be that if a narrow window of task difficulties near the intersection of the two curves were being examined, a rightward shift in the schizophrenics' curve would indeed lead to more ACC hyperactivations, not less. But this theory would also predict that the ACC should be hyperactive in unmedicated schizophrenics not engaged in tasks (a window of difficulty at the left end of the graph), yet it has been shown to be hypoactive in two studies with a combined patient number of 120 (Siegel et al 1993; Haznedar et al 1997).

Callicott et al (2003) have a different explanation for the mixture of prefrontal hyperactivations and hypoactivations, which also relates to the second question under consideration here: why prefrontal activation varies so widely within experiments. They point out that in order to support Manoach's (2003) model, data must show that a specific region moves from hyperactivity to hypoactivity as performance falls. This has not yet been achieved. Another possibility is that there are many areas of hyper- and hypoactivity throughout the frontal cortex, which remain relatively hyperactive or hypoactive, with their absolute activation varying with performance (and, it could be added, medication status). They therefore divide their patients into two broad groups. The first group demonstrate a mixture of hyperactivations and hypoactivations throughout prefrontal cortex whilst maintaining similar task performance to that of controls. The second group are much more uniformly "hypofrontal", with poorer task performance than that of controls. Whether these hypothetical patient types can be related to other variables such as length of illness or current symptoms remains to be seen.

There is insufficient evidence here to support or deny Callicott et al's proposition—one would have to look at individual patients' results. Their model is consistent with the observation that taking antipsychotic medication may normalise or even lead to overactivation of some schizophrenic patients' ACC's which ordinarily cannot activate sufficiently. In some, performance may be maintained by recruiting larger prefrontal areas or "hyperactivating" those already in use; in others, this may not be possible, and so performance will suffer. As to why ACC activation does not appear to be proportional to task performance, one must conclude that the ACC is obviously not the most important brain area involved in the task.

Finally, this review must be put into context. Despite much experimentation, relatively little is known about the cognitive function of the ACC in either healthy volunteers or schizophrenia patients. Even less is known about the ACC's emotional or limbic roles, least of all how these may be compromised in schizophrenia. Numerous imaging studies have shown the ACC to be hyperactive in schizophrenics during auditory verbal hallucinations (Silbersweig et al 1995; Shergill et al 2000; Copolov et al 2003) and passivity phenomena (Spence et al 1997), although whether this reflects an attentional or a generative process is uncertain. Damasio (1999) believes that the ACC is largely responsible for "core consciousness" (consciousness without its autobiographical component), as it receives both external and internal sensory input, which would allow it to map images of external objects, images of the body, and the former's effect on the latter. As object images are associated with possible motor responses, he also proposes that it produces our sense of agency, that "these images are mine and I can act on the object that caused them" (Damasio 1999). The potential importance of ACC pathology in schizophrenia, therefore, is clear. A malfunctioning ACC may underlie the disconnection of world, self, and action which is the hallmark of psychosis. It is therefore significant that the administration of sufficient ketamine to reactivate psychotic hallucinations and delusions in stable schizophrenic patients is associated with increased ACC rCBF (Lahti et al 1995). Any ACC contribution to mere cognitive dysfunction in schizophrenia may be just the tip of the iceberg.

In conclusion, one may make the following points about abnormal ACC activations in schizophrenia.

- *Location*
  Points of maximal activation in normal subjects performing both mnemonic and executive tasks all lie in rCZp. Points of abnormal activations (hyper- and hypo-) during mnemonic or executive tasks in schizophrenia are documented in over one third of experiments, and lie in both rCZa and rCZp.
- *Direction*
  Hypoactivations outnumbered hyperactivations by around two to one. Hypoactivations were found in all tasks (the n-back, encoding, recognition, retrieval, Stroop, CPT, verbal fluency and Go/NoGo tasks). Hyperactivations were largely confined to the n-back task (4/6).
- *Relationship to performance/other variables*
  Hypoactivations are unlikely to be due to (or even associated with, in most cases) poor performance.

The ACC may be regularly hypoactive during Go/NoGo tasks due to a more demanding control condition. There is no evidence that chronicity of illness increases task-related ACC hypoactivation, although it is possible that those with ACC hypoactivity due to acute psychosis are masking this effect here. These results do not support the application of Manoach's (2003) model of DLPFC dysfunction in schizophrenia to the ACC, as the model would explain neither the variable ACC activations nor the relationship of ACC activation to task performance.

- *Effect of anti-psychotic medication*
  Patients on medication performed better and showed greater ACC activation (less hypoactivations and more hyperactivations), although symptomatology may confound this result. Those on atypical anti-psychotics performed best of all, despite showing more hypoactivations.
  This point illustrates a common difficulty in linking increases in rCBF to improvements in performance, and suggests that the relationship between rCBF and performance is not a straightforward one.

Future directions

Clearly future studies must include larger numbers of participants so that potential confounds between patients and controls may be controlled in the analysis or by stratification. In terms of meta-analysis, it would be greatly beneficial to the field if authors reported clinical and imaging parameters more consistently. The use of the same test materials including baseline task is another obvious issue which would aid data pooling and analysis. Finally, there is also a need to develop generally accepted standards for reporting fMRI data which includes areas of brain activation as probabilistic maps in 3 dimensions (see Costafreda et al 2006).

Limitations

This study looks at a wide selection of experiments which make a variety of cognitive demands. It was therefore designed as a simple comparative work, and not as a complex meta-analysis. This design obviously limits the interpretative capacity of the study, especially as studies with positive findings which do not quite reach statistical significance are not included in the totals (eg, there may be non-significant ACC hyperactivity in other tasks besides the n-back). It was also felt that performing simple post-hoc statistical tests (eg, the chi-square test) would add little to the reliability of the conclusions. Overall, this study was not intended to be a definitive examination of the ACC in cognitive tasks in schizophrenia, but merely to raise important questions for further studies.

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