CHAPTER 30

The Cingulate Gyrus in Schizophrenia: Imaging Altered Structure and Functions

Adrian Preda, Laurie M. Rilling, Ronald B. Chin, and Carol A. Tamminga

Chapter contents

Several convergent lines of evidence suggest the involvement of the cingulate cortex in the manifestations of schizophrenia: (1) the cingulate mediates specific aspects of cognition that are abnormal in the illness (predominantly, attention and executive function; Gold & Weinberger, 1995; Green *et al.*, 1992; Posner & Petersen, 1990), as well as evidences (2) postmortem histological and neurochemical abnormalities (Benes & Bird, 1987; Benes *et al.*, 1987; Benes, 1993; Benes & Tamminga, 2002), and (3) *in vivo* imaging changes in the illness (Tamminga *et al.*, 2000a; Carter *et al.*, 1998; Gold & Weinberger, 1995; Green *et al.*, 1992; Posner & Petersen, 1990).

Early *in vivo* imaging data gathered using whole-brain, unbiased sampling approaches, raised the possibility of ACC involvement in schizophrenia, especially when volunteers were drug-free, at rest, and floridly psychotic (Tamminga *et al.*, 1992). Indeed, in the drug-free condition, correlations could be detected between neuronal activity in anterior cingulate cortex (ACC) and the level of psychotic symptoms (Tamminga *et al.*, 1992), correlations that were not present during antipsychotic drug treatment. More detailed analyses have followed, also showing ACC dysfunction during the performance of tasks shown to be mediated by ACC (Carter *et al.*, 1997). Even in test conditions where performance

is matched between the patient and control groups, function is still abnormal in ACC (Holcomb *et al.*, 2000). These early *in vivo* data have provided ample rationale to suggest careful study of the ACC in schizophrenia with the goal of increasing our understanding of the mechanisms of the illness and developing rational treatments for dysfunctions associated with the illness.

Studies of ACC in schizophrenia have been critically advantaged by the application of modern brain imaging methodologies, positron emission tomography (PET) and especially functional magnetic resonance imaging (fMRI), and further technical, analytic, and advances in the design of paradigms to test cognitive functions promise even more important gains in the future. As the role of the ACC in normal cognition is understood, the possibility of defining aspects of alteration that contribute to manifestations of illness is increasingly possible. With improved understanding of the specific molecular and functional abnormalities of schizophrenia, the development of rational and successful treatments can be expected.

Goals of This Chapter

This chapter will review an aspect of this evidence: the *in vivo* structural, functional, and cognitive findings gathered from individuals with schizophrenia compared with healthy controls. In general these studies implicate alterations in the ACC in its dorsal aspect in schizophrenia, but have not yet progressed to implicate specific, replicated molecular changes defining the mechanism of the *in vivo* abnormality. The specific goals of this chapter include the following:

1 Present the rationale of why schizophrenia deficits are thought to involve the cingulate cortex, especially the ACC.

2 Discuss the evidence of ACC structural abnormalities in schizophrenia as presented by *in vivo* structural MRI studies.

3 Discuss the ACC-mediated cognitive deficits in schizophrenia and present the fMRI and PET evidence substantiating such deficits.

4 Present the PET literature for evidence regarding specific *in vivo* ACC neurotransmitter deficits and discuss the treatment implications of such deficits for schizophrenia.

Schizophrenia

Schizophrenia is a lifelong illness, with symptoms beginning in late adolescence/early adulthood and persisting throughout life (Carpenter, Jr. & Buchanan, 1994; Tamminga *et al.*, 2000b). The illness has a significant genetic risk (Harrison & Owen, 2003; Weinberger *et al.*, 2001), as well as replicated developmental risk factors (Cornblatt *et al.*, 1999; Cornblatt *et al.*, 2002; Murray & Van Os, 1998; Yung *et al.*, 2004). Symptom manifestations are apparent in positive (hallucinations and delusions), negative (anhedonia, thought paucity), and cognitive (attention, executive dysfunction, and memory) domains. Positive psychotic symptoms fluctuate over the course of illness, but negative symptoms and cognitive dysfunction remain more constant (Carpenter, Jr. *et al.*, 1988). Whether these are distinct aspects of a similar pathophysiology or distinct syndromes in themselves (with distinct symptoms, pathophysiology, and etiology) is still not clear. Cognitive impairment is intrinsically linked to schizophrenia and is often taken to be a relatively independent symptom domain in the disorder (Dickinson *et al.*, 2004; Flashman & Green, 2004; Hill *et al.*, 2002; Kolb & Wishaw, 1983; Palmer *et al.*, 1997). An emphasis on cognitive dysfunction in the illness has recently developed and focused on novel therapeutics for cognitive enhancement (Buchanan *et al.*, 2005).

Although the pathophysiology of schizophrenia remains unknown, many clues to its biology exist. Among these pieces of data are evidence of alterations in ACC structure (Benes & Bird, 1987; Benes *et al.*, 1987, 1991, 2001), neurochemistry, and function (Tamminga & Holcomb, 2004). We would not suggest that alterations in ACC function could in themselves cause schizophrenia. But, ample evidence suggests that the alterations in ACC biology are likely to be involved in some of the manifestations of the illness. Certain cognitive functions are known to be mediated in ACC, specifically, selective attention, monitoring conflicting response demands, detecting errors, word generation, working memory, and evaluating the emotional significance of events (Bush *et al.*, 2000; Posner, 1994). These aspects of cognition are involved in executive functions and are consistently impaired in schizophrenia (Carter *et al.*, 1997; Paus, 2001; Petersen *et al.*, 1988). The ACC is also involved in the integration of cognition and emotion, the modulation of emotion-related autonomic activity, and emotional responses to pain (Devinsky *et al.*, 1995; Malamud, 1967; Vogt, 2005). The extensive connections that the ACC and adjacent medial frontal cortices have with the lateral prefrontal cortex (PFC) (Bates & Goldman-Rakic, 1993; Lu *et al.*, 1994; Morecraft & Van Hoesen, 1993; Paus *et al.*, 2001; Wang *et al.*, 2001, Chapter 5) suggest a shared-modulation of cognitive tasks across both cerebral regions. In light of the ACC modulatory and regulatory roles, the emotional processing and executive function deficiencies noted in schizophrenia may be a reflection of a deficit in the

ACC integrative and monitoring functions. A possible contribution of the ACC to positive symptoms has been suggested as well, in that electrical stimulation of ACC can generate negativism and hallucinations, and ACC dysfunction correlates with positive symptoms in schizophrenia (Tamminga *et al.*, 2000b). In addition, the ACC is a component of the limbic cortex (Papez, 1937) and, as such, is intrinsically associated with the function of medial temporal lobe structures, anterior thalamus, and the limbic striatum. Functional imaging studies have also linked dysfunction in the limbic circuit with psychotic symptoms (Tamminga *et al.*, 2000b); moreover, the extensive connections between the limbic cortex and frontal brain regions also support a role of PFC alterations in this set of symptoms.

The posterior cingulate cortex (PCC) is well connected to both the visual and auditory sensory areas and the posterior parahippocampal region and plays a role in monitoring eye position, visuospatial orientation, and visual memory (Vogt *et al.*, 1992). Patients with schizophrenia have abnormalities of certain eye movements (Thaker, Levy *et al.*, 1994) as well as cognitive impairments involving visuospatial orientation (Gold & Harvey, 1993) which suggest that this region may also be part of a dysfunctional circuit contributing to the pathophysiology of schizophrenia.

Using voxel-based morphometry (VBM; Pantelis *et al.*, 2003) reported decreases in the PCC gray matter in a prodomal sample while Sowell *et al.* (2000) reported specific gray matter decreases in area 23 in schizophrenia volunteers with early onset illness (Pantelis *et al.*, 2003). Decreased gray matter volumes were also found in the PCC in studies of adults with chronic schizophrenia (Hulshoff Pol *et al.*, 2001). Ha *et al.*, (2004) reported a correlation between the lack of insight and judgment and gray matter decrease in the left PCC. Zhou *et al.*, (2005) reported bilaterally decreased gray matter in areas 23 and 31 in their large sample of chronic schizophrenics, and Mitelman *et al.*, (2005) reported increased white matter volumes in the right PCC (area 31) in adults with schizophrenia. Clearly, PCC is one of the regions that needs to be better studied in the context of schizophrenia but to date, as the major part of the evidence in schizophrenia implicates the ACC, this will be the focus of our review.

Volumetric Brain Imaging

The structural studies of schizophrenic brain, including the ACC, began with pneumoencepalography and gained momentum with the use of Computer Tomography (CT) (Johnstone *et al.*, 1976) and early magnetic resonance imaging (MRI) (McCarley *et al.*, 1993). These studies reported mainly reduction in whole brain volume and an increase in the ventricular volume in the illness (Gur & Pearlson, 1993).

Magnetic Resonance Imaging (MRI)

When the higher resolution techniques of MRI became available, structural volumes could be measured more safely, reliably and with greater sensitivity. Several region-of-interest (ROI) studies showed a reduction in left anterior cingulate gyrus (Goldstein *et al.*, 1999; Haznedar *et al.*, 2004; Yamasue *et al.*, 2004).

Yamasue *et al.*, (2004) reported a bilateral reduction in ACC (BA 24) gray matter, as well as a negative correlation between abstract thinking reduction and gray matter volume, and with motor retardation and right gray matter volume in patients. Ohnuma *et al.*, (1997) found that untreated disorganized type schizophrenics had significantly smaller left ACC gray matter. Studies on gender differences have reported smaller ACC pregenual gray matter in females, pregenual white matter in males (Takahashi *et al.*, 2003), a loss of normal ACC asymmetry in female patients (Takahashi *et al.*, 2002a,b), and a reversion of normal patterns of sexual dimorphism in schizophrenia (Takahashi *et al.*, 2004; Goldstein *et al.*, 1999), suggesting that gender may influence structure in schizophrenia. Marquardt *et al.* (2005) reported decreases in ACC volume with age and a loss of the normal asymmetry in children with schizophrenia. Pantelis reported a bilateral reduction in gray matter volume in cingulate (including both the anterior and posterior cingulate gyrus) in psychosis prodromal subjects. This group showed a further loss in ACC volume 1 year after psychosis onset (Pantelis *et al.*, 2003). Mitelman *et al.* (2005) also found reduced gray matter volume in schizophrenia in both ACC and PCC. Several ROI studies, however, reported no differences in the volume of the subgenual cingulate volume (Hirayasu *et al.*, 1999) or the ACC volume in first episode patients (Crespo-Facorro *et al.*, 2000) or in chronic schizophrenic persons (Convit *et al.*, 2001; Noga *et al.*, 1995; Szeszko *et al.*, 1999; Woodruff *et al.*, 1997).

Investigators using voxel based methods have reported a reduction in ACC gray matter in early schizophrenia volunteers (Kubicki *et al.*, 2003) in right area 32 (Job *et al.*, 2002; Salgado-Pineda *et al.*, 2003). Decreased gray matter has also been reported in chronic schizophrenia volunteers (Goldstein *et al.*, 1999; Kubicki *et al.*, 2003; Shapleske *et al.*, 2002; Suzuki *et al.*, 2002), although reports differ as to which hemisphere is affected or whether correlations exist with duration of illness (Velakoulis *et al.*, 2002). Shapleske reported some correlation of ACC gray matter reduction and hallucinations (Shapleske *et al.*, 2002). Job reported volume decreases in at-risk persons (Job *et al.*, 2003) and Sigmundsson reported ACC volume reductions associated with negative symptoms in schizophrenia (Sigmundsson

et al., 2001). It is important to note that several VBM studies report no differences in ACC volume in schizophrenia (Bagary *et al.*, 2003; Hulshoff Pol *et al.*, 2001; Kawasaki *et al.*, 2004; Tsunoda *et al.*, 2005; Wilke *et al.*, 2001; Zhou *et al.*, 2003; Ananth *et al.*, 2002). However, a recent study reported decreased ACC volume, in parts of ACC and PCC with the VBM approach, but without confirmation in the same individuals using an ROI approach (Riffkin *et al.*, 2005). In studies examining the ACC sulcal-gyral morphology, schizophrenia volunteers may lack normal ACC sulcal asymmetry (Yucel *et al.*, 2002). Yucel *et al.*, (2003) and Wood *et al.*, (2005) both report a trend for reduced paracingulate folding and cingulate sulcus interruption on the left, although it did not reach significance.

Other investigators have examined correlations between disease symptoms, clinical outcomes and ACC measurements in schizophrenia. Suzuki reported both a volume decrease in the ACC gray matter and an inverse correlation between right PCC gray matter volume and psychosis in patients (Suzuki *et al.*, 2005). Szesko reported a correlation between reduced ACC volume and executive functioning deficits in male patients with first episode schizophrenia (Szeszko *et al.*, 2000). Noga showed a trend toward an inverse relationship between left anterior cingulate size and positive symptoms (Andreasen, 1984; Noga *et al.*, 1995). This is an interesting finding as portions of the ACC project to the lateral nucleus of the amygdala (Pandya *et al.*, 1971, 1979), a common destination for multimodal sensory fibers from regions as diverse as the superior temporal gyrus, parietal cortex, and principal sulcus in the monkey brain (Jones & Powell, 1970) and for auditory path fibers from the posterior thalamus in the rat brain (LeDoux *et al.*, 1990). Using VBM, Paillère-Martinot found an inverse correlation between peri-cingulate white matter and negative symptoms of schizophrenia, and Ha reported both significantly decreased gray matter concentration in the ACC (BA 32) in patients with schizophrenia, as well as a negative correlation between the level of insight and gray matter concentrations in the right ACC and left PCC (Ha *et al.*, 2004; Paillere-Martinot *et al.*, 2001). Mitelman (2005) reported a reduction in ACC and PCC volumes in poor outcome individuals, especially in areas 25, 31, 23, and 29.

In summary, the majority of volumetric studies of the ACC in schizophrenia (i.e., 32 out of 43 studies) report a reduction in volume in the ACC, with some also reporting a reduction in the posterior portion (Fig. 30.1). No studies report volume increases. Some (i.e., 11 out of 43 studies) fail to find a difference (i.e., a reduction) from control populations. Based on this review, it would be reasonable to conclude that ACC volume is reduced in schizophrenia, albeit mildly and perhaps only in a subgroup of persons with the illness. What is not clear, however, is the mechanism of the reduction. Studies in the prefrontal cortex have shown a reduction in the space between neurons, generally filled with neurophil, suggesting a reduction in the number of neuronal processes locally (Selemon & Goldman-Rakic, 1999). These possibilities are more fully discussed by Benes *et al.* in the next chapter.

Included in the speculations on the mechanism of volume reduction in schizophrenia is the question of whether this volume-associated lesion is local, part of a circuit lesion, or associated with a distant lesion. Identification of a functional or neurochemical alteration in the ACC could represent a primary abnormality in this area in the illness. Alternatively, the change could signal a more distant lesion, generating a system or circuit malfunction with an ACC expression. An abnormality found in ACC could even be a generalized alteration present in all gray matter, but selectively expressed in function in the ACC. Despite the source or etiology of this volume-associated dysfunction, it could, nonetheless, be expected to result in a common set of behavioral and psychological outcomes, representing manifestations of ACC dysfunction. These manifestations could be detectable with *in vivo* imaging techniques and result in alterations in cognitive behaviors. Of course, a reduction in ACC volume caused by antipsychotic medication (APD), while never demonstrated, has to be considered. APD reduces regional cerebral blood flow (rCBF) in the cingulate cortex and may also affect volume.

Diffusion Tensor MRI

The cingulate cortex has dense reciprocal connections with limbic- and neocortex; moreover, evidence from functional, anatomical, and microscopic studies suggest that these connections may be altered in schizophrenia (Benes, 1993). As the direct connections

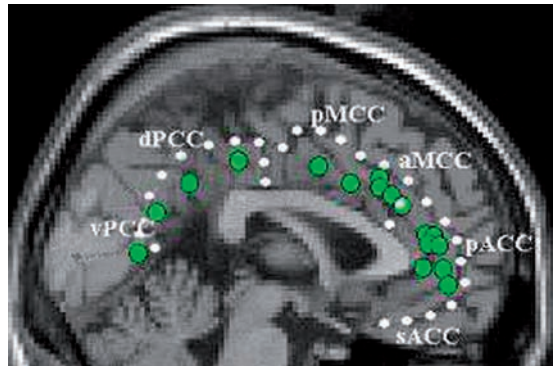

Fig. 30.1 Green dots indicate areas of significant structural abnormality in schizophrenia from reported studies. All coordinates are mapped onto Talairach space with x-plane set to 0. Table lists full Talairach coordinates.

between distant brain regions are mediated by white matter fiber tracts, abnormalities in these connections could produce dysfunction of the circuits. Diffusion tensor imaging (DTI) is a magnetic resonance technique that provides information about tissue microstructure and architecture through quantification of water molecules *in vivo* (Basser & Pierpaoli, 1996). Water molecules move along the long axis of axons, thus indicating axonal direction. In the white matter, changes in the direction of diffusion represent alterations in axon direction while changes in the isotropy of diffusion suggest a disturbance of the white matter integrity.

Hypothesis driven ROI DTI have been used to explore white matter anisotropy of. the cingulate fasciculi or cingulum bundle (Burns *et al.*, 2003; Kubicki *et al.*, 2003; Wang *et al.*, 2004). Abnormalities have been reported bilaterally in the anterior cingulum bundle (CB) in volunteers with schizophrenia (Wang *et al.*, 2004; Sun *et al.*, 2003). In addition, the normal left-greater-than-right asymmetry was reduced in the patients, implicating the left anterior CB in schizophrenia. No differences were found between the posterior CB in schizophrenia (Wang *et al.*, 2004). Kubicki reported bilateral differences in area and mean fractional anisotropy (FA) for the CB, where patient volunteers showed a smaller volume and less anisotropy than controls. Interestingly, decreased anisotropy of the left CB correlated significantly with attention and working memory alterations in the schizophrenia group (Kubicki *et al.*, 2003). Nestor reported that executive function errors related to performance monitoring correlated with reduced FA in the left CB in schizophrenia volunteers (Nestor *et al.*, 2004).

DTI studies using the exploratory voxel-based analysis (VBA) reported similar abnormalities. Kubicki *et al.*, (2005) found decreased diffusion anisotropy in schizophrenia bilaterally in the CB. Park *et al.*, (2004) reported a trend toward loss of the normal hemispheric asymmetry of FA in schizophrenia, with CB being one of the affected regions (Kubicki *et al.*, 2005; Park *et al.*, 2004). Others reported no differences in the FA in ACC white matter in patients experiencing their first episode (Szeszko *et al.*, 2003) or chronic patients with schizophrenia (Burns *et al.*, 2003).

In summary, the majority of the DTI studies in schizophrenia (i.e., 6 of 8 studies) report abnormal FA in CB, with some reporting abnormalities in the anterior CB. The implication is that ACC connectivity is disrupted in schizophrenia. Some of the differences in the DTI studies results may be accounted for purely methodologically, by differences in the study populations or by ROI analysis differences versus measurements limited to the CB tract dorsal to the body of the corpus callosum (Kubicki *et al.*, 2003) study but considering the preponderance of the evidence, it is unlikely that such methodological caveats can explain all the DTI reported CB abnormalities in schizophrenia.

Anisotropy measures are made up of several measures together: white matter fiber size, density, myelination, and fiber coherence; an alteration in any one of these factors can perturb the anisotoropy measure. Thus, the interpretation of the DTI remains complex. Furthermore, FA values also depend on fiber crossings, especially in areas of abundant crossings/connections and CB is such a region. The reported FA changes could indicate differences in indices of the anatomical connectivity, such as the number of fibers or myelination or alternatively, could be a reflection of a disrupted, abnormal regional connectivity of the ACC in schizophrenia. Based on other biological data we favor the interpretations that these data represent a change in the amount of cortical 'wiring' rather than change in the local pattern of connectivity, possibly disturbing function. Further and more refined data using DTI fiber tracking will be essential to answer questions about mechanism and implications in a more informative manner.

Functional Brain Imaging and Cognition

Cognitive performance has been extensively examined in schizophrenia (D'Esposito, 1998; Gur *et al.*, 2001; Heinrichs & Zakzanis, 1998). While a generalized compromise in cognition is widely acknowledged, certain domains of function stand out as being particularly affected, including aspects of executive function and memory. Cognitive disabilities in schizophrenia have a similar scope and magnitude in young and in chronic schizophrenics, even in vulnerable young persons before the psychosis onset (Gur *et al.*, 1998, 1999; Saykin *et al.*, 1994; Bilder *et al.*, 1991; Kristian Hill *et al.*, 2004). To some degree cognitive disabilities show the same pattern in family members and in vulnerable (not yet psychotic) persons as in persons with the full illness (Barch *et al.*, 2003; Fitzgerald *et al.*, 2004). Moreover, cognitive deficits show only small to moderate correlations with clinical state (Censits *et al.*, 1997) and little change with antipsychotic treatment (Goldberg and Weinberger, 1996). Altered performance on working memory and verbal episodic memory has often been singled out as the most significantly impaired aspect of cognition in the illness (Green *et al.*, 2000; Cannon *et al.*, 2000; Egan *et al.*, 2001). However, there exists a great deal of diversity in the magnitude and type of cognitive defect in populations with the illness (Hill *et al.*, 2002; Bruder *et al.*, 2004).

People with schizophrenia have varying degrees of alteration in attention and in several aspects of executive functioning such as organization, planning, self-monitoring and mental flexibility. As these cognitive functions are mediated at least in part by the ACC,

these deficits suggest a careful look at persons with schizophrenia.

Functional imaging allows for a dynamic measure of the cognitive processes affected by schizophrenia. Form and function can be correlated based on significance testing between an activated area and performance data. Differences in performance on cognitive tasks between normal and schizophrenia volunteers can thereby be localized to areas of activation that differ significantly between the two groups. Techniques such as fMRI, PET and event-related potential (ERP) have revealed specific areas of the brain that are activated in response to specific cognitive tasks. Selectively employing robust tasks in conjunction with functional imaging has been fruitful in mapping out areas of cognitive impairment and in explaining performance differences between normals and individuals with schizophrenia. In particular, this method has revealed differences in patterns of activation with regards to structures involved in attention and the executive circuit, both of which involve the ACC (see Figure 2.)

Complex Attention and Executive Functions

The ACC is a part of the circuit involved in attention (Devinsky & Luciano, 1993), receiving inputs from the posterior parietal lobe and the dorsolateral prefrontal cortex (DLPC) (Braver, 2001; Bush *et al.*, 2000; Menon *et al.*, 2001; van Veen & Carter, 2002; Goldman-Rakic, 1988). A number of lines of evidence support the ACC as having an essential role in attention. Human studies following patients who sustained ACC lesions have reported evidence of neglect and attentional deficits, with severity reflected upon degree of ACC damage (Devinsky & Luciano, 1993). People with lesions in the ACC show deficits in intention at self-initiation and also, but less prominently, in sustained attention, even akinetic mutism (Cohen *et al.*, 1999). Additionally, microelectrode recordings of individual neurons in the human ACC have revealed active neuronal modulation during attention-demanding tasks such as the Stroop, backwards digit span, and word generation (Davis *et al.*, 2000). Most recently, functional neuroimaging studies have produced activation maps that link the ACC to other structures involved in attention (Ardekani *et al.*, 2002; Bench *et al.*, 1993; Carter *et al.*, 1995; Laurens *et al.*, 2005; Morey *et al.*, 2005; Peterson *et al.*, 1999; Taylor *et al.* 1997). Of interest, imaging studies have shown that the ACC can subserve different kinds of attention. In an fMRI study using the Stroop task, Brown found greater activation in the ACC and right parietal cortex on trials requiring selective attention than on baseline trials (Brown *et al.*, 1999). Using an auditory stimulation task, Ortuno showed that the ACC, along with DLPFC and parietal cortex are activated during conditions requiring sustained attention (Ortuno *et al.*, 2002). Functional MRI studies in which healthy controls were imaged during performance on the trail making test (TMT) and Wisconsin Card-sorting Test (WCST) have also demonstrated the ACC's participation in attentional set-shifting (Moll *et al.*, 2002; Perianez *et al.*, 2004; Shafritz *et al.*, 2005).

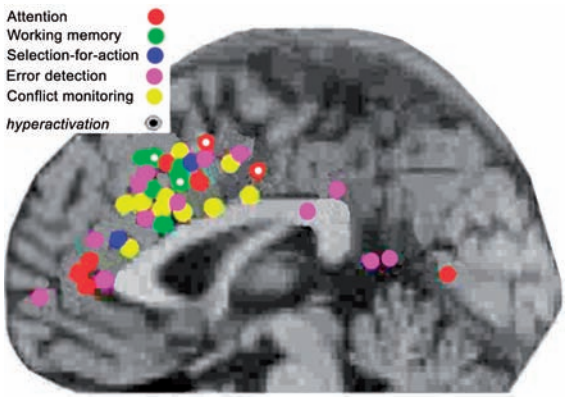

Fig. 30.2 Activation differences between schizophrenia and normal volunteers; Activations are color-coded by cognitive domain; coordinates were taken from reported studies and plotted onto Talairach space with x-plane set to 0. Dots with a white center represent schizophrenia hyperactivation and all others are for schizophrenia hypoactivation.

In schizophrenia, the different domains of attention and executive function mediated by the ACC have been consistently targeted by studies using a variety of behavioral, neuropsychological and functional imaging methods. Neurocognitive measures of sustained and divided attention, such as the continuous performance task (CPT) and the Stroop have provided abundant, though sometimes inconsistent, evidence that patients with schizophrenia have impairments in both selective and sustained attention, respectively (Brebion *et al.*, 1996; Gold & Thaker, 2002). Deficits in set-shifting, a paradigm testing ACC modulated attention, have also been repeatedly demonstrated in schizophrenia using traditional measures of frontal functioning, such as the WCST (Li, 2004). As expected, performance of such neuropsychological tests during functional neuroimaging has revealed differences in the neural substrates activated in volunteers with schizophrenia when faced with specific attentional demands. In a recent study using a novelty visual oddball task during event-related fMRI, Laurens *et al.*, (2005) reported that medicated patients with schizophrenia were not only significantly slower and less accurate than healthy

controls but also showed reduced ACC activation. Morey *et al.*, (2005) used a visual oddball CPT task to examine frontal and striatal functioning in ultra high-risk prodromal, early, and chronic schizophrenia patients and found significant reductions in ACC activation in the ultra-high risk group relative to healthy controls, with further reductions in the early and chronic patient groups. Interestingly, while there was no difference between the controls and the ultra-high risk subjects, early and chronic patients demonstrated similarly impaired accuracy rates relative to controls. Several studies employing a modified version of the Stroop task during O^{15} PET have shown reduced ACC activation in medicated schizophrenic patients (Carter *et al.*, 1997; Yucel *et al.*, 2002). Deficiencies in ACC activation were particularly acute during trials that required highly selective attention (incongruent probes), which corresponded to higher error rates. Using PET and fMRI to examine sustained attention during the CPT, several investigators have demonstrated similar patterns of hypoactivation in the attentional circuit during sustained attention, with schizophrenia volunteers showing a significant reduction in the activation of the ACC (Grady & Keightly, 2002; Salgado-Pineda *et al.*, 2003; Volz *et al.*, 1999). Similarly, ACC hypoactivation has also been found to occur during attention-demanding word generation tasks (Boksman *et al.*, 2005; Fu *et al.*, 2005). On the other hand, when looking at nonpsychotic relatives of schizophrenia patients during sustained attention, as measured by an auditory version of the CPT, Thermenos *et al.* (2004) reported greater ACC activity in the relatives compared with healthy controls.

Studies with healthy controls have consistently identified the ACC as having an active role during set-shifting demanding tasks (Moll *et al.*, 2002; Perianez *et al.*, 2004; Shafritz *et al.*, 2005). Perianez, using MEG, found that the ACC was one of three localized regions that was significantly activated during shift conditions on the WCST (Perianez *et al.* 2004). This phenomenon was also seen in fMRI studies by Moll (2002) and Shafritz (2004). Taking this into consideration, along with the results of multiple studies that have consistently shown deficits in attentional set-shifting in schizophrenic patients (Li, 2004; Tyson *et al.*, 2004) it can be argued that an impairment in the ACC may be at least partially responsible for the attentional deficits of set-shifting in schizohprenia.

Decreased ACC activity during attention tasks in schizophrenia patients have also been demonstrated in EEG studies using an auditory choice reaction task (Gallinat *et al.*, 2002; Mulert *et al.*, 2001). In these studies, drug-free patients had significantly longer reaction times during task performance and current density values were significantly lower during the second N1 peak. When projected onto Talaraich space using low-resolution electromagnetic tomography (LORETA), activation differences between the patient and control groups were localized to the ACC (Gallinat *et al.*, 2002; Mulert *et al.*, 2001).

Although most studies report a decrease in ACC activity in schizophrenia, several investigators have found abnormal increases in ACC activation during attentional tasks. In an fMRI experiment by Weiss, a modified version of the Stroop task was used, whereby only patients with performances comparable to controls were imaged. Results indicated that patients with schizophrenia had a bilateral increase in blood oxygen-level dependent (BOLD) signal in ACC while only the right ACC was activated in normal controls (Weiss *et al.*, 2003). This suggests that schizophrenia patients can perform attentional tasks at a level equivalent to normal controls, but require more cognitive resources. This idea is seen again in an ^{15}O-PET study when performance of an auditory sustained attention task between patients and controls was matched (Ojeda *et al.*, 2002). Using this paradigm, Ojeda found activation in both the ACC and PCC in the schizophrenia group, relative to only ACC activation in healthy controls. Differences between groups were not found in the level of activation, but in the extent of the activation as the schizophrenia group activated more subregions of cingulate cortex in order to perform the task (Ojeda *et al.*, 2002). Futhermore, another explanation of ACC-related impairment in attention is inefficiency in neuronal activity. In an 18-fluoro-2-deoxyglucose PET study, where performance on the CPT by the schizophrenia group was worse relative to normal controls, hyperactivity was found in the ACC of schizophrenia patients, suggesting that there may be cases of neuronal inefficiency in which increased activation does not necessarily imply improvement of attentional performance (Siegel, Jr. *et al.*, 1995).

To summarize, functional neuroimaging studies show that the ACC and attentional circuit in schizophrenia are markedly different compared with healthy volunteers. While there may be instances where schizophrenics can attend on the same level as normal controls, they must exert increased effort, seen in either greater signal change or the recruitment of additional areas not normally used by normals. In addition, there are instances when even with increased effort, performance remains sub-optimal. Thus, functional imaging studies provide a consistent, though not always identical, line of evidence for the ACC's involvement in attentional impairment in schizophrenia.

Working Memory

The ACC has a dynamic role in working memory (Kondo *et al.*, 2004; Carter *et al.*, 1998). The ACC has been shown

to activate during a number of working memory tasks, including backwards digit span, reading span, and number subtraction tasks (Osaka *et al.*, 2004; Spinks *et al.*, 2004; Gerton *et al.*, 2004). In studies that compared good and poor healthy control performance on working memory, it was found that higher performers, who were able to meet more demanding memory spans, showed increased ACC activation (Kondo *et al.*, 2004; Osaka *et al.*, 2004). Similarly, in schizophrenia subjects, Jansma *et al.*, (2004), using a parametrically increased load on an n-back task, reported a linear increase in ACC activation correlated with difficulty of the task until performance capacity was exceeded. This result is consistent with a meta-analysis conducted by Glahn *et al.* (2005), who used the activation likelihood estimation method to examine activation patterns in schizophrenia during performance on various modified versions of the n-back task from twelve neuroimaging studies. Glahn *et al.* (2005) found that task performance in the schizophrenic group was significantly worse in all but one study, and that while the DLPFC was hypo-activated, the ACC, as measured along the midline, and left frontal pole regions were hyperactivated when compared with healthy controls.

In contrast to the results aforementioned, a number of studies report a lack of ACC activation or hypoactivation during working memory performance in schizophrenia. In an ^{15}O PET study using a random number generation task (subjects had to produce long strings of random numbers without repetition), Artiges (2000) reported that normal controls performed better than patients and exhibited increased ACC activation that was proportional to the randomness of their responses. Conversely, the schizophrenia subject group performed worse than controls and showed decreased ACC activation that was not correlated with response randomness.

In an ^{15}O-PET study using a spatial n-back task, Meyer-Lindenberg *et al.* (2001) reported strong DLPFC and ACC activation in normal controls relative to greater inferotemporal, parahippocampal and cerebellar activation in a group of medication-free (for at least 2 weeks) schizophrenia patients. No ACC activity was found in this subject group. In addition, activation patterns during the working memory task condition had more variance for the subject group than the normal group (Meyer-Lindenberg *et al.*, 2001). Kindermann (2004), used fMRI to examine middle-aged and older patients with schizophrenia during performance on a spatial working memory task. Increased activation was found in the left ACC, parietal cortex, left basal ganglia and superior temporal gyrus in normal controls. The schizophrenic group lacked activation of the ACC but exhibited greater activation in the left fusiform gyrus, medial frontal area and right anterior cerebellum (Kindermann *et al.*, 2004).

In an fMRI study of auditory working memory, Menon *et al.* (2001), using an ROI analysis, found deficits in activation of components of the working memory network for the schizohprenia group. Regions of hypoactivity included the left and right DLPFC, frontal operculum, inferior parietal gyrus, but not the ACC, which did not differ significantly from ACC activation in normals (Menon *et al.*, 2001). Although this finding is inconsistent with the previous studies discussed in this chapter, a few important differences may have contributed to the disparate results. These include the modality of the task (auditory as opposed to visual), the schizophrenia group demographics (exclusively males), and the use of ROI as opposed to whole brain analysis, which may have imposed higher cluster values that inadvertently excluded areas that otherwise would have been activated.

To summarize, despite discrepancies among study paradigms, most studies assessing the ACC's contribution to working memory indicate that patients with schizophrenia tend to perform worse during working memory tasks and that, regardless of the modality through which working memory is tested, the ACC activation in subjects with schizophrenia is consistently different. These differences have varied among studies, but common results include a deficit in ACC activation compared with healthy controls, and recruitment of different brain areas to compensate for such hypoactivity in cingulate function during working memory performance. Finally, it is worth mentioning that while the ACC is widely studied for its role in working memory, there have been studies indicating potential ACC involvement in other aspects of memory such as encoding, recognition, and retrieval (Hofer *et al.*, 2003; Quintana *et al.*, 2004; Ragland *et al.*, 2001). While it is not the intention of this chapter to examine these other areas of memory, it is important to note that the ACC may be involved in multiple memory systems in addition to the domain of working memory, and that abnormalities in the ACC may contribute to very complex disturbances among memory systems that can contribute to the cognitive impairments in schizophrenia.

Cingulate-mediated Executive Dysfunction

It is generally accepted that the ACC plays an integral role in attentional or executive control (Posner & Petersen, 1990; Smith & Jonides, 1999). Specifically, functional neuroimaging studies examining healthy individuals have revealed ACC activation during tasks of selective attention, working memory, word generation, and information processing. The extent to which

this brain region is involved in these cognitive processes, however, remains a topic of intense study and debate. Several theories have emerged to explain the conditions under which the ACC is activated (Carter *et al*., 2000; Cohen *et al*., 2000).

Selection-for-action

It has been proposed that the ACC, together with the DLPC, is part of an executive circuit responsible for the top-down selection of strategic processes during complex attentional tasks (Frith *et al*., 1991; Paus *et al*., 1993; Petersen *et al*., 1989; Posner *et al*., 1988; Posner & Raichle, 1994). Activation of the ACC is believed to reflect a strategic process known as "selection-for-action," in which the selection of environmental objects as triggers of or targets for action is guided by a set of cognitive rules (Botvinick *et al*., 1999). Investigations of patients with schizophrenia have consistently identified deficits on tasks requiring the controlled allocation of attention, including traditional neuropsychological measures such as the WCST (Heaton, 1981; Randolf *et al*., 1993) and experimental paradigms utilizing a modified version of the Stroop task (Carter *et al*., 2000; Nordahl *et al*., 2001) and an attentional set-shifting task (Downes *et al*., 1989; Owen *et al*., 1991; Pantelis *et al*., 1999). Functional neuroimaging studies have demonstrated reduced activation in the several frontal regions during the WCST in medicated (Berman *et al*., 1986) and unmedicated schizophrenic patients (Weinberger *et al*., 1986; Weinberger *et al*., 1988) as compared with normal controls. Studies employing the Stroop task have also found altered ACC activation in patients with schizophrenia compared with normal controls (Bench *et al*., 1993; Carter *et al*., 1995; Peterson *et al*., 1999; Taylor *et al*., 1997). The Stroop paradigm is commonly used as a measure for executive or attentional control. In this task, the subject is presented with color words that are printed or displayed in compatible or incompatible colors (e.g., the word 'red' displayed in red versus the word 'red' displayed in green). Successful performance on the Stroop task requires such cognitive processes as inhibitory control, conflict resolution, and response selection, all of which depend upon the integrity of a complex network of frontal-subcortical connections (Brown *et al*., 1999; MacLeod, 1991; Weiss *et al*., 2003). Furthermore, improvements in WCST performance have been reported in several training studies in which schizophrenic patients were provided with card-by-card instructions or cues (Goldberg *et al*., 1987), suggesting that patients benefit from external sources of attentional control. Taken together, these findings lend support for a deficit in the top-down attentional mechanisms that control the selection of appropriate cognitive or response sets (Goldman *et al*., 1996). Despite much discussion of the rich interconnections with the DLPC, an area reported to be involved in response selection, there is little empirical data available to support the ACC as a primary neuroanatomic substrate for selection-for-action in human subjects (Rushworth *et al*., 2004; Woldorff *et al*., 1999).

Error Detection

An alternative explanation of ACC function argues that this structure is not directly responsible for selecting the task set or strategy *per se*, but that the ACC is part of a circuit responsible for error detection and compensation (Bernstein *et al*., 1995; Falkenstein *et al*., 2000; Gehring *et al*., 1993; Scheffers & Coles, 2000). This theory emerged from electrophysiological studies (Falkenstein *et al*., 1990, 1991; Gehring *et al*., 1993) utilizing ERP paradigms to measure error-related negativity (ERN), a change in signal which peaks 100–150ms after the execution of an incorrect response (Falkenstein *et al*., 2000). The ERN is believed to reflect a comparative process by which a rapid, preconscious error-detection system determines when a mismatch has occurred between the intended response and the actual response (Laurens *et al*., 2003). These results and dipole localization analysis of dense array ERP data (Dehaene *et al*., 1994; Holroyd *et al*., 1998; Luu *et al*., 2000; Miltner *et al*., 1997) suggest that the ACC is involved in monitoring performance and detecting errors in normal individuals. Functional neuroimaging data have also demonstrated increased ACC activation in healthy adults during error-eliciting tasks (Carter *et al*., 1998; Kiehl *et al*., 2001; Ullsperger & von Cramon, 2001).

Patients with schizophrenia are often reported to have difficulty with self-monitoring and interpretation of social cues (Corrigan & Green, 1993; Corrigan & Toomey, 1995; Koren *et al*., 2004; Baker & Morrison, 1998), resulting in impaired interpersonal and vocational functioning. Deficiencies in error detection could certainly contribute problems in psychosocial functioning by reducing the likelihood that the schizophrenic individual would identify and subsequently correct misinterpretations of cues or behavioral errors during social interactions. Kopp and Rist (1999) utilized a flanker priming task to measure response monitoring in schizophrenia patients and found that, although all patients demonstrated normal error correction, patients classified as 'paranoid' showed reduced ERN relative to non-paranoid patients and healthy controls. Carter *et al*., (2001) reported attenuation of ACC activation on fMRI in schizophrenia patients compared with healthy controls during incorrect responses but not correct responses on a CPT. Moreover, schizophrenic patients showed significantly less slowing following an

incorrect response, a phenomenon that is commonly observed in normal individuals and is thought to reflect a performance adjustment aimed at reducing subsequent errors (the Rabbitt effect; Rabbitt, 1966). Taken together, these results suggest that ACC dysfunction is associated with impaired performance monitoring and error detection in schizophrenia.

ACC activation was recently examined by Holcomb and colleagues (Holcomb *et al.*, 2000) using [^{15}O] H_2O PET to evaluate rCBF in schizophrenia patients during a high-error attention demanding task. In this study, schizophrenia patients and healthy controls were trained to criteria (80% accuracy) on a forced-choice auditory recognition task. Results indicated that a subset of schizophrenia patients required a significantly greater frequency to reach criteria than controls. Despite similar accuracy performances, ACC rCBF was reduced in the patient group, especially in those with abnormal frequency disparity. In contrast, patients with normal frequency disparity showed a slight increase in ACC rCBF, similar to the larger increase seen in healthy controls. Thus, in a subset of schizophrenic patients, ACC dysfunction may account for an increased likelihood of erroneous responses to subtle differences in target characteristics. Rubia *et al.*, (2001) have also reported reduced ACC activation using fMRI to examine schizophrenic patients' performance on a 'stop' and a 'Go-No-Go' task. Abnormally high ACC metabolic activity has been observed in schizophrenic patients during a modified Stroop task (Nordahl *et al.*, 2001), but this may reflect differences in patient characteristics, medications, and imaging quality.

Conflict Monitoring

An alternative theory argues that the ACC is not directly responsible in selecting the task set or strategy *per se*, but that it is concerned with the response competition that ensues once a novel task set has been selected (Botvinick *et al.*, 1999; Carter *et al.*, 1998, 2000; Casey *et al.*, 2000; MacDonald, III *et al.*, 2000; Paus *et al.*, 1993; Taylor *et al.*, 1994). In this scenario, the role of the ACC is to detect and signal the occurrence of conflict between incompatible responses. This information is then utilized by other frontal regions involved in attentional control, such as the DLPC, in the selection of the appropriate response. Response competition could account for findings of increased ACC activation in healthy individuals during the Stroop task (MacLeod, 1991). Carter and colleagues have tested this hypothesis in a series of experiments using a variety of tasks, including the flanker task, CPT, and the Stroop task (Botvinick *et al.*, 1999; Botvinick *et al.*, 2004; Carter *et al.*, 1998, 2000). Based upon their results, they proposed that the ACC detects conflict between competing responses in healthy individuals and triggers strategic adjustments in cognitive control in order to avoid future conflict. This sequence of events tends to occur in one of three circumstances: (1) when the task requires the individual to override a prepotent but incorrect response, (2) when the task requires the individual to select among conflicting but equally plausible responses, and (3) when an error is made despite transient activation of both the correct and incorrect responses (Botvinick *et al.*, 2004; Carter *et al.*, 1998, 2000).

Over the past decade, the introduction of new APD has contributed to the improved response in schizophrenia. Nevertheless, many patients continue to struggle with persistent social and functional impairment. Findings from several recent studies lend support for a neurocognitive etiology; specifically, a lack of insight and poor self-monitoring (Carter *et al.*, 1998, 2000; Green, 1996; Jensen *et al.*, 2004; Nilsson & Levander, 1988; Rasmussen & Levander, 1993). Turken *et al.*, (2003) examined internal monitoring of erroneous actions, as well as three components of attentional control in a group of schizophrenia patients described as 'high-functioning.' Compared with healthy controls, the patients showed a disproportionately pronounced impairment in action monitoring as evidenced by their inability to correct errors without external feedback. In contrast, no differences were evident between patients and controls on any of the three dimensions of attentional control, suggesting that self-monitoring may be mediated by a distinct neuroanatomical substrate, such as the ACC. In a large sample of schizophrenia patients, Perry *et al.* (2001) found that patients who were instructed to verbalize their sorting strategy performed similar to healthy controls, despite poor baseline performance. Thus, the commonly reported finding that schizophrenic patients perform poorly on card sorting tasks may reflect deficient self-monitoring skills rather than impairment in executive control (i.e., shifting of attention) *per se*.

Recently, functional neuroimaging techniques such as PET and event-related fMRI have been employed in an attempt to delineate the areas of neural activity associated with self-monitoring deficits in schizophrenia (Carter *et al.*, 1997, 2001; Ford *et al.*, 2004; Heckers *et al.*, 2004). Using a version of the CPT, Carter, *et al.* (2001) found that following errors of commission, medicated patients with schizophrenia exhibited significantly less slowing of reaction times than a group of matched healthy controls. Furthermore, relative to control subjects, the patients showed reductions in error-related activity in the ACC. Taken together, these results provide support for the ACC as a neural substrate for impaired self-monitoring in a subset of schizophrenia patients. Reduced ACC activity was also found in a group of schizophrenia patients in a study using PET to examine neural activation associated with detection of

response conflict elicited during the Stroop task (Carter *et al.*, 1997). Similar to the study discussed earlier, all patients in this study were taking neuroleptics, raising the possibility that diminished ACC activation may reflect medication effects rather than a pathophysiologic process. Several studies have reported reduced ACC activation during other frontally-mediated tasks in unmedicated patients (Andreasen *et al.*, 1992; Fletcher *et al.*, 1996) suggesting that impaired ACC function in this population is unrelated to medication use. Although additional studies are needed to improve the generalizability and the ecologic validity of these findings, the majority of studies reviewed above provide support for the association between ACC dysfunction and deficient conflict monitoring in schizophrenia. Table 32.1 provides an overview of Broadman Areas and Talairach coordinates reported in the studies reviewed for this chapter.

Effect of Antipsychotic Drugs on Anterior Cingulate Function

All effective antipsychotic drugs have a measurable affinity for the D2 dopamine receptor; the new antipsychotics also have an equal or higher affinity for serotonin 2a receptors. In addition, each drug has its own individual affinity profile for other receptor proteins as well, including other of the serotonin receptors (5HT-1a, –2c, –4, –6, –7), other dopamine receptors (D1), noradrenergic, histaminergic, cholinergic, and others. Any antipsychotic drug when administered to humans can affect the anterior cingulate function locally through these receptors, depending on receptor density. In addition, activities of anterior cingulate neurons are regulated by long tract neurons from frontal cortex, subiculum, thalamus and basal ganglia; as such, these afferent neuronal populations can influence signaling and activity in ACC neurons. It is activity in the basal ganglia-thalamo-cortical circuit(s) that are most well known in ACC (Chapter 28).

The effect of antipsychotic drugs on ACC function has been repeatedly seen in persons with psychotic illness. Often the effect of the illness (as ACC function is altered in schizophrenia) confounds an attempt to examine the effect of drug alone. It is in those studies where images are collected with and without medication in the same individuals, that the effect of drug can be clearly seen. In addition, while some studies examine a single drug, many studies have looked at a variety of medications, also adding variability to the final results. Moreover, it has been mainly in schizophrenia where these studies have been carried out, not in other psychotic illnesses, as yet. More recently the effect of medications on ACC activation has been examined with task activation, using fMRI techniques. This approach requires the task to activate/inhibit a brain region before the effect of medication can be thoroughly tested, adding more complexity to the question.

Several studies have demonstrated antipsychotic-induced alterations in brain function using functional imaging techniques. In the older literature with lower resolution techniques, antipsychotic drugs were shown to increase basal ganglia activity and alter neocortical activity, but with variability in cortical measures. Holcomb *et al.* (1996) examined schizophrenia volunteers on, 5-days off and 30-days off a fixed dose of haloperidol. The 5-day-off condition did not differ significantly from the on-medication condition, suggesting inadequate withdrawal time. But the 30-day withdrawal confirmed the increase in basal ganglia activity with haloperidol; moreover, the study found an increase in thalamic rCBF and a decrease in ACC and DLPC rCBF with haloperidol. The decrease in ACC activity by the haloperidol is in the same direction as the illness effect (seen in drug-free schizophrenia patients). Miller *et al.* (1997) found similar results, including the reduction in ACC activity with medication. In this study delusions were associated with reduced ACC rCBF. The decrease in ACC activation with antipsychotic drugs is in contrast to the increase produce in ACC activity with psychotomimetic drug action, including ketamine (Lahti *et al.*, 1995) and amphetamine (20) and its correlation with the psychotomimetic action of ketamine (Holcomb *et al.*, 2005).

To contrast 1st with 2nd generation APD, N-acetyl aspartate was measured in ACC in individuals on traditional (1st) and new (2nd) treatments; the 2nd generation drugs produced a higher N-acetyl aspartate in ACC than the 1st generation ones, suggesting a normalizing effect with newer drugs in ACC (Braus *et al.*, 2001). Contrasting 1st and 2nd generation drugs has also been carried out with functional imaging using haloperidol contrasted with clozapine. Lahti *et al.* (2003) showed that rCBF in ACC was increased with clozapine compared with haloperidol with the same action in DLPFC. Moreover, in a hierarchical task design, clozapine could be shown to normalize ACC rCBF during performance of the task component, while haloperidol only modified ACC rCBF slightly from the drug free condition (Lahti *et al.*, 2004).

In summary, drugs that reduce psychosis (anti-dopaminergic drugs) reduce levels of neuronal activity in ACC, sometimes with a correlation between symptoms and rCBF. Drugs that produce psychosis correlate with activity elevations in the ACC. Clozapine causes lesser ACC reductions than haloperidol, suggesting that ACC rCBF is a complex reflection of function. Because ACC function is so disordered in psychosis and quantifiable using functional imaging, we should be able to use these measures as an index or surrogate of antipsychotic efficacy. But, this has not been done to date.

Functional Imaging Ear Marks Cingulate Pathology

Overall, there is a rich body of task-associated *in vivo* functional activation studies of the ACC in schizophrenia. These studies, in the main, show an alteration from normal in response of the ACC to tasks dependent on ACC mediation. However, the specifics of the response alterations are quite varied, usually decreased, but occasionally reported as increased, in activation characteristics in the patient group. It is clear that the persons with schizophrenia who participate in these studies are sometimes medicated (including with different medications), sometimes not; sometimes early schizophrenia, sometime chronic; sometimes extensively cognitively impaired, sometimes only mildly; and so forth. So the diversity of the schizophrenia populations looked at with functional imaging methodologies might be confounding the goal of identifying a single ACC defect. As described here, there appear to be several complex ACC functional defects among individuals with the illness, even though, not always the same. But, the majority of the studies do report an alteration in the ACC.

The functional neuroimaging and neuropsychology literature implicates the ACC in a number of cognitive processes, namely in the domain of executive function. These include well-established areas such as attention and working memory and also relatively new, more theoretical roles such as selection-for-action, error detection and conflict-monitoring. In schizoprenia, the functional imaging data suggest that the ACC characteristically shows dysfunction especially with increasing cognitive load. Clearly, there is a great deal of variability among patients in their cognitive capacity for ACC mediated tasks, but almost all can show disability with a sufficient load.

A number of variables need to be considered when interpreting the literature we reviewed here regarding the ACC, schizophrenia, and the potential explanations for cognitive impairments in schizophrenia. One issue is that of indirect measurement. While a functional technique such as fMRI measures is the BOLD signal, which is an indirect measure of blood flow, at best. From the BOLD signal, an inference is made about neuronal activity that is altered with the task being performed. Therefore, the characteristics of task performance and its equivalence across groups are of considerable importance. Any differences in performance parameters can complicate interpretations of the mechanism of impairment during cognitive testing, begging the question of whether the deficit is due to the specific cognitive process of interest, or an underlying metabolic difference that is more global (Ford *et al.*, 2004; Schultz *et al.*, 2002). As mentioned, medication effects are another factor to consider when interpreting results, as are the patient volunteer variability across subject groups. Studies have shown that metabolism and rCBF can be altered in specific regions of the brain and that different medications can affect different regions (Holcomb *et al.*, 1996; Miller *et al.*, 2001).

Despite potential technical confounds and occasional inconsistencies among the studies, there are a few observations and generalizations that seem to emerge regarding the ACC and schizophrenia. One is that of regional tissue recruitment in task performance. It is often the case that schizophrenic patients require greater activation or enlist additional cortical areas not activated in normal controls when performance is matched between the two groups. The meta-analysis by Glahn of working memory performance in schizophrenic patients, in comparison to controls, showed that the patient group in general required a greater extent of cingulate activation for the same task (Glahn *et al.*, 2005). Another general finding is a reduction in activation magnitude during task performance in the schizophrenia group. Neuroimaging studies show that the ACC is often insufficiently activated in schizophrenia during tasks where patient performance is worse than performance by healthy controls. Finally, consistent with post-mortem studies and neuropsychological experiments, functional neuroimaging studies provide evidence that the ACC is one of several cortical regions which appears abnormal in the illness. It is not every neocortical region whose function is altered in the illness. Related limbic cortex such as the hippocampus, the middle frontal cortex and the insular cortex also function abnormally in volunteers with schizophrenia. It is still not clear whether these sites represent a common regional set altered in all affected individuals or represent variability in individually affected areas.

The evidence shows that both the ACC structure and function are frequently disrupted in schizophrenia. This may lead to deficits in the ACC mediated cognitive functions, which are commonly disturbed in schizophrenia. Additionally, the ACC may also play a role in the positive symptoms of schizophrenia as evidenced by ketamine challenge studies reporting increased rCBF in the ACC in schizophrenia volunteers and haloperidol PET challenge studies reporting an elective decrease in the glucose metabolism in the ACC in schizophrenia (Tamminga *et al.*, 2000a).

Our current working hypothesis posits that the ACC abnormalities, which are clearly present in schizophrenia, may represent a generalized molecular defect present throughout brain, but only manifest in limited cerebral regions because of the characteristics of the local tissue microarchitecture of those regions and the functional demands made of the tissue during

demanding tasks. Evidence has suggested a generalized defect of the synapse that would alter synaptic transmission and neuronal plasticity (Frost *et al.*, 2004; Mirnics *et al.*, 2001). This is a more parsimonious model than merely suggesting that a different molecular defect occurs in each functionally affected brain region, but speculative, nonetheless. The idea that psychological assessment and functional imaging measures can ear mark a cerebral region likely to carry a defect would be reasonable. Then proposing to analyze those regions with assessments based on molecular hypotheses would be a more rational approach than without those introductory clues. Whether the ACC defect is primary, part of an affected neural circuit, or projected from a distant affected site, has yet to be determined. But, the dominant conclusion from the *in vivo* studies is that ACC structure and function is altered in schizophrenia.

TABLE 30.1 Brodmann areas and/or Talairach coordinates of functional neuroimaging studies cited in this chapter

Citation	Domain	Task	Area(s)	Talairach coordinates
Ortuno *et al.* (2002)	Attention	Auditory Counting Task	32, 24	(2, 8, 48), (−8, 16, 24)
Moll *et al.* (2002)	Attention	Verbal Adaptation of TMT	6, 32	(−06, 3, 49)
Perianez *et al.* (2004)	Attention	Wisconsin Card Sort Task	24, 32	(0, 23, 42)
Shafritz *et al.* (2004)	Attention	Visual Target Detection Task	24, 32	
Laurens *et al.* (2005)	Attention	Auditory Oddball Task	24, 32, 10	(0, 32, 28), (4, 28, 36), (8, 28, 32), (8, 48, 8)
Carter *et al.* (1997)	Attention	Stroop Task	10	(12, 46, 4)
Grady and Keightly *et al.* (2002)	Attention	summary result	32	
Salgado-Pineda *et al.* (2003)	Attention	Continuous Performance Task	32, 24, 31	(02, 24, 32), (06, 45, 10), (−08, −68, 08)
Boksman *et al.* (2005)	Attention	Verbal Fluency Task	8, 32	(6, 20, 42)
Gallinat *et al.* (2002)	Attention	Auditory Choice Reaction Task	24, 25, 32	(−3, −11, −6), (4, 17, 29), (−3, 17, 29)
Mulert *et al.* (2001)	Attention	Auditory Choice Reaction Task	32	(−10, 10, 36)
Weiss *et al.* (2003)	Attention	Stroop Task	6, 24, 32	(12, 12, 40), (−4, −8, 56), (0, −8, 40)
Ojeda *et al.* (2002)	Attention	Auditory Counting Task	31, 23, 32	(8, −46, 40), (6, −24, 22), (−6, 8, 44)
Kondo *et al.* (2004)	Working memory	Operation Span Task	32	(−8, 20, 40), (4, 24, 36)
Carter *et al.* (1998)	Working memory	Continuous Performance Task	24, 32	
Osaka *et al.* (2004)	Working memory	Reading Span Test	32	(−6, 20, 46), (6, 24, 42)
Spinks *et al.* (2004)	Working memory	Number Subtraction Task	24, 32	(−1, 19, 45), (15, −9, 43)
Gerton *et al.* (2004)	Working memory	Digit Span Forward, Digit Span Backward	32	
Jansma *et al.* (2003)	Working memory	N-back	8	(1, 24, 44)
Glahn *et al.* (2005)	Working memory	N-back	6, 32	(0, 8, 48), (6, 17, 40)
Artiges *et al.* (2000)	Working memory	Random Number Generation Task	24, 32	(6, 26, 44), (16, 16, 38)
Meyer-Lindenberg *et al.* (2001)	Working memory	N-back	32	(−4, 17, 41)
Menon *et al.* (2001)	Working memory	N-back	24, 32	(−4, 24, 34), (2, 22, 24)
Carter *et al.* (2000a)	Selection-for-action	Computerized Stroop Task	32	(0, 15, 41)
Bench *et al.* (1993)	Selection-for-action	Stroop Task	24, 25, 32	

(*Continued*)

TABLE 30.1 Brodmann areas and/or Talairach coordinates of functional neuroimaging studies cited in this chapter
Continued

Citation	Domain	Task	Area(s)	Talairach coordinates
Carter *et al.* (1995)	Selection-for-action	Single-trial Stroop	6	(10, 8, 48)
Peterson *et al.* (1999)	Selection-for-action	Stroop Interference	12, 24, 25, 32	
Taylor *et al.* (1997)	Selection-for-action	Stroop Task	24, 32	(−3, 35, 18)
Laurens *et al.* (2003)	Error Detection	Go/NoGo task	8, 10 (29)	(8, 28, 40), (0, −44, 12), (−12, 60, 0)
Carter *et al.* (1998)	Error Detection	Continuous Performance Task	24, 32	
Kiehl *et al.* (2001)	Error Detection	Novelty Dection Task	6, 32 (31)	(0, 11, 45), (8, 26, 25), (0, −34, 35)
Ullsperger & von Cramon, (2001)	Error Detection	Flanker Task	24c′, 32 (31)	(7, 19, 30), (4, 19, 41), (4, −25, 27)
Carter *et al.* (2001)	Error Detection	Continuous Performance Task	24, 32	(0, 27, 36), (2, 21, 36)
Holcomb *et al.* (2000)	Error Detection	Tone Frequency Recognition Task	24, 32 (29, 30)	(4, 8, 48), (4, −50, 12), (−4, −2, 44)
Rubia *et al.* (2001)	Error Detection	Stop Task, Go/NoGo Task	10, 24, 32	(−5, 40, 7), (−5, 42, 18)
Botvinick *et al.* (1999b)	Conflict Monitoring	Flanker Task	32	(−2, 31, 29), (−2, 28, 31)
Carter *et al.* (2000b)	Conflict Monitoring	Computerized Stroop	6	(0, 15, 44)
Casey *et al.* (2000)	Conflict Monitoring	Flanker Task	32	(−8, 22, 32)
MacDonald *et al.* (2000)	Conflict Monitoring	Task-Switching Stroop	24, 32	(4, 1, 43)
Paus *et al.* (1993)	Conflict Monitoring	Oculomotor, Manual, and Speech Tasks	6, 8, 24, 32 (23, 31)	(−5, −7, 49)
Botvinick *et al.* (2004)	Conflict Monitoring	(Review of several tasks)	24, 32	
Carter *et al.* (1997)	Conflict Monitoring	Single-Trial Stroop	10	(12, 46, 4)
Ford *et al.* (2004)	Conflict Monitoring	Go/NoGo Task	24, 31, 32	
Heckers *et al.* (2004)	Conflict Monitoring	Novel Multi-Source Interference Task	32	(8, 22, 28)
Fletcher *et al.* (1996)	Conflict Monitoring	Verbal Fluency Task	24, 32	(−4, −6, 32), (6, 16, 28), (6, 6, 28), (8, 32, 16)

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